THE UNIVERSITY of EDINBURGH

Anne Rowling Regenerative Neurology Clinic

NHS Lothian

MS STAT2

We are inviting you to take part in a research study titled – Multiple Sclerosis - Simvastatin Trial 2 (MS-STAT2)

- Please take time to read the following information carefully. Discuss it with friends and relatives if you wish. Take time to decide whether or not you wish to take part.
- You are free to decide whether or not to take part in this research study. If you choose not to take part, this will not affect the care you get from your own doctors in any way.
- You can stop taking part in the study at any time, without giving a reason.
- Ask us if there is anything that is not clear or, if you would like more information.
- Thank you for reading this information. If you decide to take part you will be given a copy of this information sheet and asked to sign a consent form.

Important things that you need to know

- We want to find out if the drug simvastatin is effective at slowing down disease progression in patients with secondary progressive multiple sclerosis (SPMS).
- 1180 patients will be recruited to this trial across approximately 30 hospitals/neurology centres in the UK and Eire.
- If eligible, you will be selected at random to receive either **simvastatin OR placebo.**
- The trial will last for 36 months. You will be required to complete 10 study appointments over this period. This will involve nine (9) visits to your local study assessment unit and at least one (1) telephone call.

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If you have any questions about this trial, please talk to your study doctor or nurse:

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1 Why are we doing this trial?

Multiple Sclerosis (MS) is a progressive neurological disorder of the brain and spinal cord. It affects approximately 120,000 people in the UK and 2.5 million people globally.

Most people with MS experience two stages of the disease:

Early MS – Relapsing-Remitting MS (RRMS), which is partially reversible, and

Late MS – Secondary Progressive MS (SPMS), which affects the majority of patients, usually after 10 to 15 years after diagnosis.

People with SPMS experience continuous degeneration of the nervous system. This often results in irreversible impairments (disease effects) affecting walking, balance, manual function, vision, cognition, pain control, bladder and bowel function.

In an earlier study (MS-STAT1), 140 people with SPMS were randomly assigned to receive either placebo or simvastatin for a period of two years. The investigators found that the rate of brain atrophy (loss of neurons - 'brain shrinkage'), as measured by magnetic resonance imaging (MRI), was reduced in patients receiving simvastatin compared to those taking placebo.

Several other long term studies have also reported that there might be a relationship between the rate of brain atrophy and the degree of impairment. Therefore, we need to conduct a study over a longer period of time in patients like you to find out if simvastatin is truly effective at reducing the time before people with SPMS experience greater disease effects.

What are we trying to find out?

The purpose of this trial is to determine how effective simvastatin is at slowing down disease progression in people with SPMS.

2 Why am I being asked to take part?

You are being asked to take part in the MS-STAT2 trial for these reasons:

- You have a confirmed diagnosis of multiple sclerosis and have entered the secondary progressive stage (SPMS)
- You are aged between 25 and 65 years old
- You are able to walk at least 20 metres (with or without a walking aid)
- Your condition has worsened over the last 2 years based on your medical history

3 What do I need to know about the treatments in this trial?

As part of this trial, you may receive either simvastatin OR placebo. You will be randomly allocated to receive one of these.

Simvastatin

Simvastatin is a cholesterol-lowering drug that is already used in millions of patients with heart disease. There has been recent evidence to suggest that simvastatin may also be of benefit to people with MS.

This is because simvastatin may also be neuro-protective. This means that it may stop your nerves from being damaged by inflammatory cells that enter your brain in MS.

Placebo

The placebo is identical in appearance to simvastatin but contains NO ACTIVE drug.

4 What will I need to do if I take part?

Can I definitely take part?

Not everyone will be able to take part in the trial. Only patients that meet the trial entry requirements and, are willing to participate may take part. If you are suitable, you will be invited to attend your local study assessment unit for a screening visit. At this pre-study visit, you will have the opportunity to ask any questions you may have regarding the trial. You will be asked to sign a consent form should you wish to continue. The trial doctor will examine you and take your medical history.

At this stage, blood samples will be taken from all participants. In addition, urine samples from female patients will be tested to check if they are pregnant.

Pregnant women cannot take part in this trial due to unknown risks posed by the study drug in an unborn baby, or a breastfeeding child. You will also be asked to complete pre-study assessments and questionnaire.

The results from all assessments, blood test, urine pregnancy test and questionnaire will be analysed by the study team to determine if you are suitable for inclusion in this trial.

We will inform your GP once you join the MS-STAT2 trial.

What if the tests show I can take part?

If you meet all the entry requirements for the MS-STAT2 trial you may be enrolled to the trial. The nurse/doctor will go through the next key steps with you.

The two treatment groups in this trial are as follows:

Simvastatin - patients in this group will start off taking one tablet. The number of tablets will increase to two after a month.

- **One** (1 = 40mg) simvastatin tablet once daily at night **for 1 month**
- **Two** (2 = 80mg) simvastatin tablets once daily at night, for the next **35 months**

Placebo - patients in this group will start off taking one tablet. The number of tablets will increase to two after a month.

- **One** (1) placebo tablet once daily at night for **1 month**
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- **Two** (2) placebo tablets once daily at night, for the next **35 months**

Which group will I be in?

It is important that the groups of patients receiving each treatment are as similar as possible at the start of the study. To ensure that this happens, **a process called randomisation is used to allocate people to a treatment group**.

Randomisation means you will not be able to choose which study drug you receive. You will have a 50/50 chance of being randomly selected to receive either simvastatin or placebo.

The doctor or clinical team member will use an online software application on a computer that will randomly determine which study drug you will receive.

This is a double blind trial. This means neither you nor your doctor (including all the clinical team members) will know which group you are in, and which treatment you are receiving. Your doctor will be able to find out which group you are in should there be a need for it, although this does not usually happen while you are taking part in the trial.

What will happen to me during the study?

You will be required to attend nine (9) study appointments and will receive at least one (1) telephone call over a 36 month period.
At each study visit, you will be asked to complete a number of study assessments including questionnaires. All participants will be expected to provide blood samples at each study visit.

Following randomisation at visit 2, you will start to take low dose (40mg = 1 tablet) of the study drug (simvastatin or placebo). The doctor will increase the dose of the study drug (80mg = 2 tablets) at visit 3, provided you have not experienced any side effects since your last appointment. You will receive an adequate supply of the study drug at each visit to last you until the next study visit.

Your final study appointment will take place at visit 10 (36 months following randomisation).
At the end of this study session, the trial doctor will inform you if you can stop taking study drug. Most people will stop taking study drug and revert back to standard medical care following this appointment. Some people may be asked to continue the drug, but only if their impairment levels have increased at visit 10.

The Expanded Disability Status Score (EDSS) is assessed at each visit throughout the study period. It is used to monitor the changes in the level of disability (impairment) over time. If your score on the EDSS increases for the first time at visit 10, the trial doctor will organise an additional appointment in 6 months' time (visit 11) to repeat the EDSS and other study assessments. You will continue to take the study drug during this period before your appointment at visit 11.

You will stop taking the study drug and resume your standard medical care following this appointment.

We estimate the screening visit assessments will take an hour and a half for the majority of patients, but no more than two hours in total.

We anticipate that trial specific activities at subsequent follow up visits will be completed in under two and a half hours, apart from visit 4 which is a telephone consultation. Please note that the completion times for trial specific activities may vary as it will be tailored to meet the need of each individual patient according to their abilities. Allowing for breaks as required, we currently expect patients' entire visit to be around three to three and a half hours.

Please refer to the summary of procedures at the end of this document for further information.

5 What are the possible side-effects?

What are the most common side-effects?

All treatments can have unwanted side-effects. The most common side effects reported for the drugs used as part of this trial are reported below.

Simvastatin: This is a well-tolerated drug and side effects are rare. However, in this trial, simvastatin will be given at a higher dose than is normally given to patients who use it to lower their cholesterol levels. Side effects can occasionally include muscle pain, tummy pain, blurred vision, dizziness and very rarely severe liver damage. Minor side effects include constipation, diarrhoea, fatigue and headaches.

Placebo: There are no anticipated side effects from taking the dummy treatment.

6 What are the possible benefits of taking part in this study?

If you are randomised to receive simvastatin, this may help to slow down the gradual worsening of your condition. You will have a 50/50 chance of receiving either simvastatin or placebo. Although there is no promise that this trial will help you, the results generated may help to improve the treatment options of people with MS.

In addition, taking part in this trial (regardless of the drug you are randomly allocated to receive) will mean regular review of your MS by an experienced neurologist.

7 What are the possible disadvantages and risks of taking part?

All medical procedures involve the risk of harm, but this is usually a low risk. In addition, there might be risks associated with this study that we do not yet know about. Information on the most common or serious side effects of procedures carried out in this study is listed

below. If you have questions about side effects, please ask your trial doctor.

Blood tests: This trial requires blood tests to be carried out at each clinic follow up appointment.

At visit 4 (telephone consultation), there will be an option to have your blood sample taken either at your local Gp surgery, or your usual study assessment centre. Please discuss with your study doctor/nurse who will organise this for you.

You will be asked to give a small amount of blood sample (Approximately 20ml or 4 teaspoons of blood) at each study visit. We will ensure the total amount of blood taken is within the safe limit for blood donation. Please note there are currently no plans to store blood samples donated for this trial. Blood samples will be discarded once all study specific tests have been completed.

Taking blood can be uncomfortable, but rarely results in any serious problems. Reported side effects include feeling light-headed or faint, bruising and/or discomfort at the site of injection.

Interactions with other medicines: There might be a risk of serious side effects when some medications are taken with the trial drugs.

For your safety, please tell the trial doctor about all medications you are taking before and during the trial. This includes other prescribed medicines, over the counter medicines, recreational drugs, herbal medicines or supplements.

Please note that **grapefruit juice** is known to interact unfavourably with simvastatin. You are advised not to drink grapefruit juice for the duration of the trial.

If you suffer any unpleasant effects or have any concerns regarding your health at any point during the trial, please tell your trial doctor or nurse. You may be asked to attend the clinic for an additional visit(s) for further examination or tests.

Avoiding pregnancy: The active study drug may pose unknown risks to a pregnant woman, an unborn baby, or a breastfeeding child. As such, pregnant women are not allowed to take part in this trial. Urine samples from female participants will be tested at the screening visit (visit 1) to make sure you are not pregnant.

All participants (male and female) are advised to use adequate contraception for the duration of the trial. Please discuss this with your trial doctor.

Other risks: All reasonable efforts are made to make this trial safe. Despite this, some risks might not be possible to predict.

New information about the treatment being studied may become available while the trial is running. We will tell you about any new findings that might affect whether you want to continue in the trial.

8 More information about taking part

Do I have to take part in MS-STAT2 trial?

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

A decision not to take part will not affect the standard of care you receive.

Expenses and Payments

You may be able to claim money to cover travel expenses incurred for study visits. Please speak to your trial doctor/nurse.

Can I stop taking part after I've joined the trial?

You can stop taking part in all elements of the trial, or in any part of it, at any time and without giving a reason. But you must talk to your trial doctor first. They can advise you about any concerns you may have.

A decision to stop taking part at any time will not affect the standard of care you receive.

What will happen to information about me collected during the trial?

If you agree to take part in this trial, the trial doctor will send information about you and your progress to the Comprehensive Clinical Trials Unit at University College London (CCTU at UCL). The information will be processed by the trial team based at the CCTU. Your hospital notes may also be looked at by CCTU staff if necessary.

Some information might be held by NHS Digital and other central UK NHS bodies. This data may be used to help provide information about your health and also about the use of NHS resources.

We will follow all legal requirements to make sure that all information about you remains confidential and is treated appropriately and ethically. Researchers working in collaboration with the CCTU will be required to treat your information in the same manner.

The CCTU is registered under the UK Data Protection Act (DPA) to store this information. There is a question about this on the consent form that we will ask you to sign before you begin the trial.

What will happen to the results of the MS-STAT2 trial?

When the trial is completed, the results will be shared with you as soon as they become available.

We will publish the results in a medical journal, so that other doctors can see them. You can ask your doctor for a copy of any publication. Your identity and any personal details will be kept confidential. No named information about you will be published in any report relating to this trial.

Who is organising and funding the trial?

Who has reviewed the MS-STAT2 trial?

The study has been reviewed and authorised by the Medicines and Healthcare products Regulatory Agency (MHRA), as well as a Research Ethics Committee, the Health Research Authority (HRA), and the Research and Development Office at all participating hospitals.

What if new information becomes available during the course of the trial?

Sometimes during a trial, new information becomes available about the treatment options being studied. If this happens, your trial doctor will tell you about it and discuss with you whether you wish to continue the trial. If you decide to stop taking part in the trial, your doctor will arrange for your care to continue outside of the trial. You will resume standard medical care. However, if you decide to continue, you might be asked to sign an updated consent form.

Your doctor might also suggest that it is in your best interest to stop taking part in the trial. Your doctor will explain the reasons and arrange for your care to continue outside the study. You will resume standard medical care.

What happens if the MS-STAT2 trial stops early?

Very occasionally a trial is stopped early. If this happens, the reasons will be explained to you. Your trial doctor will arrange for your care to continue outside of the study. You will resume standard medical care.

What if something goes wrong for me?

If you have any concerns about the way you have been approached or treated during the trial, please talk to your trial doctor or nurse. If you are still unhappy, or if you wish to complain, please use the normal NHS complaints process. If you are harmed as a result of taking part in this trial, or due to someone's negligence, then you may be able to take legal action.

9 Contacts for further information

If you want further information about the MS-STAT2 trial, please contact the trial doctor using the details provided below;

THANK YOU FOR TAKING THE TIME TO CONSIDER TAKING PART IN THE MS-STAT2 TRIAL

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MS-STAT2 - Summary of Procedures