Trial Participation FAQs

1. Side effects: what to expect?

The drugs that have been chosen are generally very safe. There are rare serious side-effects in a few people which will be fully discussed with all potential participants.

2. What tests will be required before joining the trial?

People with MS who want to join the trial will be asked to first sign a consent form and attend a hospital visit where the clinical team will do some tests and examinations to assess whether they can take part. These assessments for Analysis Stage 2 include:

- Blood and urine samples
- Medical history and physical examination
- Neurological assessments (measuring strength, coordination, arm and hand function, vision, etc)
- Wellbeing and health questionnaires (measuring pain, memory, fatigue, etc)

If the tests show that the person can take part, they will be asked to confirm if they wish to join the trial before formally entering the trial and being allocated to a treatment.

3. What tests will participants do once in the trial?

Trial participants in Analysis Stage 1 will do

- Three magnetic resonance imaging (MRI) scans
- Tests such as blood and urine tests, walking and sight tests, Expanded Disability Status Score (EDSS), tests of hand and arm function and thinking
- Questionnaires about different areas of health and wellbeing including about fatigue, pain and quality of life

Participants in Analysis Stage 2 will not have the MRI scans but will do the tests and questionnaires.

4. How long will I be involved in the trial?

The short answer is up to 5 years.

However, if you join the first part of the trial (called Analysis stage 1), then approximately 3.5 years into the trial there will be an analysis to check if the treatments are showing benefit to the participants.

- If it shows benefit, the treatment will continue.
- If they do not show benefit, those participants taking the treatment will stop.
- For those participants who stop treatment, if they would like to, after 6 month you can be screened again and re-join the trial if you are eligible to receive other treatments in the trial.

5. How frequent are the visits?

- The first 3 visits are roughly monthly. These are the screening visit, the randomisation visit (also called week 0), and the first follow up visit (called week 4)
- After that, in person visits will be every 6 months
- There will be a telephone call in between (every 3 months) for participants on trial treatment

6. What will happen at each visit?

This will vary at each visit. For a list of what will take place at each visit can be found on the visit information leaflet. Some examples of the assessments are:

- Physical assessments to assess your neurological system including strength, co-ordination, walking and tests of arm function such as the 9-holed peg test and 25-foot walk
- A general physical examination
- A check of your medical history
- Written (or completed electronically) some assessments asking about pain, fatigue, and your quality of life
- Some blood and urine tests
- 4 magnetic resonance imaging (mri) scans over 2 years (for those in analysis stage 1 only)

7. When do I have MRI scans?

All people with MS who were screened for the trial for Analysis Stage 1 had one MRI scan at screening, before starting the trial. These participants who went on to enter the trial will have three more: at 6 months, 18 months, and 24 months - all on the same scanner.

8. When will we have results?

We won't know if these drugs slow disability progression until 2028 at the earliest. This is because the trial is combining what would normally be two separate trials into one.

9. Who will be at the visits?

At visits, participants will be seen by different members of the hospital study team including research nurses, doctors responsible for overseeing the treatment, and other doctors responsible for carrying out neurological assessments. There will also be an admin support team, who will help book appointments either at the visit or by telephone.

10. Will there be travel reimbursement available?

Yes. Please speak to your hospital study team to find out how to claim these costs.

11. What happens to participants if a study arm stops early?

As part of the trial study design, if a treatment does not appear to be of benefit at the end of Analysis Stage 1, it may be stopped. If this happens participants who are on that treatment arm

will have a final visit with their study doctor, who will arrange for their standard treatment to continue outside the study.

These participants, if they would like to and are still suitable for the study, may be offered the opportunity to join the study again later. This is possible after a suitable period of time (probably around 6 months). If this is the case for you, your study doctor will discuss this with you.

12. Can I withdraw from the study?

Yes. The study is completely voluntary, and any participant can withdraw from the study at any point with no explanation given, and no change to their standard of care.

If you decide to stop taking your study treatment, we may ask for you to still attend hospital visits every 6 months so we can continue collecting information about you for up to 5 years. This is important, because it helps us to ensure that the results of the study are reliable. Again, there is no obligation to do this.

13. Can I fast while taking the trial drug?

Both metformin and alpha-lipoic acid are regarded as being safe medications. With regards to their potential effects during fasting, there is less certainty however they are likely still safe.

Metformin is commonly prescribed for patients with diabetes, and it is extremely rare to develop hypoglycaemia (low blood sugar levels) from metformin use alone.

Given this, it is generally considered safe in the absence of other conditions/medications that might exacerbate the risk of low blood sugars, to fast while on metformin.

Alpha-lipoic acid seems to be similarly safe, with only very limited evidence of it potentially influencing blood sugar levels, and primarily in people with diabetes taking insulin or other antidiabetic drugs.

See the questions **What does hypoglycaemia (low blood sugar) feel like?** and **What do I do if I feel like I might be having episodes of low blood sugar?** for further information.

14. What does hypoglycaemia (low blood sugar) feel like?

The symptoms of hypoglycaemia can vary from person to person, but the most common early signs include:

- Sudden tiredness and difficulty concentrating
- Sweating heavily
- Dizziness, trembling, or shaking
- Feeling anxious or irritable
- Feeling hungry
- Tingling lips
- Going pale
- A fast, pounding, or racing heartbeat (palpitations)

15. What do I do if I feel like I might be having episodes of low blood sugar?

If you're feeling suddenly unwell with the above, you should consume a sugary drink/food item and seek the advice of your GP or attend A&E for an assessment.

If you have similar symptoms while fasting and taking the trial drug, but are not feeling that way at the time, you should contact your trial team for further advice.

16. Are the trial drugs suitable for people avoiding animal products?

Yes. the trial medications do not contain any animal products in the active ingredients or the capsules.

As all other medicines, animal testing will have been involved in the production of these medications at some point in the development process, but there are no animal-derived ingredients. Further information regarding veganism and medications is available through the Vegan Society.

17. What happens if I choose to withdraw from the trial?

Before you withdraw, please consider if there are other ways you can stay in the trial – perhaps with telephone follow ups or the trial collecting data from other places e.g. your GP or neurologist or just stopping treatment while continuing follow up with your trial team. You can discuss this with your hospital site team who will let us know what you decide.

If you do choose still to withdraw, you will have one final check for any side effects and medications that you have been taking. If you originally consented to things such as sharing your data with the UK MS Register, use of your collected biosamples in future research and passive data collection, you will be asked if you still want to allow this or if you would like to withdraw from this too.

After this check, you then will not need to attend any more follow-up appointments.

18. Can I rejoin later if I withdraw from the trial?

No, you cannot rejoin the trial later if you choose to withdraw. This rule is in place to make sure the trial is fair and that no one can influence the treatment they are randomly allocated by leaving and rejoining the trial. This is important because it makes sure that the results are scientifically accurate.

19. Do I have to withdraw if I can't attend face to face visits?

No, you don't have to leave the trial if you can't come to face to face visits. The trial has been designed to be flexible and so your Trial study team can complete follow-ups and assessments remotely.

You can also choose to complete your questionnaires using *Participate*. To do this just provide your site research team with your email address and/or phone number and they can set you up.

The only part of the trial that cannot be done remotely is the MRIs, **which only applies if you joined during Analysis Stage 1 before October 2024.**

20. What happens if new trials or treatments become available whilst I am in the trial?

This is not a problem and would not require you to leave the trial. OCTOPUS was designed to ensure that if an individual is eligible for any currently available or future treatment to benefit their MS, then they are able to start it while remaining in the trial. If this is the case for you please speak with your hospital trial team who can talk it through with you and give you more information.

21. Will the treatments in this trial improve my MS?

Unfortunately, there is no guarantee that the trial treatments tested will improve your MS. Given that people's MS changes over a long timeframe, the only way to find out if a treatment is slowing it down is to undertake a trial like OCTOPUS in a large enough number of people. However, even in the event that a treatment is not found to be effective, your participation in the trial will play a vital role in helping researchers find better ways to treat MS and improve future research into MS. It also means that you will regularly see a MS specialist and receive frequent medical check-ups and opportunities to discuss any medical issues you are experiencing.

22. How will the new medicines in the trial be chosen?

There is a process which has been set up where clinicians, trial experts, scientists, MS Society representatives, and people with MS, are given the opportunity to suggest potential treatments for consideration. These are constantly and carefully assessed for their likely potential to benefit people with MS, and the most promising treatments added as trial arms at specific timepoints.