



MRC
Clinical
Trials Unit



Supported by



OCTOPUS

Optimal Clinical Trials Platform for Progressive Multiple Sclerosis

Version: 3.0

Date: 28-Apr-2023

MRC CTU at UCL ID: ND001

ISRCTN #: ISRCTN14048364

EUDRACT #: 2021-003034-37

CTA #: CTA 20363/0445/001-0001

MREC #: 22/LO/0622

Authorised by:

Name: Professor Jeremy Chataway

Role: Chief Investigator

Signature:

Date:

Name: Mahesh Parmar

Role: Director of MRC CTU at UCL

Signature:

Date:



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GENERAL INFORMATION

This document was constructed using the MRC CTU at UCL Protocol Template Version 9.0. A modular protocol has been adopted for OCTOPUS. The main Protocol describes the overall trial aspects, and procedures applicable to all Investigational Medicinal Products (IMPs). Each IMP appendix has the background, eligibility and treatment for that specific IMP. Appendices will be added and removed throughout the course of the trial as IMPs are added or removed by substantial amendment.

The CTU endorses the Standard Protocol Items: Recommendations For Interventional Trials (SPIRIT) initiative. It describes the OCTOPUS trial, coordinated by the Medical Research Council (MRC) Clinical Trials Unit (CTU) at University College London (UCL), and provides information about procedures for entering participants into it. The protocol should not be used as an aide-memoire or guide for the treatment of other participants. Every care has been taken in drafting this protocol, but corrections or amendments may be necessary. These will be circulated to the registered investigators in the trial, but sites entering participants for the first time are advised to contact the trial team to confirm they have the most up-to-date version.

COMPLIANCE

The trial will be conducted in compliance with the approved protocol, the Declaration of Helsinki 1996, the principles of Good Clinical Practice (GCP) as laid down by the ICH topic E6 (R2), Commission Clinical Trials Directive 2005/28/EC* with the implementation in national legislation in the UK by Statutory Instrument 2004/1031 and subsequent amendments, the UK Data Protection Act 2018 (DPA number: Z6364106), and the UK Policy Framework for Health and Social Care Research.

SPONSOR

UCL is the trial Sponsor and has delegated responsibility for the overall management of the OCTOPUS trial to the MRC CTU at UCL. Queries relating to UCL sponsorship of this trial should be addressed to the Mahesh Parmar, MRC CTU at UCL Director, MRC CTU at UCL, Institute of Clinical Trials & Methodology, 90 High Holborn 2nd Floor, London, WC1V 6LJ.

FUNDING

Funding for OCTOPUS is from the UK MS Society (reference number 135) and supportive funding from UCL.

AUTHORISATIONS AND APPROVALS

This trial was approved by London - Hampstead Research Ethics Committee and is part of the North Thames NIHR Clinical research network portfolio.

TRIAL REGISTRATION

This trial has been registered with ISRCTN Trial Register, where it is identified as ISRCTN14048364.

RANDOMISATIONS

Participants will be randomised at each site via the OCTOPUS eDC system after the eligibility criteria has been entered and confirmed

Serious Adverse Event (SAE) and Notable Event (NE) REPORTING

**Within 24 hours of becoming aware of an SAE or NE,
please report all SAEs and Notable Events via the OCTOPUS eDC system**
If you have any issues with entering the SAE/NE or have any questions, please email
mrcctu.octopus@ucl.ac.uk

TRIAL ADMINISTRATION

Please direct all queries to the OCTOPUS Trial Team at MRC CTU at UCL in the first instance; clinical queries will be passed to the Chief Investigator via the Trial Team via **mrcctu.octopus@ucl.ac.uk**.

CO-ORDINATING SITE

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OCTOPUS TRIAL TEAM: MRC CTU AT UCL STAFF

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CO-INVESTIGATORS AND TRIAL MANAGEMENT GROUP (TMG) MEMBERS

Name	Title	TMG Role	Organisation
Amanda Adler	Professor of Diabetic Medicine and Health Policy	Metformin Advisor	University of Oxford, Oxford
Frederik Barkhof	Professor of Neuroradiology	Chair of MRI Group	UCL Queen Square MS Centre, (QSMSC) Institute of Neurology (ION), London
Marie Braisher	Research Manager QSMSC	Co-Investigator	UCL QSMSC ION, London
Siddharthan Chandran	Professor of Neurology	Co-Investigator	University of Edinburgh, Edinburgh
Olga Ciccarelli	Professor of Neurology	Co-Investigator	UCL QSMSC ION, London
Denise Fitzgerald	Professor of Neuroimmunology	Co-chair of Treatment Advisory Committee (TAC)	Queens' University Belfast, Belfast
Emma Gray	Assistant Director of Research, MS Society	Funder Representative	MS Society, UK
Dawn Lyle	Lead Research Nurse	Research Nurse	Anne Rowling Regenerative Neurology Clinic, Edinburgh
Rod Middleton	MS Register Project Manager and System Architect	Co-Investigator and management of MS Register	Swansea University, Swansea
Jenny Nicholas	Associate Professor of Medical Statistics	Unblinded Statistician	London School Hygiene of Tropical Medicine, London
Sue Pavitt	Professor in Translational & Applied Health Research	Co-Investigator	University of Leeds and NIHR, Leeds
Susan Scott	(not applicable)	Patient and Public Involvement (PPI) representative	UK
Emma Tallantyre	Clinical Senior Lecturer	Chair of Biobank sub-group and Recruitment and Retention sub-group	Cardiff University, Cardiff
Sam Loveless	Lab Manager	Biorepository Manager	Cardiff University, Cardiff
Alan Thompson	Dean of Faculty of Brain Sciences	Co-Investigator	Faculty of Brain Sciences, UCL, London
Anna Williams	Professor of Regenerative Neurology	Co-chair of TAC	University of Edinburgh, Edinburgh

For full details of all trial committees, please see [section 14](#).

NB: throughout this document, "MRC CTU at UCL" is generally abbreviated to "CTU".

SUMMARY OF TRIAL

SUMMARY INFORMATION TYPE	SUMMARY DETAILS
Acronym or short title	OCTOPUS - Optimal Clinical Trials Platform for Progressive Multiple Sclerosis
Long Title of Trial	Optimal Clinical Trials Platform for Progressive Multiple Sclerosis
Version	2.6
Date	27-Apr-2023
MRC CTU at UCL ID	ND001
ISRCTN #	ISRCTN14048364
EudraCT #	2021-003034-37
Study Design	A multicentre, interventional, multi-arm, multi-stage trial including randomisation, double blinding, placebo control evaluation of treatments for slowing the progression of disability in participants with Secondary Progressive Multiple Sclerosis (SPMS) and Primary Progressive Multiple Sclerosis (PPMS), together termed Progressive Multiple Sclerosis (PMS)
Setting	Neuroscience sites across the UK
Type of Participants to be Studied	Adults with PMS
Sponsor	University College London (UCL)
Interventions to be Compared	Arm A: Standard of Care (SOC) plus Placebo Arm B: SOC plus R/S Alpha Lipoic Acid (R/S-ALA) Arm C: SOC plus Immediate Release Metformin
Definitions of stages	<p>Analysis Stage 1 will evaluate the effect of R/S-ALA or metformin on whole brain atrophy rate, compared to control (placebo). 125 participants per arm will be included and will receive a final MRI scan at 104 weeks (24 months) follow-up from randomisation.</p> <p>Only the treatments showing sufficient promise at Analysis Stage 1 will continue to Analysis Stage 2.</p> <p>Analysis Stage 2 - Treatments that show sufficient promise at Analysis Stage 1, will be evaluated by comparing 6 month confirmed disability progression (CDP) against control (placebo). This will include 600 participants per arm, who will be followed up for up to 5 years from randomisation. Participants included in evaluation at Analysis Stage 1 will also be included in the Analysis Stage 2.</p> <p>Please refer to Figure 2 for Recruitment and Analysis time points.</p>
Study Hypothesis or Objective	Selected treatments that target key neurodegenerative, neuroprotective and/or remyelinating pathways in PMS will slow disability progression compared to standard of care.
Analysis Stage 1 Primary Outcome Measure(s)	Whole brain atrophy rate, as measured by the SIENA technique

SUMMARY INFORMATION TYPE	SUMMARY DETAILS
Analysis Stage 1 Secondary Outcome Measure(s)	<p>MRI outcome measures:</p> <ol style="list-style-type: none"> 1. Regional atrophy rates 2. Cervical cord atrophy rates 3. T2 lesion volume change <p>Clinician reported outcome measures</p> <ol style="list-style-type: none"> 1. Time to initial disability progression¹ 2. Expanded Disability Status Scale (EDSS) 3. Timed 25 Foot Walk (T25FW) 4. 9 Hole Peg Test (9HPT) 5. Symbol Digit Modalities Test (SDMT) 6. MS Functional Composite Z score comprising of the following: <ol style="list-style-type: none"> a. Timed 25 Foot Walk (T25FW) b. 9 Hole Peg Test (9HPT) c. Symbol Digit Modalities Test (SDMT) 7. Sloan Low contrast visual acuity (SLCVA) 8. Relapse rate <p>Patient reported outcome measures</p> <ol style="list-style-type: none"> 1. Multiple Sclerosis Impact Scale v2 (MSIS29v2) 2. Multiple Sclerosis Walking Scale v2 (MSWSv2) 3. Fatigue (MFIS-21 and CFQ) 4. Pain Assessment (Neuropathic Pain Scale and overall pain intensity)
Analysis Stage 1 Exploratory Analysis	Paramagnetic rim lesions (PRLs) collected at baseline only
Analysis Stage 2 Primary Outcome Measure(s)	<p>Time to initial disability progression. The initial disability progression event is finalised as positive if disability is sustained and confirmed ≥ 26 weeks (≥ 6 months) later. This is termed confirmed disability progression (CDP).</p> <p>This is based on a multicomponent measure of sustained disability progression comprising the Expanded Disability Status Scale (EDSS), timed 25-foot walk (T25FW) and 9-hole peg test (9HPT). These will be measured on a 26-weekly (6 monthly) basis from randomisation until last available score recorded at last attended clinic appointment.</p> <p>Progression of disability is defined by progression on at least one of the three parameters:</p> <ol style="list-style-type: none"> 1. EDSS – an increase of at least 1 point if EDSS score at baseline measure is < 5.5, or an increase of at least 0.5 point if EDSS score at baseline measure is ≥ 5.5. 2. Increase of 20% or more from baseline measure on the T25FW. 3. Increase of 20% or more from baseline measure (on either hand) on the 9HPT.

¹ Progression must be confirmed at least 26 weeks later.

SUMMARY INFORMATION TYPE	SUMMARY DETAILS
Analysis Stage 2 Secondary Outcome Measure(s)	<p>Clinician reported outcome measures</p> <ol style="list-style-type: none"> Expanded Disability Status Scale (EDSS) Timed 25 Foot Walk (T25FW) 9 Hole Peg Test (9HPT) Symbol Digit Modalities Test (SDMT) MS Functional Composite Z score comprising of the following: <ol style="list-style-type: none"> Timed 25 Foot Walk (T25FW) 9 Hole Peg Test (9HPT) Symbol Digit Modalities Test (SDMT) Sloan Low contrast visual acuity (SLCVA) Relapse rate <p>Patient reported outcome measures</p> <ol style="list-style-type: none"> Multiple Sclerosis Impact Scale v2 (MSIS29v2) Multiple Sclerosis Walking Scale v2 (MSWSv2) Fatigue (MFIS-21 and CFQ) Pain Assessment (Neuropathic Pain Scale and overall pain intensity) <p>Health related quality of life and resource use</p> <ol style="list-style-type: none"> EQ-5D-5L Health Questionnaire Client Services Receipt Inventory (CSRI)
Randomisation	<p>Participants will be randomised at each site via the OCTOPUS eDC System, a centrally managed system hosted by MRC CTU, accessible to authorised members of the research teams at recruiting site using a web-based interface.</p> <p>Eligibility and consent will be verified before each participant is randomised and is then confirmed within the system at the time of randomisation. If participants are ineligible for a specific research arm, they can be assessed for eligibility and randomised to other open arms.</p> <p>Participants will be allocated into one of the three arms in a 1:1:1 ratio utilising minimisation based on key prognostic factors and a random element.</p>
Number of Participants to be Studied	<p>Analysis Stage 1: 375 participants (125 per arm)</p> <p>Analysis Stage 2: 1200 participants assuming one active arm continues (inclusive of those randomised in Analysis stage 1)</p> <p>Please note the number of participants will be updated for the additional arms as required</p>
Duration	<p>7 years for evaluation of initial interventions, assuming one continues to analysis stage 2.</p> <p>Please note this may increase following the addition of further arms.</p>
Funder	UK MS Society with supportive funds from MRC CTU at UCL
Chief Investigator	Professor Jeremy Chataway

TRIAL SCHEMA

Figure 1: Trial Screening, Randomisation and Treatment

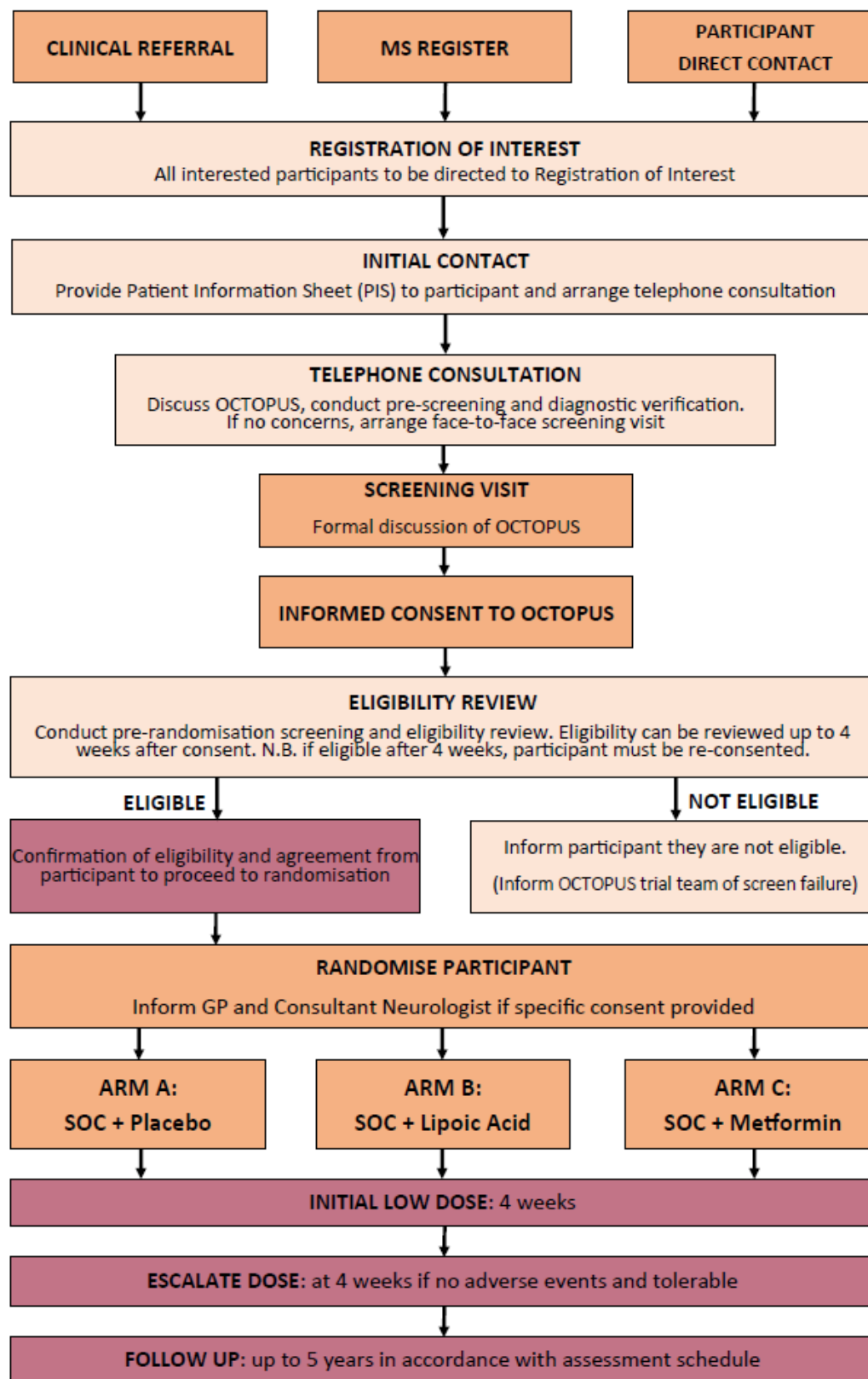
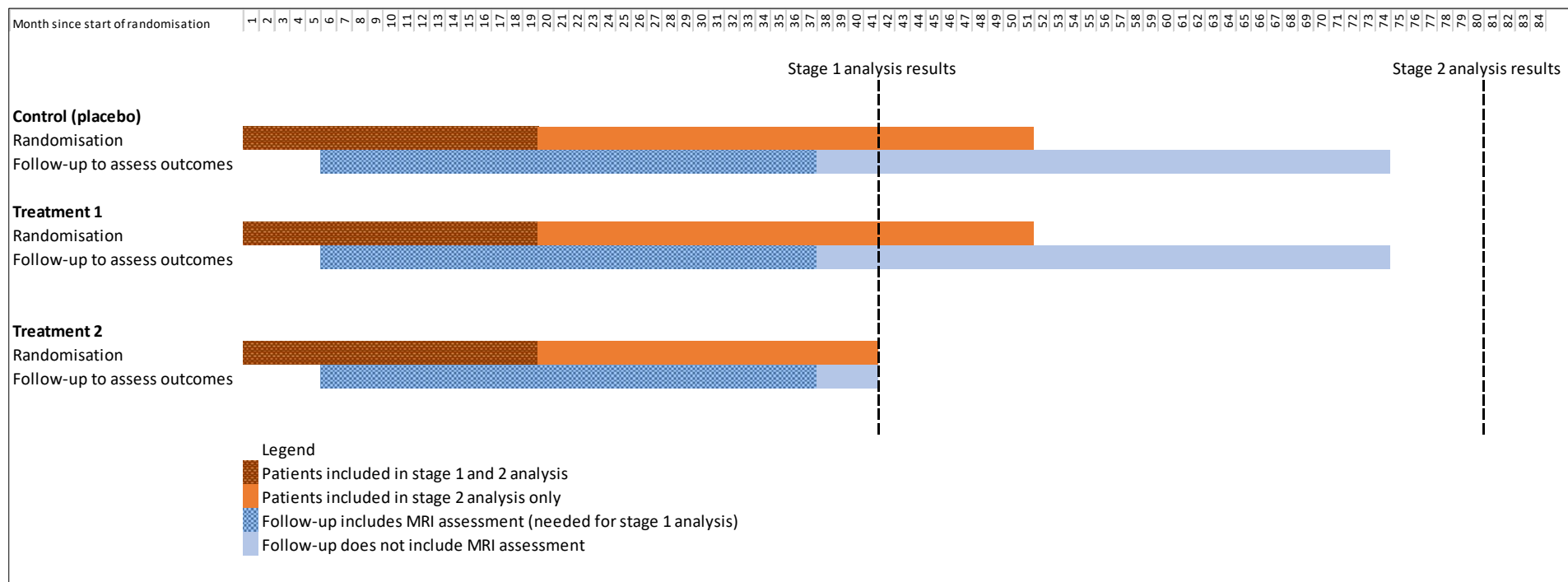


Figure 2: Recruitment and Analyses Time points



TRIAL ASSESSMENT SCHEDULE

Table 1: Trial Assessment Schedule

Week number (visit type)	-4 to 0 (Screening) [†]	0 (Randomisation)	4 (Dose escalation)	12	26	38	52	64	78	90	104	116	On treatment - every 26 weeks until 260 weeks or until trial arm closes (whichever occurs first)	Completed treatment - every 26 weeks until 260 weeks or until trial arm closes (whichever occurs first)	Unscheduled visit
Window		- 4 weeks	+/- 1wks	+/- 2wks	+/- 2wks	+/- 2wks	+/- 2wks	+/- 2wks	+/- 2wks	+/- 2wks	+/- 2wks	+/- 2wks	+/- 2wks	+/- 4wks	
Location of Visit*	In person	In person	In person	Telephone or in person	In person	Tele- phone	In person	Tele- phone	In person	Tele- phone	In person	Tele- phone	In person and 12- weekly Telephone [J]	In person	As required
Informed consent	x														
Height	x														
Weight [L]	x		x	x	x		x		x		x		x		x[C]
Inclusion/exclusion criteria review	x	x													
Demography and EDI	x														
Medical and MS History	x														x[C]
Physical Examination	x		x		x		x		x		x		x	x	x[C]
Vital signs	x		x		x		x		x		x		x	x	x[C]
Drug Compliance assessment			x	x	x		x		x		x		x		x [C]
Adverse events		x	x	x	x		x		x		x		x		x [C]
Concomitant Medication	x	x	x	x	x		x		x		x		x	x	x [C]
Randomisation		x													
Prescription issued [E]		x [E]	x	x	x		x		x		x		x		x [C]
Dose escalation			x												x [C]
MRI Scans		x [F]			x				x		x [B]				x [C]
Screening and safety tests															
Haematology (FBC), & Biochemistry (Bilirubin, LFTs (ALP plus AST or ALT), potassium & sodium ‡	x		x	x	x		x		x		x		x		x [C]
Renal function – eGFR ‡	x		x	x	x		x		x		x		x		x [C]
Thyroid Profile [G] ‡	x		x	x	x		x		x		x		x		x [C]
Vitamin B12 [H] ‡	x		x	x	x		x		x		x		x		x [C]
Urine Dipstick [G; J]	x		x	x	x	x	x	x	x	x	x	x	x (12-weekly)		x [C]
ACR [K; G] ‡	x		x	x	x	x	x	x	x	x	x	x	x (12-weekly)		

Week number (visit type)	-4 to 0 (Screening)†	0 (Rando- misation)	4 (Dose escalation)	12	26	38	52	64	78	90	104	116	On treatment - every 26 weeks until 260 weeks or until trial arm closes (whichever occurs first)	Completed treatment - every 26 weeks until 260 weeks or until trial arm closes (whichever occurs first)	Unscheduled visit
Window		- 4 weeks	+/- 1wks	+/- 2wks	+/- 2wks	+/- 2wks	+/- 2wks	+/- 2wks	+/- 2wks	+/- 2wks	+/- 2wks	+/- 2wks	+/- 2wks	+/- 4wks	
Location of Visit*	In person	In person	In person	Telephone or in person	In person	Tele- phon e	In person	Tele- phone	In person	Tele- phone	In person	Tele- phone	In person and Telephone 12- weekly [J]	In person	As required
Screening and safety tests (continued)															
Urine pregnancy test	x [A]	x [A]	x [D]	x [D]	x [D]		x [D]		x [D]		x [D]				x [C, D]
Alcohol assessment	x														x [C]
Lipid profile (Total Cholesterol, LDL and HDL) ‡	x														
Non-fasting HBA1C [H] ‡	x		x	x	x		x		x		x		x		x [C]
Clinical reported outcomes															
EDSS - [Treating clinician]	x														
EDSS - [Assessing clinician]		x			x		x		x		x		x	x	x [C]
Relapse assessment (count / grade)	x	x	x	x	x		x		x		x		x	x	x [C]
9HTP, T25FW, SDMT		x			x		x		x		x		x	x	x [C]
SLCVA		x			x		x		x		x		x	x	x [C]
Patient reported outcomes															
MSIS-29v2		x			x		x		x		x		x	x	x [C]
MSWSv2		x			x		x		x		x		x	x	x [C]
MFIS-21		x			x		x		x		x		x	x	x [C]
CFQ		x			x		x		x		x		x	x	x [C]
Pain Assessment (Neuropathic Pain Scale & overall pain intensity)		x			x		x		x		x		x	x	x [C]
EQ-5D-5L		x			x		x		x		x		x	x	x [C]
CSRI		x			x		x		x		x		x	x	x [C]
Biorepository sample collection §															
2 red-top tubes (coated, anti- coagulant-free vacutainer ®)		x			x		x		x		x		x	x	
1 purple top tube (EDTA vacutainer ®) for DNA extraction		x													
1 purple top tube (EDTA vacutainer ®) for plasma collection		x			x		x		x		x		x	x	

Week number (visit type)	-4 to 0 (Screening) [†]	0 (Randomisation)	4 (Dose escalation)	12	26	38	52	64	78	90	104	116	On treatment - every 26 weeks until 260 weeks or until trial arm closes (whichever occurs first)	Completed treatment - every 26 weeks until 260 weeks or until trial arm closes (whichever occurs first)	Unscheduled visit
Window		- 4 weeks	+/- 1wks	+/- 2wks	+/- 2wks	+/- 2wks	+/- 2wks	+/- 2wks	+/- 2wks	+/- 2wks	+/- 2wks	+/- 2wks	+/- 2wks	+/- 4wks	
Location of Visit*	In person	In person	In person	Telephone or in person	In person	Telephone	In person	Telephone	In person	Telephone	In person	Telephone	In person and Telephone 12-weekly [J]	In person	As required
Staff Present															
Treating clinician	x	x	x	x	x		x		x		x		x	x	x
Assessing clinician		x			x		x		x		x		x	x	x
Study Nurse	x	x	x	x	x		x		x		x		x	x	x

Notes/Annotations

A = Must occur prior to MRI for WOCBP, **AS WELL AS** at or within 1 week prior to the randomisation visit. Repeat testing will be dependent on timing of assessments (refer to [Section 3.6](#)).

B = Must occur within 2 weeks prior to the week 104 visit (final MRI visit). All participants must have week 104 visit MRI regardless of treatment status as per schedule. Those on trial treatment must continue to take trial treatment.

C = At PI discretion (on unscheduled visit) and should be strongly considered but not mandatory based on clinical opinion

D = Pregnancy checks for WOCBP to be performed prior to all MRIs following local MRI practices and guidelines regardless of treatment status. At follow up visits when no MRI performed, clinical discretion should be exercised if a pregnancy test is required for WOCBP prior to dispensing.

E = Prescription after randomisation

F = QC approved MRI must occur between screening and randomisation visits (within 4 weeks prior to randomisation). This can be before or on day of the randomisation visit but not before consent. Gadolinium is only required at this timepoint.

G = Not required if ineligible for R/S-Alpha Lipoic Acid (R/S-ALA) or if stopped OCTOPUS Trial treatment

H = Not required if ineligible for metformin

J = Participant to perform urine dipstick every 12 weeks (at home or in clinic if attending) then submit the result to site who will action as required. Site staff to report all results.

K = ACR may be required dependent on the result of the urine dipstick. Refer to [Section 6.3.2](#) for further detail.

L = Weight should be taken at follow-up visits if clinically indicated

* Remote or telephone follow-ups: Screening and randomisation visit must be an in-person visit. Week 12 visit can be a telephone visit if bloods can be collected via GP or other phlebotomy clinic and provided to the site team. Visit week 38, week 64, week 90 and week 116 and all 12-weekly visits for urinary dipstick should be telephone visits and if clinically required, should also be in-person visits. All other visits can only be telephone/remote visits in extenuating circumstances.

† Screening and randomisation procedures can be done at the same visit **if** a) the date when the participant is randomised is no more than 1 week later than the date of all screening/randomisation procedures and b) both site staff and participants are aware that the participant may still be ineligible (in which case none of the data or biosamples performed as part of randomisation procedures will be used in the trial. Biosamples should be destroyed in this scenario).

‡ Samples processed at local site laboratories

§ If participant consents to biorepository collection

|| Ideally 1 purple top tube for DNA extraction should be collected at randomisation and sent to WNRTB. If it is not possible to collect at randomisation, this sample can be collected at any time-point during the trial.

LAY SUMMARY

BACKGROUND

Multiple Sclerosis (MS) affects more than 130,000 people in the UK, over 2.5 million people worldwide and is one of the most common causes of disability in young adults. The body's immune system, which normally fights infection, starts to attack the myelin, which covers the nerve cells in both the brain and spinal cord. The job of myelin around the nerves is similar to the insulating layer around an electrical cable. It allows the current to reach its destination without losing power as it travels along the cable. In the same way, myelin protects the nerves and allows the messages to travel safely from the brain to reach the muscles and organs of the body.

MS often begins with a relapsing-remitting phase (RRMS). People with RRMS have 'relapses', which are flare-ups of the symptoms caused by attacks on the myelin. They then partially or completely recover (remissions). However, over time, many people with RRMS start to find that they no longer recover after a flare-up and actually get steadily worse, resulting in increased disability. This is known as Secondary Progressive MS (SPMS). A smaller number of people will find that they experience gradual decline from the beginning, known as Primary Progressive MS (PPMS). SPMS and PPMS together are known as progressive MS.

Most treatments for RRMS aim to control the body's immune system and limit the attacks on the myelin surrounding the nerve cells in the brain and spinal cord. In progressive MS, on the other hand, researchers think that these immune attacks are less frequent, so targeting them is less effective. In progressive MS, treatments need to particularly focus on protecting the nerve cells from damage.

Recently, the first treatments have become available through the NHS for people with progressive MS. These treatments include Ocrelizumab (Ocrevus) for people with PPMS and Siponimod (Mayzent) for people with SPMS. However, the treatments are only available to those who have had a relapse or have shown activity on an MRI scan. Currently, people with increasing disability in the absence of recent relapse or MRI activity are ineligible for disease modifying treatment.

Compared to people with RRMS, people with progressive PMS generally have higher levels of disability. There are few clinical trials testing therapies to develop effective neuroprotective treatments in progressive MS even though it is a major unmet need.

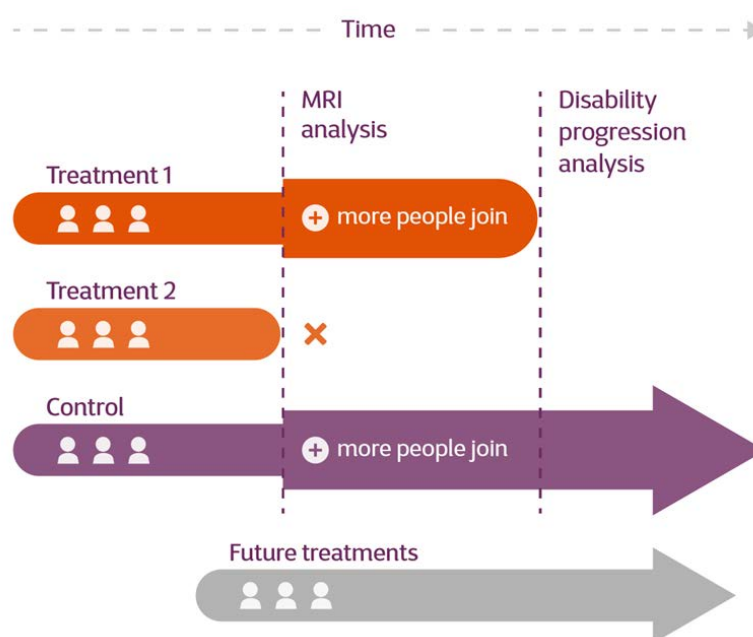
A NEW TYPE OF CLINICAL TRIAL IN MS

Traditionally, potential new treatments are developed and tested through clinical trials. In addition to their current care and treatment (known as standard of care or SOC), participants are randomly allocated to have either the test treatment or a control. The control is sometimes another treatment or may also be a "dummy" control (such as a sugar pill) often referred to as a placebo treatment. Everyone has the same data collected and measured (such as level of disability) at the same study visits, often for several years. At the end of the trial, these measurements allow researchers to compare people from both groups and see if the new treatment has been beneficial, compared to the control treatment. Traditionally potential new treatments are tested in different phases to ensure they are safe and have an indication that they will be useful. Usually, a phase is completed and the

results analysed before moving the potential treatment to the next phase. Each phase takes time, effort and cost, meaning that the process to show if a new treatment is effective takes many years and is very expensive.

Because of these challenges, new ways are being developed to make the process of testing and finding new treatments faster and cheaper. One method is to use a multi-arm multi-stage (MAMS) design (see [Figure 3](#)) and this has already been shown to be useful in testing new approaches for people with cancer. There are many advantages to this method, one being that it allows several treatments to be tested at the same time against a common control (i.e. “multi-arm”). It also allows data to be analysed while the trial is ongoing (Analysis Stage 1), rather than only at the end.

Figure 3: Multi-arm multi-stage (MAMS) design



The trial is designed so that early results should be able to predict longer-term outcomes, such as whether the treatment has a reasonable chance of slowing the rate of worsening of disability. This means that decisions can be made on early results about stopping treatments that do not show promise. Additionally, when new information about different treatments becomes available, these treatments can be added into the trial. Another advantage of this method of trial is that treatments which appear to be effective from the early data can continue onto the next trial phase without the team having to stop and set up a new trial (i.e. “multi-stage”).

A team of experts have looked at a number of treatments already used in other conditions and produced a shortlist of those most likely to help in slowing down disability in people with progressive MS. As these treatments are already in use for other conditions they are referred to as “repurposed” treatments. This means there is already an understanding of their safety and possible side effects and it will take less time to test them in for progressive MS.

HOW HAVE PEOPLE WITH MS BEEN INVOLVED IN SETTING UP THIS TRIAL?

People affected by MS have been actively involved since the earliest study concept meeting in 2018, taking part in study sub groups and UK-wide focus groups. These groups considered trial design, the choice of treatments, ways of recruiting and communicating with trial participants, as well as the practicalities of study visits and assessments. This has led to direct changes to the trial design and analysis outcomes. For example input from people with progressive MS led to the selection of a composite disability measurement score. This is to take into account of people with progressive MS who use wheelchairs and need to preserve arm and hand function for as long as possible. Their input also resulted in the option to allow participants who initially receive an ineffective treatment, to be re-randomised to the trial following an appropriate wash-out period.

A person affected by MS was a co-applicant on the grant application to the MS Society who are funding the majority of the trial. There are also patient representatives on the four committees who oversee the trial. A patient and public involvement group has been assembled by the MS Society to act as a sounding board for decisions and ideas, which arise throughout the study preparation, recruitment and reporting phases.

WHAT IS THE AIM OF THE OCTOPUS TRIAL?

The main aim of OCTOPUS is to find treatments that can slow down, and ultimately stop, the progression of disability in people with progressive MS. This will be done initially by testing “repurposed” treatments over a number of years using the multi-arm multi-stage (MAMS) trial design. By using this approach with new research treatments added when appropriate and by using “repurposed” treatments, it aims to be a more efficient trial, for the reasons outlined above.

HOW WILL THIS TRIAL BE CARRIED OUT?

The OCTOPUS trial will begin in a number of hospital and university trial sites across the UK, with several “repurposed” treatment groups and a control (often referred to as a placebo) group. These are known as “arms”. People who are eligible to join OCTOPUS treatments will be randomly assigned (by a computer programme) to one of the arms. To ensure a fair and unbiased trial neither the research team nor the participant will know which treatment they are taking.

All groups will receive the current standard of care for people with progressive MS (i.e. the same care they would receive if they were not part of OCTOPUS) and the treatment they have been randomly allocated to.

Disability will be measured in different ways, including testing strength, coordination and sensation, walking assessments and tests of upper limb function. Results will be measured at the trial visits. Optional blood samples may be taken if the participant gives permission. The visits will at first be monthly and then every six months (i.e. 26 weeks).

An early sign of the potential effectiveness of a treatment is a change in brain size. To measure changes in brain size, participants will undergo brain MRIs (four scans). Based on these scans, a decision will be made on whether entry of further participants to a treatment should be stopped or continued. If a treatment is not showing sufficient promise of benefit, the arm of the trial testing that treatment will be stopped. If a treatment looks promising, it will continue into the next phase for further testing.

Participants who are on a treatment arm that is stopped will have a final visit and will be offered the opportunity to be re-randomised into a different arm, after a wash-out period.

Other assessments, done every six months (i.e. 26 weeks) will include tests of memory, vision; and questionnaires about symptoms of MS including fatigue, mobility and quality of life. Blood tests will also be performed approximately every six months (i.e. 26 weeks) to check the safety of the treatments. New clinical trial processes may allow some of these assessments to be done at home, such as the questionnaires.

There will be an independent committee (known as the Independent Data Monitoring Committee) made up of clinicians, statisticians and other experts who are not part of OCTOPUS. This committee will review the trial data regularly throughout the trial. If a treatment does not appear to be sufficiently effective in the analysis, then the committee will recommend participants on that treatment arm to be contacted to safely stop their treatment. These participants, if they meet the current eligibility criteria, will have the option of re-entering the trial and being randomly assigned to a different arm. However, they will need to wait for a set amount of time to ensure the effects of the previous treatment have worn off. They will then be re-allocated to one of the treatment arms that are still being tested or the control group.

OCTOPUS will be publicised to people with PMS in multiple ways to maximise awareness. These include, but are not limited to: the UK MS Society and other charitable organisations, neurologists and other healthcare professionals at clinics in participating sites, talks at participant groups, the UK MS Register and a dedicated trial website. Both printed and online information will be available.

HOW WILL WE SHARE OUR RESULTS?

Participants will have regular updates on the progress of OCTOPUS, through newsletters, MRC CTU website and the MS Register. These updates include reports and videos about recruitment rates, results and details of any treatments that have been stopped or added to OCTOPUS.

As well as any results from OCTOPUS being published in academic journals, they will also be publicised through a number of channels, including major conferences, via the MS Society and other MS groups' websites, newsletters and social media. The study website will also include updates accessible by the general public.

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ABBREVIATIONS

ABBREVIATION	EXPANSION
9HPT	9-Hole Peg Test
ACE	Angiotensin-converting enzyme
ACR	Albumin/Creatinine ratio
AE	Adverse event
ALA	Alpha-lipoic acid
ALP	Alkaline phosphatase
ALT	Alanine aminotransferase
AMP	Adenosine monophosphate
AMPK	AMP-activated protein kinase
ANTs	Advanced normalisation tool
AR	Adverse reaction
ASM	Active Surface Model
AST	Aspartate aminotransferase
BBSI	Brain boundary shift integral
bd	Bis in die (twice a day) i.e for medication dosing
BET	Brain extraction Tool
CDP	Confirmed Disability Progression
CF	Consent Form
CFQ	Chalder Fatigue Questionnaire
CGM	Cortical Grey matter
CI	Chief Investigator
CI	Confidence interval
CIS	Clinically Isolated Syndrome
CPM	Clinical Project Manager

ABBREVIATION	EXPANSION
COX	Cyclooxygenase
CRF	Case Report Form
CROMs	Clinician Reported Outcome Measures
CSF	Cerebrospinal fluid
CSRI	Client Services Receipt Inventory
CTA	Clinical Trials Authorisation
CTCAE	<i>See NCI CTCAE</i>
CTU	<i>See MRC CTU at UCL</i>
DCF	Data Clarification Form
DGM	Deep Grey Matter
DM	Data Manager
DPA	(UK) Data Protection Act
DSMS	Drug Supply Management System
DSUR	Developmental Safety Update Report
EAE	Experimental autoimmune encephalomyelitis
eCRF	Electronic Case Report Form
EDI	Equality, diversity and inclusion
EDSS	Expanded Disability Status Scale
EDTA	Ethylenediaminetetraacetic acid
eGFR	Estimated Glomerular Filtration Rate
EQ-5D	EuroQol-5D
EMA	European Medicines Agency
ETDRS	Early Treatment Diabetic Retinopathy Study
EU	European Union
EudraCT	European Union Drug Regulatory Agency Clinical Trial

ABBREVIATION	EXPANSION
FBC	Full Blood Count
FDA	(US) Food and Drug Administration
FSH	Follicle stimulating hormone
FSL	FMRIB Software Library
FSS	Functional system scores
G3PDH	Glyceraldehyde 3-phosphate dehydrogenase
GCP	Good Clinical Practice
GI	Gastrointestinal
GIF	Geodesic Information Flow
GI-MOSES	Gastrointestinal - Monitoring of Side Effects Scale
GM	Grey Matter
GP	General Practitioner
HBA1c	Haemoglobin A1c
HCG	Human chorionic gonadotropin
HE	Health economics
HR	Hazard Ratio
HRA	Health Research Authority
HRQoL	Health-related Quality of Life
IB	Investigator Brochure
ICER	Incremental cost-effectiveness ratio
ICH	International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use
IDMC	Independent Data Monitoring Committee
IMP	Investigational medicinal product
ION	Institute of Neurology
IR	Immediate Release

ABBREVIATION	EXPANSION
IRB	Institutional Review Board
ISRCTN	International Standard Randomised Controlled Trial Number
ITT	Intention-to-treat
IUD	Intra-uterine device
IUS	Intra-uterine system
LAM	Lactational amenorrhea method
LFTs	Liver Function Tests
MAMs	Multi-arm Multi-stage
MedDRA	Medical Dictionary for Regulatory Activities
MFIS-21	Modified Fatigue Impact Scale - 21
Mg	Milligram
MHRA	Medicines and Healthcare products Regulatory Agency
MRC	Medical Research Council
MRC CTU at UCL	Medical Research Council Clinical Trials Unit at University College London (also generally abbreviated to “CTU”)
MREC	Multi-centre Research Ethics Committee
MRI	Magnetic resonance imaging
MS	Multiple Sclerosis
MSFC	Multiple Sclerosis Functional Composite
MSIS-29v2	MS Impact Scale-29 version 2
MSU	Midstream specimen of urine
MSWSv2	MS Walking Scale-12 version 2
NBV	Normalised brain volume
NCI CTCAE	National Cancer Institute Common Terminology Criteria for Adverse Events
NE	Notable Event
NHS	National Health Service

ABBREVIATION	EXPANSION
NICE	National Institute for Health and Care Excellence
NIHR	National Institute for Health Research
NIHR CSP	National Institute for Health Research Co-ordinated System for gaining NHS Permission
NSAIDs	Non-steroidal anti-inflammatory drugs
OCT	Organic cation transporters
OD	Once daily
OPC	Oligodendrocyte precursor cells
OR	Odds ratio
PBMCs	Peripheral blood mononuclear cells
PBVC	Percentage brain volume change
PI	Principal Investigator
PIS	Patient Information Sheet
PMS	Progressive Multiple sclerosis
PPI	Patient and Public Involvement
PPMS	Primary Progressive Multiple Sclerosis
PRLs	Paramagnetic Rim Lesions
PROMs	Patient Reported Outcome Measures
PwPMS	People with Progressive MS
PwRRMS	People with Relapsing-remitting phase Multiple Sclerosis
QA	Quality assurance
QALY	Quality adjusted life years
QC	Quality control
QMAG	Quality Management Advisory Group
QMMP	Quality Management and Monitoring Plan
QoL	Quality of life

ABBREVIATION	EXPANSION
QP	Qualified Person
QSMSC	Queen Square MS Centre
R-ALA	R-enantiomer Alpha-lipoic acid
R/S-ALA	R-enantiomer/S-enantiomer Alpha Lipoic Acid
R&D	Research and Development
REC	Research Ethics Committee
RGC	Research Governance Committee
RMST	Restricted Mean Survival Time
RNFL	Peripapillary retinal nerve fibre layer
RRMS	Relapsing-remitting phase Multiple Sclerosis
RSI	Reference safety information
S1P	Sphingosine 1-phosphate
SAE	Serious adverse event
S-ALA	S-enantiomer Alpha-lipoic acid
SAP	Statistical Analysis Plan
SAR	Serious adverse reaction
SDMT	Symbol Digit Modalities Test
SIENA	Structural Image Evaluation using Normalisation of Atrophy
SIENAX	Cross-sectional version of SIENA
SLCVA	Sloan Low Contrast Visual Acuity
SMP	Safety Management Plan
SOC	Standard of Care
SOP	Standard operating procedure
SPC	Summary of Product Characteristics
SPM	Statistical parametric mapping

ABBREVIATION	EXPANSION
SPMS	Secondary Progressive Multiple Sclerosis
SSA	Site-specific approval
SSG	Scientific Strategy Group
SSI	Site-specific information
SUSAR	Suspected unexpected serious adverse reaction
SWI	Susceptibility weighted images
T1-GdE	T1 gadolinium enhancing
T25FW	Timed 25 Foot Walk
T2DM	Type II diabetes mellitus
TAC	Treatment Advisory Committee
TLC	Three letter code
TMF	Trial Master File
TMG	Trial Management Group
TMT	Trial Management Team
TSC	Trial Steering Committee
UAR	Unexpected adverse reaction
UCL	University College London
UKCRN	UK Clinical Research Network (now the NIHR CRN)
U&Es	Urea and Electrolytes
ULN	Upper limit of normal
UTI	Urinary tract infection
VAS	Visual Analogue Scale
VBM	Voxel-based morphometry
WM	White matter
WNRTB	Welsh Neuroscience Research Tissue Bank

ABBREVIATION	EXPANSION
WOCBP	Women of Child-Bearing Potential
9HTPT	9 Holed Peg Test

1 BACKGROUND

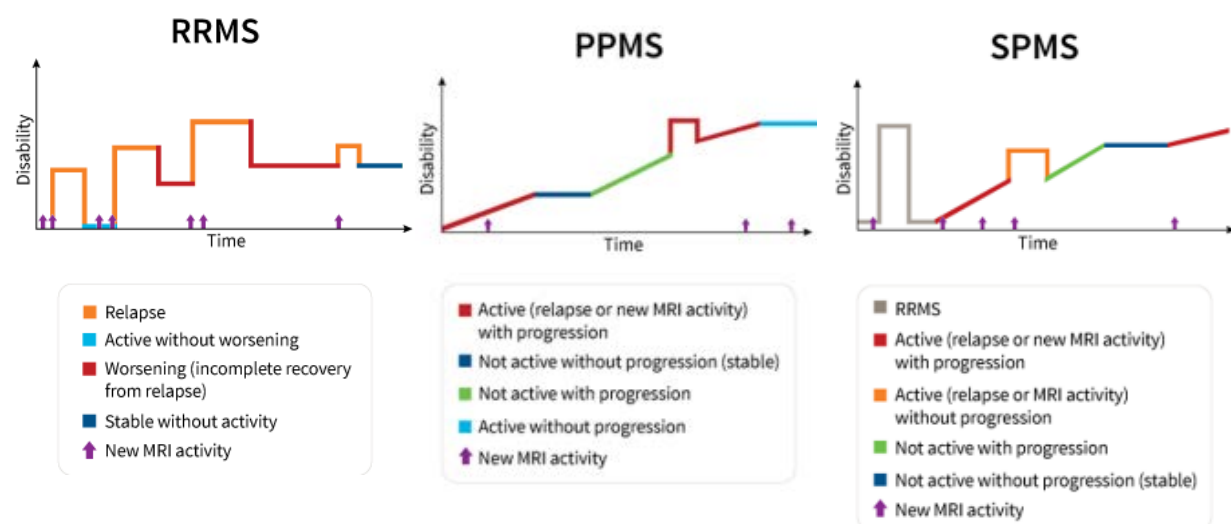
1.1 PROGRESSIVE MULTIPLE SCLEROSIS

MS is the most common acquired, disabling neurological disease affecting young adults in temperate latitudes. It is a progressive disorder of the central nervous system that affects over 130,000 people in the UK and 2.5 million globally[1].

MS has a heterogeneous clinical course. In 80-85% of people developing MS, the initial course is characterised by the occurrence, recurrence, or worsening of neurologic symptoms (relapses) followed by a complete or partial recovery (i.e. RRMS) [2]. A clinically isolated syndrome (CIS) is often the first presentation of RRMS and it is characterised by a neurological clinical event suggestive of MS not fulfilling the current diagnostic criteria [3, 4]. In 10-15% of people with MS, the initial course is characterised by a steady progression of neurologic symptoms and a slow increase in disability over time (i.e. PPMS). Almost 60% of the patients with RRMS convert to a secondary progressive course (i.e. SPMS) after 15-20 years, and more than 80% after 25 years, from initial disease onset [3, 5, 6]. SPMS is characterised by a gradual increase in disability over time, with or without superimposed relapses. SPMS and PPMS are collectively referred to as progressive MS (PMS).

Both RRMS and PMS (SPMS and PPMS) can occur with or without disease activity (as evidenced by clinical relapses or new, enlarging, or enhancing lesions on MRI) and with or without clinical progression (worsening of neurologic examination deficits, independent of relapses). Therefore, in addition to the basic MS phenotypes, the MS Phenotypes Group proposed including these descriptors as shown in [Figure 4](#) in the 2013 revision by the International Advisory Committee on Clinical Trials of MS as it can impact prognosis, therapeutic decisions, and clinical trial designs and outcomes [3].

Figure 4: Summary of the main MS phenotypes



The last two decades have seen a revolution in the treatment of RRMS, with a variety of increasingly powerful drugs becoming available to reduce relapse rate by up to 80%. Unlike RRMS, where there

are more than a dozen effective disease-modifying therapies (DMTs), there are few proven treatments for PMS. However, PMS remains, and will remain, a significant health problem, with currently limited treatment opportunities, dominantly on the (minority) inflammatory substrate rather than the (majority) neurodegenerative biological processes. PMS also has significant financial costs for healthcare systems, patients and their caregivers. In the UK, MS has been estimated to cost the NHS and society £3.3 billion to £4.2 billion per year[7]. More recent studies in 2012 and 2015 reported total mean annual cost per patient ranging from £11,400 - 11,841 for patients with mild disease, £22,700-25,894 for those with moderate disease to £36,500-59,018 for those with severe disease. A recent systematic review has also confirmed that with mean costs of RMS around €31,000 (£26,000) compared to essentially double in SPMS [8]. Overall, healthcare costs dominate in mild disease; production losses, informal care, investments and community services dominate in more severe disease [9]. These data demonstrate a clear increase in cost at higher levels of disability, as experienced by people with PMS (PwPMS). The impact of successfully repurposing/rescuing or discovering a new drug to target PMS both for the patient and for the health service cannot be understated.

1.2 NEURODEGENERATION IN PMS

Neurodegeneration is the pathological substrate of disability in SPMS and PPMS[10]. Overwhelming evidence from human pathological, radiological, clinical and animal based experimental studies have demonstrated that the dominant pathology and key determinant of disability in PMS is neurodegeneration, with similar pathogenic processes reported to occur in both SPMS and PPMS [11, 12]. Along with clinical trial based insights, MRI studies showing progressive and substantial brain volume loss in PMS along with reduction in neuroaxonal metabolites and have been influential in highlighting the significance of neurodegeneration. This has led directly to MRI based measures of brain atrophy becoming a benchmark outcome criterion for MS neuroprotection studies [13].

However, neurodegeneration being the primary driver of disability progression in PMS does not exclude an important role for continued inflammation in ongoing neurodegeneration, albeit a different form in type and extent to that found in RRMS. Indeed, the shift is from a predominantly focal and adaptive immune-mediated inflammatory demyelination, to diffuse innate immune-mediated inflammation related to widespread neuroaxonal degeneration, evident in both grey and white matter (including normal appearing white matter) in SPMS.

The cause of neurodegeneration in PMS is complex and accumulating evidence from multiple experimental systems including human studies implicate a handful of key mechanistic processes. These include oligodendrocyte loss and demyelination, mitochondrial injury and 'energy failure', altered axonal ion homeostasis, oxidative stress, iron accumulation, excitotoxicity and neuroinflammation [14].

1.3 CLINICAL TRIALS IN PMS

Although immunomodulatory anti-inflammatory DMTs are increasingly effective in reducing relapse frequency in RRMS, they have been unsuccessful in slowing disease progression in SPMS and PPMS. This was the overwhelming conclusion from a 2015 analysis of 18 phase 3 trials (n=8500), of which

70% of the population had SPMS, performed in the last quarter of a century, which concluded that there were no disease modifying treatment for PMS [15]. Modalities such as classical immunosuppression (e.g. cyclophosphamide and azathioprine), beta-interferon, intravenous immunoglobulin globulin, oral cannabinoid have all largely failed. A number of other important reasons for trial failure, apart from low biological knowledge have been repeatedly elaborated: inadequate phase 2 trials, underpowered phase 3 trials of too short a duration and the difficulties with a multi-modal outcome measure in a complex and dynamic disease [15, 16].

Since the review in 2015, four large phase 3 trials in SPMS and PPMS have reported and these are summarised in **Table 2** [16]. In the EXPAND trial, the sphingosine 1 phosphate receptor modulator siponimod significantly reduced 3-month confirmed disability progression on EDSS in SPMS [17]. Whereas in ORATORIO, the anti-CD20 monoclonal antibody ocrelizumab significantly reduced 3-month confirmed disability progression in EDSS in PPMS [18]. Natalizumab and fingolimod did not show evidence of improvement in their primary outcome endpoints in the phase 3 trials ASCEND [19] and INFORMS [20]. In the UK, both ocrelizumab and siponimod are now in clinical practice for PPMS and SPMS respectively in patients with clinical relapses or MR evidence of new focal inflammatory activity superimposed on disability progression. However, most PwPMS do not come into this category. Hence is a clear unmet need.

Table 2: Summary of four phase 3 trials in PMS since 2016 [16]

Trial	Drug	Main Mechanism	MS type	Number of participants	Primary outcome for progression	Mean age, years (SD, active; placebo)	Mean duration of progression years (SD, active; placebo)	Patients with baseline T1-GdE lesions, n/N (%)	Placebo versus active CDP, n/N (%)	Primary outcome HR or OR (95% CI) and result
INFORMS	Fingolimod	S1P receptor modulation	PPMS	823	Composite*: time to 3-month CDP	49 (8.6: 8.3)	6 (2.5: 2.4)	107/820 (13%)	338/487 (69%) vs 232/336 (69%)	HR 0.95 (0.80 – 1.12): negative
ORATORIO	Ocrelizumab	Anti-CD20 expressing B cells	PPMS	732	EDSS: time to 3-month CDP	45 (7.9: 8.3)	7 (4.0: 3.6)	193/727 (27%)	96/244 (39%) vs 160/487 (33%)	HR 0.76 (0.59 – 0.98): positive
EXPAND	Siponimod	S1P receptor 1 and 5 modulation	SPMS	1651	EDSS: time to 3-month CDP	48 (7.8: 7.9)	4 (3.6: 3.3)	351/1599 (22%)	173/545 (32%) vs 288/1096 (26%)	HR 0.79 (0.65 – 0.95): positive
ASCEND	Natalizumab	Anti-integrin-α4	SPMS	887	Composite*: proportion with 6-month CDP	47 (7.4: 7.8)	5 (3.0: 3.7)	210/884 (24%)	214/448 (48%) vs 195/439 (44%)	OR 0.86 (0.66 – 1.13): negative

*Composite: one or more progression in EDSS, 25-Foot Timed Walk Test; 9-Hole Peg Test

1.4 RATIONALE FOR ADAPTIVE TRIAL DESIGN

Despite the identified clear unmet clinical need for effective neuroprotection, which has been prioritised by patient and professional groups, comparatively few clinical trials aim to modify the PMS disease course. Novel approaches to evaluating multiple treatments concurrently, which incorporate adaptive elements such that they evolve over time to address the most current, relevant questions (sometimes termed ‘platform’ trial designs) have been highly successfully in speeding up the evaluation of therapies in other disease settings, such as the STAMPEDE trial in prostate cancer [21]

and the RECOVERY trial for the treatments of COVID-19 [22]. These have led to practice-changing advances.

Multi-arm, multi-stage adaptive platform designs offer flexible features, which can provide efficiencies at various levels, especially in a setting where there are numerous candidate drugs, which require evaluation. These include:

- simultaneous evaluation of multiple treatments against a common control arm (with efficiencies in terms of both time and the numbers of control participants)
- the ability to add new treatments as they become relevant, reducing the set-up time for new interventions, and dropping treatments that are not showing sufficient promise allowing redirection of resources

In Analysis Stage 1, PwPMS are randomised as indicated to IMP/control arms and then each followed for 104 weeks with the primary outcome being MRI based brain atrophy rate assessments. Once a participant has had their week 104 visit, they move into Analysis Stage 2, until the analysis of stage 1 is reported. Then a decision will be made whether to continue a trial arm into further Analysis Stage 2 follow-up or to terminate that arm. Once all 375 participants have been recruited into Analysis Stage 1, further participants will be recruited into Analysis Stage 2, until at analysis a trial arm continues or is terminated see [Figure 2](#).

The scientific integrity can be maintained as the overall hypothesis will be consistent through adaptations and the objectives unchanged, with arms being added and dropped on the basis of pre-specified criteria. Utilising an adaptive trial design has significant potential for delivering trials as a rolling programme. On an operational level, this maximises the use of infrastructure established at the start of the trial, thus reducing cost and set-up times, which would be associated with multiple individual trials and would further delay time to results. It also avoids issues of managing competing trials. As such, such a design will provide a structure through which re-purposed and novel neuroprotective drugs can be evaluated in a time- and cost-efficient manner in PwPMS. Although the initial focus is on re-purposed drugs, there is no reason at all why the platform cannot be expanded to include 'new' treatments, for example, in collaboration with companies.

1.5 OBJECTIVES OF THE TRIAL

1.5.1 PRIMARY OBJECTIVE

The primary aim of OCTOPUS is to find treatments that can slow down, and ultimately stop, the progression of disability in people with progressive MS compared to standard of care. This will be done initially by testing "repurposed" treatments over a number of years using the multi-arm multi-stage (MAMS) trial design. By using this approach with new research treatments added when appropriate and by using "repurposed" treatments, it aims to be a more efficient trial.

1.5.2 SECONDARY OBJECTIVES OF THE TRIAL

Secondary objectives of OCTOPUS are to determine:

- the safety and tolerability of the researched treatments for people with progressive MS when taken over a number of years

- the effects of the treatments on quality of life and patient reported outcomes in people with progressive MS
- the cost effectiveness of the treatments for people with progressive MS.

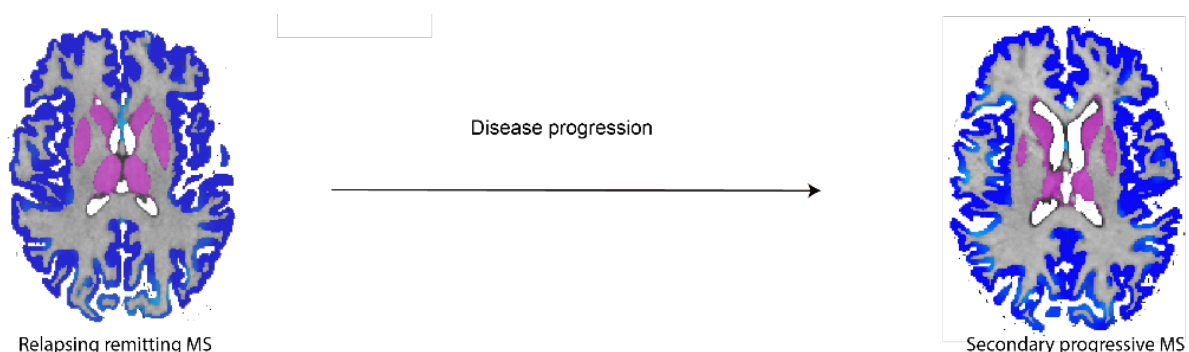
1.6 OUTCOME MEASURES

Structural MRI is used to determine the shape or size of brain structures and lesions. This is usually based on identifying boundaries using contrast variations for delineation. The method for determining this is segmentation, and segmentation varies according to whether differentiation is required at the tissue compartment level, or within tissue type, e.g. Grey Matter (GM) structures. Structural MRI also allows the determination of change of a structure over time. This may be via whole brain metrics, or looking at differences in individual tissue type in a region [23, 24].

Atrophy relates to neuronal loss and is a useful tool in MS as a correlate of the underlying pathological processes and as a reflection of clinical and cognitive disability [25]. Brain atrophy is part of normal ageing, but has been shown to be accelerated in MS [26]. Widening of the sulci, enlargement of the ventricles, and brain parenchymal loss can all be visualised on routine MRI imaging (see [Figure 5](#)). However, quantifying these changes using MRI requires the measurement of brain volumes and brain volume change. This is advantageous in longitudinal study designs, especially when scans are undertaken on the same scanner to prevent bias and to retain precision. MRI brain atrophy rate has been used as a biomarker for disease state when compared with normal ageing controls and as a measure of cognitive decline in other conditions such as Alzheimer's disease and diabetes mellitus [27-29]. As well as whole brain volume, regional volume measurements can be useful for understanding different tissue compartments and functionally significant brain areas, e.g. the thalamus and cerebellum [30, 31].

[Figure 5](#) shows MRI-derived brain atrophy in a patient with initial RRMS (on the left) and after 13 years after which SPMS had developed. Cortical grey matter is in blue and deep grey matter in purple. (courtesy of Dr Arman Eshaghi).

Figure 5 MRI-derived brain atrophy



Over the last twenty years, there has been the development of a number of techniques for measuring brain volumes and their change over time in MS. Manual segmentation is limited by time availability

and the need for trained experts. Currently, semi-automatic and automatic techniques are more widely used [25, 32, 33].

Registration-based techniques measure total brain volume change as a combination of white matter (WM) and Grey Matter (GM) atrophy. Registration techniques segment the brain, and then using image registration allowing accurate change measurements, to evaluate brain volume changes over time points [24]. Structural Image Evaluation using Normalisation of Atrophy (SIENA) [34] and the brain boundary shift integral (BBSI) [35] have been used to measure atrophy or volume change in trials.

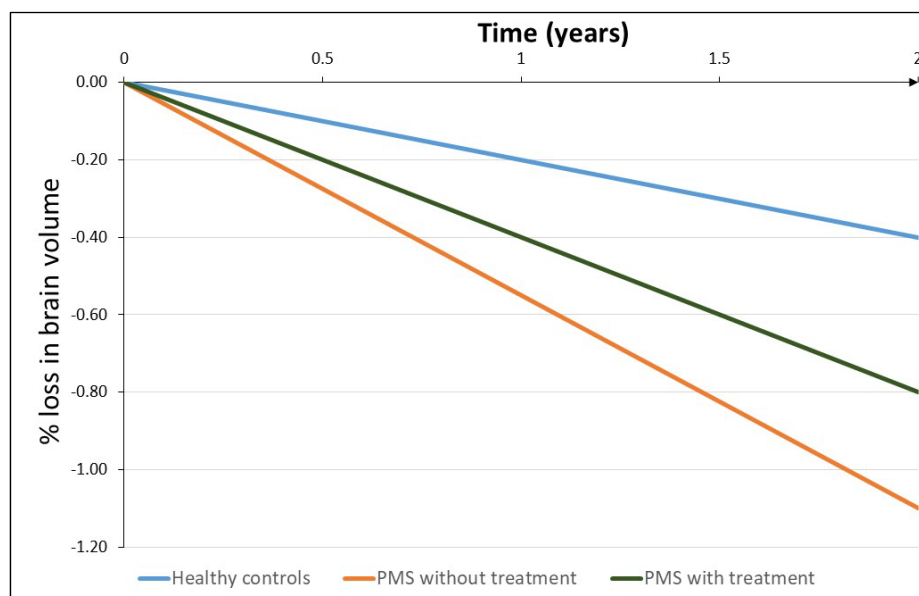
SIENA uses FSL software [36, 37] to estimate percentage brain volume change (PBVC) over two time points. We have customised the pipeline slightly as follows. Paired T1-weighted scans are first corrected for inhomogeneities [N4ITK: improved N3 bias correction, Tustison, N et al, IEEE Transactions on medical imaging 2010]. The T1-hypointense lesions filled to match surrounding tissue using a patch-based approach [A multi-time-point modality-agnostic patch-based method for lesion filling in multiple sclerosis, Prados F et al, Neuroimage 2016]. Then the brain is extracted using Geodesic Information Flow (GIF). GIF uses a graph framework with a template MRI library to segment tissues and parcellate brain areas to derive volume measures [38]. The change in signal intensity at the edge points at the interface between the brain and the cerebrospinal fluid estimates the PBVC over time [34, 39].

Segmentation techniques quantify regional brain areas, e.g. regional GM volumes; total GM volume, cortical grey matter (CGM), and deep grey matter (DGM) [24]. The cross-sectional version of SIENA is SIENAX. Following brain extraction as described above, with GIF, the image is registered to a standard brain template normalised for head size by using the external skull [39]. This process estimates the scaling factor, the normalised brain volume (NBV), and normalised GM (CGM and DGM).

Techniques vary in terms of their clinical utility; sample sizes to measure a treatment effect have been evaluated in SPMS and are dependent on the technique used. The optimised SIENA pipeline will be used in the Analysis Stage 1 of this trial.

1.6.1 WHOLE BRAIN ATROPHY

In untreated PMS participants, the rate of whole brain atrophy change is -0.5 to -1% per year [40-42] versus -0.1 to -0.3% per year for healthy controls [43]. **Figure 6** is a schematic indicating average PBVC differences in controls, those with progressive MS (PMS) with effective treatment, and those with progressive MS without effective treatment. Brain atrophy is even present early in MS, i.e. CIS [44].

Figure 6: Schematic indicating average PBVC differences in controls

Brain atrophy may be affected by changes in non-neuroaxonal tissue components (e.g. fluid in extra-cellular spaces) that may be affected by treatment in an unpredictable manner, leading to what has been labelled “pseudo-atrophy”. To specifically examine for this, a scan will be acquired 26 weeks after the start of treatment and at week 26 – week 104 volume change will also be calculated. It is possible that the week 26 scan will become the baseline measure scan for the participant.

1.6.2 REGIONAL ATROPHY

GM and subcortical atrophy are common in MS and occur in all phenotypes [25, 33, 45, 46]. Longitudinal studies have shown that the rate of GM atrophy is greater than WM atrophy in MS, and the rate of GM loss increases as MS progresses, but WM atrophy rate remained static [45, 47]. As with whole brain atrophy, studies have shown that there is a significant anti-correlation of T2 lesion load and GM volume [48]. GM atrophy was 12 times greater in SPMS than in healthy controls in a 4 year follow-up study [45], with the lowest GM and DGM volumes [49]. PPMS has a predilection for cingulate atrophy [50]. Overall GM loss correlates more with clinical and cognitive outcome measures than WM loss [32, 33, 51]. GM volume significantly impacts the development of clinically definite MS from CIS in a 3-year cohort study [52]. Eshaghi et al showed that only baseline DGM volume predicted time to EDSS progression. There was also the fastest rate of atrophy in the DGM in all MS phenotypes overall, but fastest in the SPMS cohort [49]. Regional atrophy appears to occur in different patterns in MS phenotypes and spreads dependent on disease duration and disability level in relapse-onset MS [53]. GM atrophy is therefore a useful clinical correlate in MS. Reductions in GM volume correlated with cognitive function and overall disability worsening in MS [54].

1.6.3 CERVICAL CORD

Much of the locomotor disability that occurs in PMS is attributable to spinal cord involvement. Spinal cord focal lesions and diffuse abnormalities are seen on MRI in up to 90% of patients with MS and contribute to disability. Spinal cord lesions can occur at any level, but typically are seen in the upper cervical cord and can involve both white and grey matter. Because grey matter demyelination is

associated with neuronal loss and secondary Wallerian degeneration, it is difficult to quantify whether axonal pathology in the cervical cord of MS patients is due to local damage or to retrograde and anterograde degeneration of neurons secondary to the injury of fibres traversing white matter lesions of the brain [55]. However, all the neuropathology changes occurring in the spinal cord contribute to development of cord atrophy in MS, an aspect that can be substantial in the progressive phases of the disease [56].

Although spinal cord is affected in the majority of MS patients and cord atrophy is believed to reflect neurodegeneration, the role of spinal cord MRI measures – lesions and atrophy – as clinical outcome measures in clinical trials is still under debate. In a recent systematic review and meta-analysis, which included 22 longitudinal studies of cord cross-sectional area from a pooled cohort of more than 1000 patients, Casserly and colleagues [57] supported the notion that spinal cord is atrophied in MS and that the magnitude of spinal cord atrophy is greater in progressive versus relapsing forms of the disease, and correlates with clinical disability. According to this study, the pooled annual rate of spinal cord atrophy was 1.78%/year (95% CI 1.28 to 2.27). This rate was greater than the one reported (0.4-0.6% per year) for brain atrophy in MS [58], suggesting that the measurement of spinal cord area is highly relevant as an imaging outcome in MS clinical trials. Performing quantitative spinal cord MRI measurements *in vivo* is technically challenging. This is mostly due to the small size of the cord, and the potential for cord motion during the scan, caused by both involuntary patient movement and physiological motion caused by cardiac and respiratory cycles [59], particularly at the level of the thoracic spine. The cord is surrounded by a higher amount of bone, fat and CSF than the brain. Additionally, T2 or PD weighted imaging lack sensitivity and specificity to the MS-associated pathological changes in the spinal cord and the inherent contrast of spinal cord lesions against healthy cord signal is usually lower than in the brain parenchyma [59].

Active Surface Model (ASM) has been developed for automated cord edge detection and rapid measurement of the spinal cord size [60]. The ASM technique involves the normal placement of cord markers on some representative axial slices and subsequently an outline of the spinal cord is created automatically. More recently, fully automated spinal cord atrophy measurements have been implemented and validated [61, 62]. Recently registration-based techniques similar to the ones used for quantification of brain atrophy are being implemented [63]. In addition, several metrics can be used to normalise spinal cord, such as spinal cord length, participants' height, and intracranial volume measures [64, 65].

1.6.4 T2 LESION VOLUME CHANGE

This measure has proved sensitive in detecting efficacy of immunomodulatory drugs in preventing new lesion formation in previous trials [66] and will be measured here, but it less important in trials of PMS. Gadolinium will only be used at randomisation to determine the proportion of 'active' PMS participants and characterise the trial population.

1.7 CLINICIAN REPORTED OUTCOME MEASURES (CROMS)

Clinical measures of disability progression are generally used as secondary outcome measures in phase 2 trials and primary outcome measures in phase 3 trials. Outcomes related to disability progression can be classified into five groups [67]:

1. metrics that quantify progression as a continuous phenomenon
2. metrics that consider progression as a binary phenomenon, such as the proportion of patients with or without confirmed disability progression (CDP)
3. metrics that quantify confirmed improvement in disability as a binary phenomenon
4. metrics that quantify the time to CDP; and composite outcome measures.

1.7.1 EXPANDED DISABILITY STATUS SCALE (EDSS)

The classical measurement tool and industry standard for measuring the progression of disability is the Expanded Disability Status Scale (EDSS)[4]. It is based largely on neurological examination (with some history). The EDSS quantifies disability in eight functional systems (pyramidal, bowel, bladder, cerebellar, visual, brainstem, cerebral, and sensory) and allows neurologists to assign a functional system score (FSS) in each of these. The EDSS scale ranges from 0 to 10, and each 0.5 unit increment represents increasing levels of disability.

A systematic review of the psychometric properties of the EDSS encompassing 120 relevant full-text publications concluded that it was suitable and valid to detect patient-relevant endpoints in MS. The EDSS is widely used and supported by the Food and Drugs Administration (FDA), European Medicines Agency (EMA) and pharmaceutical industries [68]. The EDSS can be collected remotely and has been validated [69].

1.7.2 TIMED 25 FOOT WALK (T25FW)

The T25FW is a quantitative mobility and leg function performance test based on a timed 25-foot walk. The participant is directed to one end of a clearly marked 25-foot course and is instructed to walk 25 feet as quickly as possible, but safely and may use an assistive device if required. The time is calculated from the initiation of the instruction to start and ends when the participant has reached the 25 feet mark. The task is immediately administered again by having the participant walk back the same distance.

1.7.3 9-HOLE PEG TEST (9HPT)

This is a simple, timed test of fine motor coordination in both hands (dominant and non-dominant) for which it has been assessed for its reliability and validity. The participant should be seated at a table with the 9HPT apparatus, a stopwatch started and the participant instructed to pick up the pegs, one at a time, as quickly as possible and put them into the peg holes and then take them out again. It is then repeated for twice for each hand.

1.7.4 SYMBOL DIGIT MODALITIES TEST (SDMT)

This is a brief measure of cognitive processing speed. It measures information processing speed for visually presented stimuli, but is self-paced, with at least equal reliability and sensitivity to the presence of worsening cognitive impairment. The SDMT [70] is a test that can stand alone or be

included in the neurocognitive batteries to assess visual processing speed and working memory. It has shown a sensitivity of 82% and a specificity of 60% for the assessment of information processing speed [71]. Furthermore, Van Schependom et al. have shown that the SDMT is an easy, low-cost and fast test useful to detect cognitive impairment in everyday clinical practice [72].

1.7.5 MODIFIED MULTIPLE SCLEROSIS FUNCTIONAL COMPOSITE (MSFC)

A score comprised of three components, the Timed 25 Foot Walk (T25FW), 9 Hole Peg Test (9HPT), and Symbol Digit Modalities Test (SDMT), combined as Z score [69].

1.7.6 SLOAN LOW CONTRAST VISUAL ACUITY (SLCVA)

SLCVA letter charts have been investigated as outcome measures in MS, as these were shown to be sensitive to visual impairment even amongst participants with Snellen acuities of 20/20 vision or better. SLCVA letter charts have a standardised format based on the Early Treatment Diabetic Retinopathy Study (ETDRS) visual acuity charts, the standard used in ophthalmology clinical trials. They have several advantages over standard Snellen charts or near vision testing cards, which are traditionally used in MS trials, which make the Sloan chart testing is a reliable, quantitative, and clinically practical measure of visual function. These are:

- (i) SLCVA letter charts are designed to be equally detectable for normal observers
- (ii) each line has an equal number of 5 letters
- (iii) spacing between letters and lines is proportional to the letter size
- (iv) change in visual acuity from one line to another occurs in equal logarithmic steps
- (v) visual acuity for high-contrast may be specified by Snellen notation for descriptive purposes by the number of letters identified correctly [73, 74]

It will be measured with binocular vision at contrast of 100%, 2.5% and 1.25%.

1.7.7 RELAPSE RATE

A relapse for OCTOPUS is defined as new or worsening neurological symptom(s) (which could be motor, sensory, balance, sphincter, visual, cognitive and fatigue) but must be:

- a) in the absence of fever, lasting for more than 24 hours
- b) preceded by a period of clinical stability of at least 4 weeks, with no other explanation other than MS.

When a relapse occurs will be recorded alongside its severity (see [section 6.5.6](#)), which will be used to determine the relapse rate.

1.7.8 PROGRESSION EVENTS

A progression event will be also defined as presence of at least one of the following changes from the randomisation visit (M0): increase in EDSS (of 1 point if randomisation EDSS was <5.5 or of 0.5 points if randomisation EDSS was ≥5.5); ≥20% increase in 9HPT; and ≥20% increase in T25FW (if ambulant) [75].

Progression will be considered confirmed where progression from the baseline measure on the same element of the composite is maintained at the next visit at least 26 weeks later (e.g., two consecutive

visits with $\geq 20\%$ increase in 9HPT compared to the baseline measure). It will be measured at randomisation and 26-weekly thereafter until the end of the follow-up. Deaths from other causes will be minimal and will be treated as censoring events as indicated in the [section 9](#).

1.8 PATIENT REPORTED OUTCOME MEASURES (PROMS)

Patient-reported outcome measures (PROMs) are assuming an increasingly important role in clinical trials, and MS-specific measures have been developed, such as the MS impact scale (MSIS-29v2) [76, 77]. These multidimensional scales measure several domains, such as health distress, sexual function, overall quality of life, cognitive function, energy, pain, walking, sleep quality, fatigue, and social function. However, patient-reported outcomes can also focus on single domains, such as ambulation (MS Walking Scale-12), depression (Beck Depression Inventory and Patient Health Questionnaire-9), or fatigue (Modified Fatigue Impact Scale) [78].

1.8.1 MS IMPACT SCALE-29 VERSION 2 (MSIS-29v2)

This consists of 29 items: 20 related to the physical impact of MS and 9 related to the psychological impact of MS. Each question is scored from 1 to 4 with higher scores denoting greater impact on life, giving score ranging 20–80 for the physical impact and 9–36 for the psychological impact [76]. The psychometric properties of the MSIS-29 have shown strong internal consistency, reproducibility and satisfaction of scaling assumptions for both components [79] and the scale has been suggested as a valuable outcome measure in intervention studies of patients with MS [80].

1.8.2 MS WALKING SCALE-12 VERSION 2 (MSWS-12v2)

This is a validated 12 item patient-reported outcome measure on the impact of MS on the individual's walking ability over the previous 2 weeks. Response categories range from 1 (not at all) to 5 (extremely). Each item will be summed to generate a total score and transformed to a scale with a range of 0 to 100 with high scores indicating greater impact on walking.

1.8.3 FATIGUE SCALES

Fatigue, an extreme feeling of weakness or exhaustion unalleviated by rest, is one of the most prevalent and disabling symptoms of MS and the most common reason patients stop working[81]. The symptom has high costs to the individual, society and the NHS as is distinct from everyday tiredness associated with busy lifestyles. Whilst measurement is challenging, the MFIS and Chalder are standard scales used in clinical trials. As per other large phase 3 trials in Progressive MS (for example, MS-STAT2) two scales will be used:

- **Modified Fatigue Impact Scale - 21 (MFIS-21)** – A 21 item questionnaire which measures the impact of fatigue on cognitive (10 items), physical (9 items) and psychosocial function (2 items) in patients with MS.
- **Chalder Fatigue Questionnaire (CFQ)** – 11 item questionnaire measuring the severity of physical and mental fatigue on two separate subscales. Seven items represent physical fatigue (items 1–7) and four represent mental fatigue (items 8–11).

1.8.4 PAIN ASSESSMENT

Pain in multiple sclerosis is a significant priority for people with MS [82]. It is common [83], and includes both neuropathic and nociceptive pain syndromes [83, 84]. Overall pain prevalence at meta-analysis is approximately 50% for RRMS, but 70% for both SPMS and PPMS, suggesting that pain is particularly common in people with progressive MS [84]. Treatment, however, is often unsatisfactory, and is largely based on evidence drawn from other disorders [85, 86]. Limitations in existing randomised trial evidence [87] were underlined by a recent Cochrane review (under review) which identified only two high quality RCTs of non-cannabinoid neuropathic pain therapies in pwMS [88].

No existing RCTs [87, 88] can answer a critical question - can successful treatment of neuroinflammation or neurodegeneration improve pain symptoms in people with MS? Inclusion of pain measures in trials of potential disease modifying therapies could help to answer this question.

In the MS-SMART multi-arm placebo controlled randomised controlled trial, three putative neuroprotectants were tested against placebo in SPMS [40]. Pain symptom measures were collected for all participants. These included overall pain severity, neuropathic pain (Neuropathic Pain Scale) [89, 90] and pain interference with function [91]. These data (under review [92]) confirm moderate pain severity in participants. However, in common with lack of effect on brain volume trajectories, no effect of the study agents was identified on neuropathic pain outcomes. In spite of negative findings, these data add to a limited evidence base, and additionally examine potential novel analgesic mechanisms.

In OCTOPUS therefore pain will be assessed using the below measures, as they were successfully used in the MS-SMART study, with good data availability, in keeping with ease of use in a population experiencing progressive MS [92].

- Neuropathic Pain Scale [89], which is validated specifically in MS [90] and recommended by international guidelines to assess treatment effects [93].
- Single item measuring overall pain intensity [91, 94] - a numerical rating scale measuring average pain intensity within the last week, with anchors at 0 and 10. This would capture pain of non-neuropathic aetiologies.

1.9 EXPLORATORY ANALYSIS: PARAMAGNETIC RIM LESIONS

The growing recognition of compartmentalized inflammation in the pathogenesis of progressive MS is the target of new therapies and will be important in future clinical trial design. Therapies that target compartmentalized inflammation might be tested using a variety of imaging biomarkers, but the optimal outcome has yet to be established [95]. Paramagnetic rim lesions (PRLs) are a natural candidate, as it identifies chronic active inflammation. PRLs can be identified using conventional MRI machines using susceptibility weighted images (SWI). Although these sequences are not acquired routinely, they are available readily on clinical scanners and can be acquired in clinically feasible acquisition times. SWI will be used at baseline to quantify PRL load.

In this exploratory analysis, we will determine firstly whether PRLs can be collected from multi-site SWI sequences; and secondly whether they are predictive in any way of disease course.

1.10 HEALTH ECONOMIC ANALYSIS PLAN AND EVALUATIONS

1.10.1 EQ-5D

The EQ-5D–5L questionnaire is a validated health status measure, developed by the EuroQol Group [96], which is used to assess and value the health of participants [97, 98]. It consists of five domains that evaluate patients’ health-related quality of life (HRQoL) (mobility, self-care, usual activities, pain/discomfort and anxiety/depression) on a scale from 1 = no problems, to 5 = severe disability. In economic studies of the cost utility of an intervention, the key feature of the EQ-5D–5L is the transformation of the health states into a single index value that represents health utility, producing an anchored score between 0 (worst possible health) and 1 (full health). This health states index is based on sets of weights that have been derived from values from the general population, which implies that these values can be associated to a societal valuation of the respondents’ health state.

1.10.2 CLIENT SERVICES RECEIPT INVENTORY (CSRI)

Questionnaire[99] that collects information on service utilisation, income, accommodation, and other cost-related variables. Its primary purpose is to allow resource use patterns to be described and support costs to be estimated for health economics purposes.

1.11 BACKGROUND AND JUSTIFICATION FOR TRIAL TREATMENT

For each trial treatment, please refer to their individual trial treatment appendix for their background and justification for use.

2 SELECTION OF SITES & CLINICIANS

The trial Sponsor, UCL, has overall responsibility for site and investigator selection.

2.1 SITE/INVESTIGATOR INCLUSION CRITERIA

Appropriate service support and research costs have been developed in partnership across participating sites to ensure that OCTOPUS is appropriately resourced to successfully deliver the desired participants to time and budget. Once a site has been identified as meeting the site evaluation requirements as per listed below, the trial team will provide the site with a copy of this protocol (when approved), a trial summary and the required documentation to obtain greenlight.

To participate in the OCTOPUS trial, investigators and clinical trial sites must fulfil a set of basic criteria that have been agreed by the OCTOPUS Trial Management Group (TMG) and are defined below. A site evaluation form must be completed to confirm these criteria.

Sites where a previous serious protocol breach has occurred should state so on the site evaluation form. These sites will be assessed and if required, visited and thoroughly reviewed before allowing participants to enter the trial.

Those sites that meet the criteria and are approved to participate by the OCTOPUS TMG will be issued with the OCTOPUS master file documentation for their local approvals and CTU activation documents. Sites must complete the OCTOPUS Activation Documentation and training at the same time.

2.1.1 PI'S QUALIFICATIONS & AGREEMENTS

1. The Principal Investigator should be a permanent staff member, qualified by education, training, and experience to assume responsibility for the proper conduct of the trial at their site and should provide evidence of such qualifications through an up-to-date curriculum vitae and/or other relevant documentation requested by the Sponsor, the REC, and/or the regulatory authority(ies).
2. The Principal Investigator should be thoroughly familiar with the appropriate use of the investigational product(s) if appropriate, as described in the protocol, in the current product information and in other information sources provided by the Sponsor.
3. The Principal Investigator should be aware of, and should comply with, the principles of GCP and the applicable regulatory requirements. A record of GCP training should be accessible for all investigators. Training must be refreshed every 2 years.
4. The Principal Investigator and site should permit monitoring and auditing by the Sponsor, and inspection by the appropriate regulatory authority(ies)
5. The Principal Investigator is responsible for supervising any individual or party to whom they delegate trial-related duties and functions conducted at the trial site.

6. If the Principal Investigator or institution retains the services of any individual or party to perform trial-related duties and functions, the Principal Investigator or institution should ensure this individual or party is qualified to perform those trial-related duties and functions and should implement procedures to ensure the integrity of the trial-related duties and functions performed and any data generated.
7. The Principal Investigator should maintain a delegation log of appropriately-qualified persons to whom the investigator has delegated significant trial-related duties.
8. The Principal Investigator should sign an investigator statement, which verifies that the site is willing and able to comply with the requirements of the trial.

2.1.2 ADEQUATE RESOURCES

1. The Principal Investigator and site should be able to demonstrate a potential for recruiting the required number of suitable participants within the agreed recruitment period (that is, the investigator regularly treats the target population).
2. The Principal Investigator should have sufficient time to properly conduct and complete the trial within the agreed trial period.
3. The Principal Investigator should have available an adequate number of suitably qualified staff and adequate facilities for the foreseen duration of the trial to conduct the trial properly and safely.
4. The Principal Investigator should ensure that all persons assisting with the trial are adequately informed about the protocol, the investigational product(s), and their trial-related duties and functions including sample collection
5. The Principal Investigator should ensure that there at least one EDSS assessor that is adequately qualified or has passed a formal Neurostatus assessment.
6. The site should have a pharmacy that is able to store and dispense the Investigational Medicinal Product (IMP) appropriately.
7. The site must have sufficient data management resources to allow prompt data return to the CTU. Sites that have previously participated in CTU-coordinated trials should have a proven track record of good data return.
8. In Stage 1, the site must have access to local Research standard MRI with sufficient capacity to scan OCTOPUS participants. All MRI scans will be subject to Quality Assurance (QA) monitoring operated by QSMSC to ensure an acquisition has passed appropriate QA. In addition, sites will be required to provide a test (dummy run) scan, from a real patient at site, to QSMSC as part of the site initiation process. Further requirements are:

- a. 3 Tesla scanner (manufacturers - GE, Siemens or Philips only) that was installed no longer than 6 years ago. For sites that do not have access to a 3 Tesla scanner it may be possible to use a 1.5 Tesla system after machine assessment and approval by QSMSC.
- b. Have harness and lifting aids to accommodate disabled participants
- c. Be able to send electronic imaging scan data to the QSMSC web-uploader
- d. No foreseen or planned major hardware updates

2.1.3 SITE ASSESSMENT

Each selected clinical trial site must complete the OCTOPUS Activation Training and Documentation, which includes the Principal Investigator Statement, Signature and Delegation of Responsibilities Log, and staff contact details. The Principal Investigator Statement verifies that the site is willing, and able to comply with the requirements of the trial. This will be signed by the Principal Investigator at the site. In addition and in compliance with the principles of GCP, all site staff participating in the trial must complete the Signature and Delegation of Responsibilities Log, indicate their responsibilities as agreed with the Principal Investigator and forward this to the CTU. The CTU must be notified of any changes to trial personnel and/or their responsibilities. An up-to-date copy of this log must be stored in the Trial Master File (TMF) at the site and also at the CTU.

2.2 APPROVAL AND ACTIVATION

The Clinical Trial Authorisation (CTA) for the trial requires that the Medicines and Healthcare Products Regulatory Agency (MHRA) be supplied with the names and addresses of all participating site principal investigators. Trial staff at the CTU will perform this task; hence it is vital to receive full contact details for all investigators prior to their entering participants.

Site training will be performed prior to the activation of the site and will include all processes for the trial including but not limited to protocol training, MRI acquisition and regular Quality Assurance (QA) monitoring system, data management procedures, procedures for handling of investigational medicinal product, adverse event and protocol deviation reporting procedures, procedures for laboratory samples, and frequency and expectations for any monitoring visits. A log of attendees will be kept in the TMF as a record of participants present at all types of training events.

Before a site can open to recruitment, formal Sponsor Site Activation (or Greenlight) will be completed in order to document that the site has met all the requirements to participate in the trial. Written confirmation of site activation (Greenlight) will be sent to the PI and required personnel. A randomisation confirmation will be provided to the site. The site's pharmacist will also be informed of the site's activation and an initial drug order will be dispatched to the named delegated pharmacist.

Following Site Activation:

1. The site should conduct the trial in compliance with the protocol as agreed by the Sponsor and, if required, by the regulatory authority(ies), and which was given favourable opinion by the REC and/or IRB.

2. The PI or delegate should document and explain any deviation from the approved protocol, and communicate this with the trial team at the CTU.

A list of activated sites may be obtained from the OCTOPUS pages of the MRC CTU at UCL website www.ms-octopus.info.

2.3 SITE MANAGEMENT

The OCTOPUS team at the MRC CTU at UCL will manage the OCTOPUS recruiting sites. UCL Queen Square MS Centre (QSMSC) Institute of Neurology (ION), will manage the MRI acquisition set up, regular Quality Assurance (QA) monitoring systems and perform the MRI analyses, which will be reported back to the OCTOPUS team at the MRC CTU at UCL.

3 SELECTION OF PARTICIPANTS

There will be **no exceptions** to eligibility requirements at the time of randomisation. Questions about eligibility criteria should be addressed prior to attempting to randomise the participant.

The eligibility criteria are the standards used to ensure that only medically appropriate participants are considered for this study. Participants not meeting the criteria should not join the study. For the safety of the participants, as well as to ensure that the results of this trial can be useful for making treatment decisions regarding other participants with similar diseases, it is important that no exceptions be made to these criteria for admission to the trial.

Participants will be considered eligible for randomisation in this trial if they fulfil all the core inclusion criteria and none of the exclusion criteria as defined below. In addition, investigators must also check and ensure participants do not adhere to the drug specific exclusion criteria, which are located in each of the separate drug appendices. If exclusion criteria are met for an arm, participants can still be considered for other arms and randomised accordingly to eligible arms.

Please note that these criteria are for Analysis Stage 1 only. They will be amended by substantial amendment for Analysis Stage 2 (e.g. removal of requirements for MRI) or for addition of future arms when and as required.

3.1 PARTICIPANT CORE INCLUSION CRITERIA

1. Participants with a confirmed diagnosis of MS [4]
2. A diagnosis of Secondary Progressive MS (SPMS) or Primary Progressive MS (PPMS) [3, 4].
3. Steady progression as assessed by the treating clinician, rather than relapse (as defined in [section 6.5.6](#)), must be the major cause of increasing disability in the **preceding 2 years**. Progression can be evident from either an increase of at least 1 point if on the Expanded Disability Status Scale (EDSS) score <5.5, or an increase of at least 0.5 point if EDSS score ≥5.5, and/or clinical documentation of increasing disability
4. EDSS 4.0 – 8.0 (inclusive) as assessed at the time of randomisation by the assessing clinician
5. Aged 25 - 70 years old inclusive on the day of randomisation
6. Adequate renal function at screening, defined as eGFR ≥60ml/min/1.73m² (as per local method)
7. Normal liver function at screening consisting of all the following:
 - a. Serum bilirubin <1.5 x ULN (except for participants with Gilbert's disease, for whom the upper limit of serum bilirubin is 51.3 µmol/l or 3mg/dl)
 - b. Either aspartate aminotransferase (AST) or alanine aminotransferase (ALT) <3 x ULN; (it must be stated whether one or both tests were performed. Where both results are available, both must confirm eligibility)
 - c. Alkaline phosphatase <3 x ULN
8. Must be able and willing to comply with the treatment and assessment schedule and requirements including being able to start trial treatment ≤ 2 weeks after randomisation.
9. Written informed consent provided

10. Must have a QC-approved (as defined in MRI guide) MRI ≤ 4 weeks before randomisation
11. Willing and able to have MRI scans in accordance with the assessment schedule and no contraindication to MRI (please refer to MRI Procedures and Protocol for further detail)

3.2 PARTICIPANT CORE EXCLUSION CRITERIA

1. Relapse (as defined in [section 6.5.6](#)) ≤ 12 weeks before randomisation
2. Significant comorbidity (as confirmed by treating clinician)
 - a. Cardiac failure (clinical diagnosis)
 - b. Significant Respiratory comorbidity
 - c. Renal failure
 - d. Malignancy (except if in complete remission) – e.g. solid organ or haematological or melanoma
 - e. Uncontrolled thyroid disease
3. Active partial or total malabsorptive disease (e.g. coeliac disease)
4. Has a history of alcohol use disorder and/or drug abuse (excluding cannabis for symptomatic relief)
5. Female participants that are pregnant or breast-feeding.
6. Women of child-bearing potential (WOCBP) who are unwilling or unable to use an acceptable method of contraception (see [Appendix 1](#)) whilst on trial treatment and up to 12 weeks after the last dose of study drug.
7. Participation in another clinical trial of an investigational medicinal product or medical device ≤ 26 weeks before randomisation
8. Men with a partner of child-bearing potential unwilling to use an acceptable method of contraception during the trial and for 12 weeks after the last dose of trial treatment.
9. Male participants unwilling to desist from sperm donation during the trial and for 12 weeks after the last dose of trial treatment.
10. Been treated with steroids (intravenous and/or oral) for MS relapse or progression ≤ 12 weeks before randomisation*
Note: Participants on steroids for another medical condition may be included in the trial provided the steroid prescription is not for any aspects of their MS.
11. Current or previous treatment with Analysis Stage 1 IMPs ≤ 26 weeks before randomisation. With the exception of participants taking health supplements, including multi-vitamins, that contain a dose of ≤ 100 mg of Alpha Lipoic Acid. These participants can be randomised but must wait 7 days from the last dose before randomisation.
12. Commencement of DMT and/or fampridine ≤ 26 weeks before randomisation*
13. Contraindicated medications that are not permitted with Analysis Stage 1 IMPs (refer to [section 5.14](#)). Please note a careful approach should be applied to those listed with caution. Please contact the OCTOPUS team if further advice is required.
14. Participants who are not eligible for any of the trial IMPs, according to the eligibility criteria listed in the individual drug appendices. Please note that participants can enter the trial if they are eligible for at least one of the trial treatment arms, but do not need to be eligible for all.

*These participants may undergo a further screening visit once the specified window has expired and may be included if no further treatment has been administered in the intervening period.

3.3 ARM-SPECIFIC ELIGIBILITY CRITERIA

In addition to the core inclusion and exclusion criteria above, there are arm-specific eligibility criteria to apply for the each arm. Please refer to individual drug appendix for such criteria and to determine to which arms a participant can be randomised.

3.4 NUMBER OF PARTICIPANTS

The sample size for the Analysis Stage 1 is 125 participants per arm (375 participants in total) after allowing for 11% drop-out. The sample size for the Analysis Stage 2 is anticipated to be 600 participants per arm (1,200 participants in total) assuming one active arm passes Analysis Stage 1. For full details, see [section 9](#).

3.5 CO-ENROLMENT GUIDELINES

Co-enrolment in previous or future trials is considered in [Section 4.3](#).

3.6 SCREENING PROCEDURES & PRE-RANDOMISATION INVESTIGATIONS

Potential participants are identified through a variety of routes such as clinician or GP referral; direct contact between potential participants and sites; PwPMS registered on the UK MS register who have registered interest in the trial (see [Figure 1](#)) or, from Analysis Stage 2, re-randomisation for participants whose arm was closed for lack of benefit. All potential participants will be asked to complete a Registration of Interest survey, which will include some high level eligibility questions. This will empower potential participants to self-screen their own eligibility. Following this, potential participants may be contacted via telephone by their potential site (pre-screening), prior to the screening visit to determine the participants' interest and potential eligibility. Sites may utilise different approaches to encourage efficiencies. This will not include any trial-specific procedures. The only procedures that may be performed in advance of written informed consent being obtained, are those that would be performed on all participants in the same situation as usual standard of care. Participant Information Sheet (PIS) will be made available to the participant ideally prior to the pre-screening telephone call but if not at least 24 hours before attending for the screening visit. PIS are available on the OCTOPUS website (www.ms-octopus.info).

Written informed consent to screen and randomise into the OCTOPUS trial must be obtained from participants, after explanation of the aims, methods, benefits and potential hazards of the trial and BEFORE any trial-specific procedures are performed or any blood is taken for the trial. This will occur at the face-to-face screening visit.

It must be made completely and unambiguously clear that the participant is free to refuse to participate in all or any aspect of the trial, at any time and for any reason, without incurring any penalty or affecting their treatment.

Signed consent forms must be kept by the investigator and a copy given to the participant. The full consent process must be documented in the participant's medical notes (and required elements in the OCTOPUS eDC system) including: the date the PIS was provided; when initial eligibility and telephone consultation was conducted; when the consent form was signed and when further eligibility was assessed. Remote monitoring of the completed consent forms will be utilised through the course of the trial.

Once consented, a participant identification number and a three letter code (TLC) will be allocated and details confirmed on the OCTOPUS eDC system. The eligibility assessments will be then carried out to evaluate participant eligibility at the screening visit.

If any of the screening blood test results or urine pregnancy tests are classified as ineligible, these should be repeated. The repeat safety blood result(s) should be used to assess eligibility. If the participant is considered eligible based on the repeat results they can proceed to randomisation. Tests can be repeated as many times as required as long as they are within maximum of 4 weeks between the initial screening visit and randomisation.

The randomisation visit must occur within 4 weeks of the screening visit. These visits can be combined if it is more practical and possible, whilst ensuring all screening tests and eligibility checks are performed. If the screening visit and the randomisation visit is combined, randomisation must be within 1 week of screening, due to urine pregnancy test requirements and outcome assessments collected. If randomisation does not occur within this window (e.g. for blood test result(s) or logistical reasons), then an additional randomisation visit must be conducted. If the randomisation visit does not occur within 4 weeks of the screening visit, the participant should be re-consented and re-screened and given a new participant identification number.

If a participant is eligible, the site must inform the participant (which can be face-to-face or via telephone) and confirm that they are happy to proceed to randomisation. This conversation must be documented within the participant's medical notes. If proceeding with randomisation, then the site will randomise the participant and provide the participant with further instructions and guidance on collection and taking trial treatment and other trial procedures. It is recommended trial treatment should start within 2 weeks of randomisation. If the situation changes following randomisation and a participant is unable to start within 2 weeks of randomisation, then the site team must contact the OCTOPUS Trial Team to determine how to proceed.

A letter should also be sent to the general practitioner (GP) and neurologist informing him/her of the trial and the participant's involvement in it. This process is summarised in [Figure 1](#). If the participant states that they no longer want to participate in the trial they should not be randomised. This decision must be documented in the participant's medical notes and reported on the OCTOPUS eDC system.

If a participant is ineligible at screening (including participants who remain ineligible after retesting for screening bloods after 4 weeks) or the participant does not want to proceed, the reason for not proceeding to randomisation should be added to the OCTOPUS eDC system as well as being documented within the participant's medical notes. These participants can be re-screened at a later date where appropriate. If a participant is re-screened they should be re-consented and re-screened using a newly provided participant identification number. This also applies if a participant is being re-randomised (please refer to [section 4.4](#)).

4 RANDOMISATION

Please refer to [section 3.6](#) for screening procedures & pre-randomisation investigations.

4.1 RANDOMISATION PRACTICALITIES

Further details on the process of randomisation can be found in [section 3.6 and 9.1](#).

RANDOMISATIONS

Participants will be randomised at each site via the OCTOPUS eDC system after the eligibility criteria has been entered and confirmed

4.2 CO-ENROLMENT GUIDELINES AND REPORTING

Concurrent participation in another clinical trial of an investigational medicinal product (IMP), medical device or other intervention such as a physiotherapy trial, is not allowed. Participants on trial treatment may join observational studies at any point during their participation, but OCTOPUS data must continue to be collected and entered into the OCTOPUS eDC system as per the OCTOPUS Assessment schedule.

Questions regarding co-enrolment should be directed to the OCTOPUS team (mrcctu.octopus@ucl.ac.uk).

4.3 RE-RANDOMISATION INTO OCTOPUS

Participants who are on an arm that completes at Analysis Stage 1 and therefore does not continue to Analysis Stage 2, are able to be re-screened and considered for re-randomisation to an arm is continuing in the trial. This can only be after a 6-month period from trial arm closure and 6-month washout from last trial treatment dose. At this point, they will be considered a new screening participant and repeat the process described in [section 3.6](#).

Participants are not able to re-randomise if their arm has not been closed and follow-up continues.

5 TREATMENT OF PARTICIPANTS

Initially two different mechanistic classes of potential neuroprotective drugs are planned to be tested against a control (placebo) in participants with PMS in the first iteration of the trial platform. Further treatments and arms will be added in future amendments. All participants will continue to receive their normal Standard of Care (SOC) through routine prescribing practice. Instructions on how and when to take the trial treatment will be provided to participants following randomisation.

5.1 INTRODUCTION

The Treatment Advisory Committee (TAC) are responsible for recommending treatments and related dosing to the OCTOPUS TMG. Working within the wider MS Society Expert Consortium on Progression in MS Clinical Trials, potential treatments have been reviewed and ranked, with a focus on repurposed drugs that have already demonstrated safety in humans.[100] This sub-group of the TMG will continue to identify gaps in knowledge/methodologies and make recommendations to the TMG on strategies to address these gaps. The TMG will then make strategic decisions on which treatments are included into OCTOPUS.

OCTOPUS will be randomised double-blind, placebo-controlled comparisons. For Analysis Stage 1, following advice from the TAC, the TMG determined that participants with progressive MS and confirmed eligibility will be randomly assigned in the ratio 1:1:1 to one of the following research arms:

- Arm A: SOC plus Control (Placebo)
- Arm B: SOC plus R/S-Alpha Lipoic Acid (ALA)
- Arm C: SOC plus Immediate Release (IR) Metformin

All participants will be encouraged to continue their SOC on all arms, but SOC is not being investigated as part of this trial. Please refer to [section 5.3](#) for details.

The Patient Information Sheet (PIS) will provide further information relating to administration and side effects of the trial treatments. Trial treatment should start as soon as possible after randomisation. If the situation changes following randomisation and a participant is unable to start within 2 weeks of randomisation, then the site team must contact the OCTOPUS Trial Team to determine how to proceed.

Please refer to [section 5.6](#) for Dose modifications, interruptions and discontinuations for all IMPs. It is the responsibility of the treating clinician to ensure the treatment regimen is followed; in particular, dose modifications should only be made after consulting this written protocol.

5.2 PRODUCTS

Blinded IMPs, including placebo, will be supplied to sites for the OCTOPUS trial. The IMPs will be packaged and labelled in accordance with local regulations (Annex 13) and Good Manufacturing

Practice, stating that the drug is for clinical use only and should be kept out of the reach, out of direct sunlight and sight of children. The IMPs are purchased, over encapsulated, packaged, labelled and distributed by Sharp Clinical Services and supply will be managed via a Drug Supply Management System (DSMS). For further information on the background and product details for each IMP, please refer to their individual drug appendix.

The packaging and capsules will be identical for both active and placebo treatments to ensure blinding is maintained throughout OCTOPUS. The label attached to each package of blinded trial material will have a unique treatment bottle number that is linked to DSMS.

Each site will be provided with bottles of trial treatment with bottle numbers. The DSMS will allocate the appropriate bottle number from those available at the clinical site.

Participants randomised in the trial will be dispensed bottles of capsules (placebo or trial treatment) as determined by DSMS. Participants will be supplied with sufficient trial treatment to last them until their next visit. There will be sufficient capsules in the bottle to cover the visit window.

5.3 STANDARD OF CARE (SOC)

NHS SOC is not being investigated as part of OCTOPUS and therefore is not an IMP. It is individualised for each PwPMS by their NHS neurologist and MS teams. It is guided by NICE Technology Appraisal Guidance (TAG) documents. Examples of current SOC may include (but are not limited to):

1. Participants receiving no Disease Modifying Treatment (DMT)
2. PPMS: Ocrelizumab 600mg/6 months given by intravenous infusion [Technology Appraisal guidance (TA585) 12-Jun-2019]
3. SPMS: Siponimod 1-2mg/day given orally [TA656 18-Nov-2020]

It is recommended that a new DMT or trial IMP is not started within 2-4 weeks of each other to ensure any reported AEs can be assessed accurately. However, this is subject to clinical discretion.

5.4 TREATMENT SCHEDULE

Following randomisation in Analysis Stage 1 OCTOPUS, participants will receive:

5.4.1 INITIAL OR LOW DOSE

Two capsules taken once daily for 4 weeks from randomisation. This will be blinded and will consist of one of the following:

- Arm A: SOC plus 2 x Control (Placebo) capsules
- Arm B: SOC plus total daily dose of 600 mg of R/S-ALA
- Arm C: SOC plus total daily dose of 1000 mg of IR metformin

The trial treatment will be supplied in capsule form and each will look identical to each other. It is advised that these capsules are taken in the evening after food with an adequate amount of water. A description of how to take the capsules including what to do if doses are missed is provided in the participant information sheet.

At the week 4 visit, if the participant is tolerating this dose with no adverse events or complications, the dose will be escalated to:

5.4.2 HIGH DOSE

Two capsules taken twice a day (four capsules in total) after food with an adequate amount of water and therefore participants receiving the following dosage:

- Arm A: SOC plus 4 x Control (Placebo) capsules
- Arm B: SOC plus total daily dose of 1200 mg of R/S-ALA (ALA) [101]
- Arm C: SOC plus total daily dose of 2000 mg of IR metformin

The high dose should continue until dose modifications, interruptions and discontinuations are required. The first 24 weeks post randomisation will determine the participant's dose, following this period, no further dose escalations should occur, only dose reduction or discontinuation. Please refer to [section 5.6](#) for further information.

5.5 DISPENSING AND STORAGE

All trial treatment dispensed for OCTOPUS should be documented on a drug accountability log as per OCTOPUS Pharmacy Manual as well as in DSMS. At each site, a named trial pharmacist will be required to maintain complete records of all trial treatment dispensed.

Procedures for drug labelling, accountability, storage and destruction will be detailed in the OCTOPUS Pharmacy Manual and must be in compliance with applicable local regulations, GCP and the protocol. Staff from the MRC CTU will monitor drug accountability at site visits.

All trial treatment will be dispensed by pharmacy departments within participating sites to coincide with the dispensing schedule documented in the OCTOPUS Pharmacy Manual.

5.6 EXPECTED TOXICITIES, DOSE MODIFICATIONS & DISCONTINUATIONS

From randomisation to 24 weeks, dose modifications can be performed to determine the appropriate dose to be tolerated by the participant. At 24 weeks, maximum dose for the remainder of the trial will be determined. Doses can then only be reduced, paused or stopped due to safety reasons, clinician choice, or participant choice. This dose change must be performed by the treating clinician.

5.6.1 RENAL IMPAIRMENT

Whilst on trial treatment, renal function must be monitored at least 26-weekly (as per the assessment schedule) in participants with stable renal function. In line with published prescribing recommendations, [Table 3](#) describes the required active monitoring of renal function:

Table 3: Monitoring for renal function

eGFR	ACTION
≥60 ml/min/1.73m ²	Continue on trial treatment
50 - 60 ml/min/1.73m ²	Repeat eGFR 4 weeks post test and continue on current dose. On repeat eGFR, result remains <60 ml/min/1.73m ² ; Treatment must be permanently stopped
<50 ml/min/1.73m ²	Treatment must be permanently stopped

If the participant experiences obstructive uropathy (e.g., urinary retention or ureteric obstruction), trial treatment must be paused and only restarted when renal function confirmed to be stable or returned to the participant's baseline.

Prior to receiving Iodinated contrast agents, trial treatment should be paused for 24 hours prior to receiving the contrast. It should then be restarted 48 hours post-administration only after eGFR has been confirmed as >50ml min/1.73m².

5.6.2 GASTROINTESTINAL

Gastrointestinal disturbances can be common with the trial treatment and include nausea, vomiting, diarrhoea, abdominal pain, dehydration and loss of appetite. If such toxicities occur, a dose reduction to a low dose or pause is required, as described in [Table 4](#) below.

Table 4: Management of trial treatment for related gastrointestinal toxicity

TOXICITY EVENT	ACTION
CTCAE (v5.0) Grade 1	<ul style="list-style-type: none"> If on high dose, clinician discretion if consider switching to low dose, until stable If on low dose, clinician discretion if consider 1 week treatment pause until stable
CTCAE (v5.0) Grade 2 or higher	<p>If on high dose, reduce to low dose then re-attempt dose escalation after minimum of 1 week if symptoms improve, aiming to continue at the high dose</p> <p>If on low dose, pause. then re-start after minimum of 1 week if symptoms improve.</p> <p>If grade 2 toxicity persists consider the following:</p> <ul style="list-style-type: none"> Pause treatment for 2 weeks, and re-start And re-attempt a dose escalation at clinical discretion if toxicities are ≤ grade 1 if within 24 weeks of randomisation.

5.6.3 PROTEINURIA

If a participant is eligible for the R/S-ALA arm, proteinuria might be seen with the trial treatment. If proteinuria occurs, a dose reduction to a low dose or pause may be required, as described in [Table 5](#) below.

Table 5: Management of trial treatment for proteinuria

URINARY DIPSTICK RESULT	ACTION
0 – trace proteinuria	No action required – continue on current dose
1+ or higher on repeat urinary dipstick	Measure Albumin/creatinine ratio (ACR) <ul style="list-style-type: none"> • If ACR is ≤ 300 mg/g (< 34 mg/mmol), participant continues treatment • If ACR is 301 – 999 mg/g (≥ 34 mg/mmol – 113 mg/mmol) reduce to low dose or pause (if on low dose) for up to 4 weeks from the ACR result (as per Figure 7); retest then if: <ul style="list-style-type: none"> ▪ ACR is ≤ 300 mg (< 34 mg/mmol) re-attempt dose escalation after minimum of 1 week, aiming to continue at the high dose. ▪ ACR remains at 301 – 999 mg/g (≥ 34 mg/mmol – 113 mg/mmol) pause treatment for 2 weeks. Restart at clinical discretion following renal advice and only should reattempt dose escalation if ACR improves to ≤ 300 mg/g • If ≥ 1000 mg/g (> 113 mg/mmol) stop treatment immediately

5.6.4 VITAMIN B12 DEFICIENCY

Participants that were eligible for the metformin arm will have their vitamin B12 checked at every scheduled in-person visit. If a deficiency occurs, a treatment pause will be required, as described in [Table 6](#) below.

Table 6: Management of Vitamin B12 deficiency

VITAMIN B12 LEVEL	ACTION
>200 ng/l (>200 pg/ml) (148 pmol/l)	Continue on trial treatment
≤ 200 ng/l (≤ 200 pg/ml) (148 pmol/l)	Stop trial treatment for 3 months and replace vitamin B12. Re-check at 3 months and commence trial treatment if > 200 ng/l (148 pmol/l). If ≤ 200 ng/l (148 pmol/l) at 3 months, participant remain off IMP and replace Vitamin B12 for a further 3 months and re-check. If ≤ 200 ng/l (200 pg/ml) (148 pmol/l) after 9 months post initial test, discontinue trial treatment

5.6.5 OTHER TOXICITIES

Other toxicities considered to be medically significant for these trial treatments and therefore should be monitored are:

- Asthenia
- Constipation
- Dizziness
- Dyspnoea
- Muscle Cramps
- Paraesthesia
- Skin reactions (including rash and urticaria)
- Taste disturbance

If these toxicities are Grade ≥ 3 (using NCI CTCAE v5.0) or persistent, clinical investigators should adhere to the below modifications.

The below instructions can also be used for other toxicities not listed or if the participant is not tolerating the dose, in the clinical investigator's opinion.

If a participant is on the low dose:

- Participants on low dose trial treatment (2 capsules) reporting adverse events (with the exception of MS related relapses) prior to dose escalation at visit week 4, are not required to dose escalate. They may remain on the low dose (2 capsules) at the discretion of the clinical investigator in accordance with [Figure 7](#). If within 24 weeks of randomisation, this does not prevent a subsequent increase to high dose trial treatment (4 capsules) once the adverse event(s) reported are resolved, and following clinical evaluation by the clinical investigator.
- If a participant cannot tolerate the low dose (2 capsules), due to adverse events experienced, trial treatment should be paused. The participant should continue with all clinical follow-up assessments. If the participant is within 24 weeks since randomisation, they should be re-challenged with low dose of trial treatment within 4 weeks, at the discretion of the clinical investigator. Re-challenging can occur twice in succession at each AE presentation prior to discontinuation.
- Upon re-challenge, if the participant can now tolerate the low dose and is within the 24 weeks since randomisation, then they can be escalated to the high dose.
- Upon re-challenge, if the participant is unable to tolerate low dose trial treatment, they should discontinue trial treatment for the remaining duration of the trial. The participant should remain in trial follow-up and complete all clinical assessments.

[Figure 7](#) and [Figure 8](#), below, summarises the dose modification process for participants on low and high doses.

If a participant is on the high dose:

- If a participant cannot tolerate high dose trial treatment (4 capsules), the dose should be reduced to the low dose (2 capsule). The participant can be re-challenged with high dose trial treatment (4 capsules) within up to 4 weeks of reduction and if within 24 weeks post randomisation.
- If upon re-challenge with high dose trial treatment (4 capsules) the participant is unable to tolerate trial treatment at this dose, they should be placed back on low dose trial treatment (2 capsule). If the participant is within 24 weeks since randomisation, the participant can subsequently be re-challenged with 4 capsules, if within 4 weeks of reduction.
- Upon challenge on high dose (4 capsules) of trial treatment on a second occasion, if participant cannot tolerate the high dose again, the clinical investigator must reduce to low dose trial treatment (2 capsule) for the remaining duration of the trial.

Figure 8 below, summarises the dose modification process for participants on high doses.

Participants should be advised that in the case of acute medical illness (e.g. severe or serious infections, severe dehydration or other acute illnesses requiring medical attention) they should cease taking trial treatment and consult their trial neurologist as soon as possible to be advised accordingly.

Figure 7: Treatment and dose diagram - Low dose

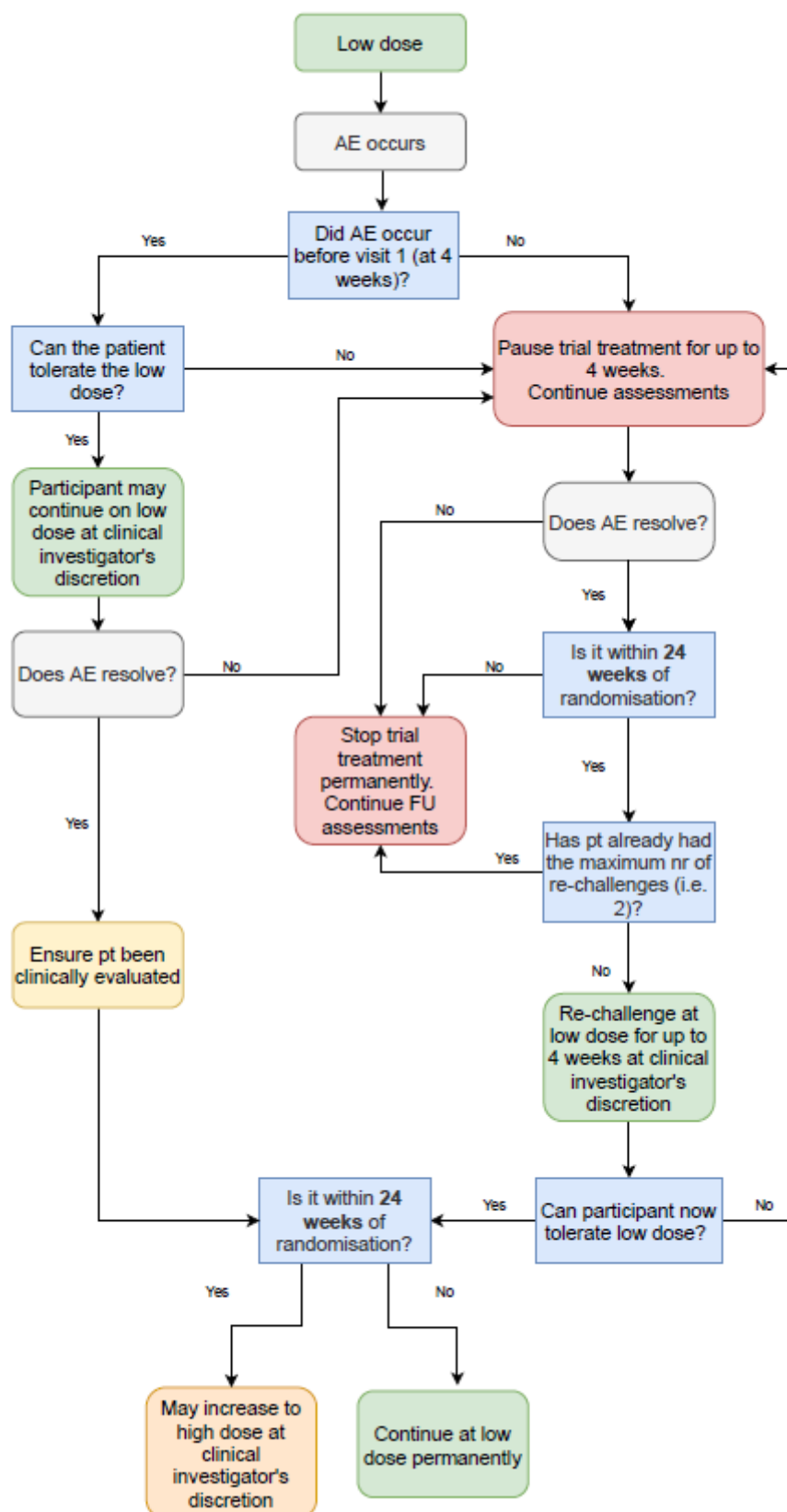
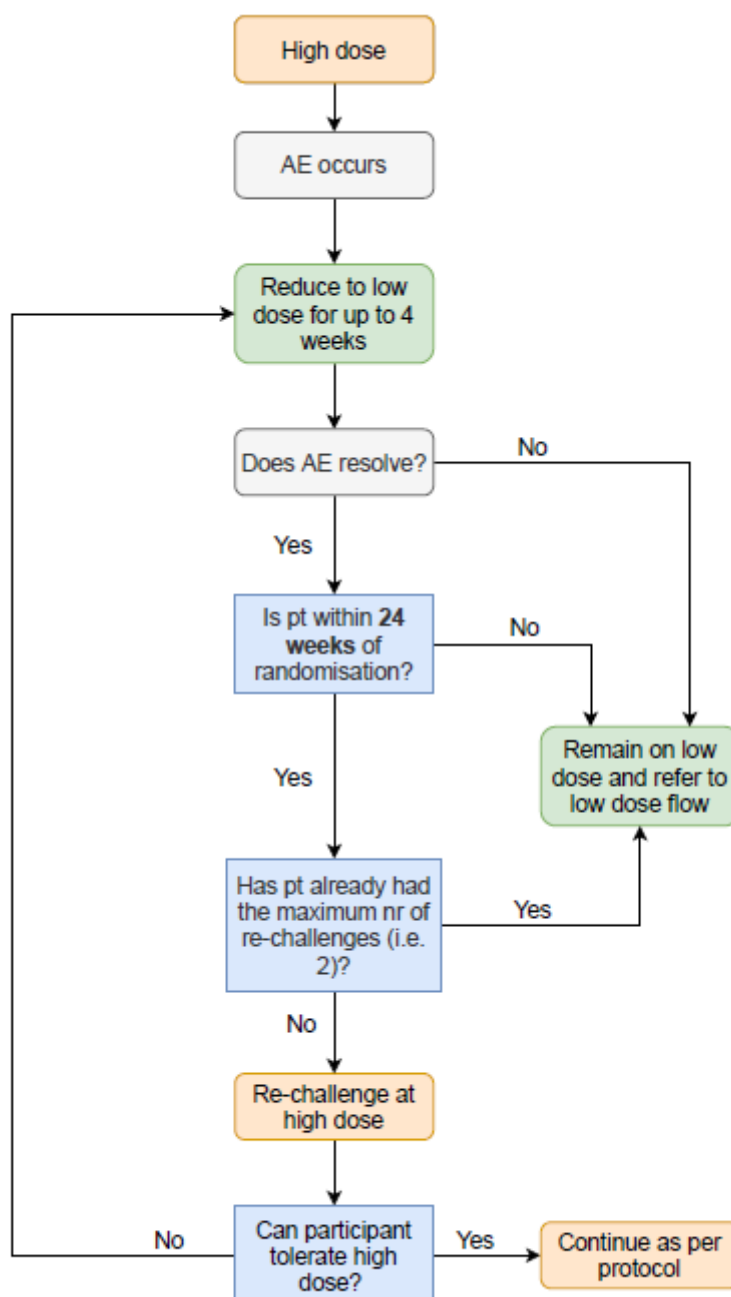


Figure 8: Treatment and dose diagram – High dose

5.6.6 SURGICAL AND OTHER PROCEDURES

Trial treatment must be discontinued at least 24 hours prior to any surgery, for general care (e.g. a fracture) under general, spinal or epidural anaesthesia. Trial treatment may be restarted no earlier than 48 hours following surgery or resumption of oral nutrition and provided that renal function has been re-evaluated and found to be stable.

5.6.7 STOPPING TRIAL TREATMENT EARLY

Discontinuation criteria are considered in [section 5.12](#)

5.7 CONTRACEPTION

Male participants must agree to use an acceptable method of contraception during sexual contact with a pregnant female or a woman of childbearing potential (WOCBP) while taking trial treatment, during dose interruptions and for at least 12 weeks after the last dose of trial treatment. Male participants must also agree to not perform any sperm donation while taking trial treatment, during dose interruptions and for at least 12 weeks after the last dose of trial treatment. Partners of male participants are encouraged to use acceptable methods of contraception.

OCTOPUS female participants who are WOCBP must agree to use an acceptable method of contraception while taking trial treatment and for at least 12 weeks after the last dose of trial treatment. For WOCBP, pregnancy checks prior to MRI will be performed, in line with local MRI practices and guidelines and this may include a urine HCG pregnancy test. This will be documented in the MRI checklist or notes. WOCBP participants and participants with WOCBP partners should be reminded of the use of contraception at each scheduled visit ([section 6.3.3](#)) whilst on trial treatment period and for a period of 12 weeks after the last dose of investigational product. At trial visits, clinical discretion should be exercised if a pregnancy test is required prior to dispensing.

Please refer to [Appendix 1](#) for acceptable methods of contraception.

5.8 ACCOUNTABILITY & UNUSED DRUGS/DEVICES

The dose of trial treatment administered to each participant will be recorded on worksheets or medical notes and in the OCTOPUS eDC system. Reasons for any dose modification, interruption or discontinuation on the Treatment log on the OCTOPUS eDC system, with missed doses recorded in Drug Diary card on the OCTOPUS eDC system.

The trial pharmacist at each participating site will be responsible for accountability of trial treatment supplies. Accountability must include tracking all IMP received at site, dispensed to participants and destroyed as unused or expired. Accountability will be through DSMS and templates, where required, will be provided in the Pharmacy Information Pack. The trial pharmacist will sign a document to confirm that local hospital systems and standard operating procedures (SOPs) are in place to cover drug ordering, drug receipt, drug storage and dispensing, and their systems will enable accurate traceability of all trial drugs. The SOPs will be submitted and a documented review performed by the OCTOPUS team.

At each visit, the research team will review and summarise the participant's drug compliance. All the packaging and unused capsules should be returned by participants and can be destroyed as per standard local procedures by pharmacy. This summary will be documented on the Drug Diary Card eCRF.

A Pharmacy Manual and templates will be provided to all participating sites prior to activation.

5.9 COMPLIANCE & ADHERENCE

Participants will be made aware of the importance of compliance with the trial protocol at screening, randomisation and subsequent follow-up visits. Participants will be provided with a paper drug diary card (which should be returned at each clinic visit) to assist them to record whether they have taken their trial treatment as per their prescription for the first 4 weeks after their in-person visit (0, 2, 4 capsules/day, depending on tolerance). Participants will be informed missed doses should not be made up if not taken on the relevant day but should be noted to enable them to inform the site team at their visits.

Participants will also have the option of completing a summary of their diary card on the electronic Drug diary card directly on the OCTOPUS eDC system. A link will be sent a link to complete 2 days prior to their week 4 visit and 30 days post all other clinic visits to complete.

Compliance will be discussed at each follow-up visit to determine 4 weeks following the participant's last visit, how many days of their prescribed dose (0, 2, 4 capsules/day, depending on tolerance) have been taken. Site staff may wish to review the participant's diary card to facilitate the conversation but it should be collected for source data at each visit. Reasons for non-compliance will be sought and addressed where appropriate. If the electronic Drug Diary card has not been completed prior to the visit, the Research team should complete this on the OCTOPUS eDC system.

Reasons for any dose delay, reduction, or missed doses will also be recorded in in medical notes (or worksheets) and the OCTOPUS eDC system.

5.10 HANDLING CASES OF TRIAL TREATMENT OVERDOSE

Any dose in excess of that specified according to the protocol will constitute an overdose. Measures will be taken to minimise accidental overdose of trial treatment by providing adequate education to trial participants. After accidental or deliberate overdose of trial treatment, if medically required participants should be unblinded to their trial treatment, (please see [section 5.11](#)) and then treated accordingly. Further details for each trial treatment can be found in their individual trial treatment appendix. If the overdose was accidental, the re-introduction of trial treatment dosing will be determined by the clinical investigator at the participating site with consultation with the OCTOPUS team (without unblinding them to treatment allocation).

Any participant taking a deliberate overdose of trial treatment should discontinue trial treatment for the remaining duration of the trial and no further supply of trial treatment given. The participant should remain in trial follow-up and complete all clinical assessments.

5.11 UNBLINDING

Unblinding participants' trial treatment is discouraged during the trial as blinding is considered critical to its integrity. The treatment allocation must not be broken except in medical emergencies when the appropriate management of the participant necessitates knowledge of the treatment allocation. In

many cases, particularly when the emergency is clearly not investigational product related, the problem may be properly managed by assuming that the subject is receiving an active treatment without the need for unblinding.

All participants will be unblinded at the end of the trial when data are mature, database lock and primary analysis has taken place or earlier, at the recommendation of the IDMC.

5.11.1 EMERGENCY UNBLINDING

Unblinding of allocation to trial treatment, can be performed if required only in a medical emergency, where knowledge of the participant's treatment allocation would change clinical management. This can be performed in medical emergencies by any treating doctor as well the participant's trial site PI, delegated site clinicians, OCTOPUS CI or Trial Physicians via the OCTOPUS website. The doctor requiring the unblinding may wish to contact or notify the participant's site prior to unblinding to discuss the circumstances and their details can be found on the Participant's Card along with location of the OCTOPUS website where the unblinding can be performed. If it has not been possible to contact the participant's local site, the UCLH emergency number can be used to contact the OCTOPUS CI or Trial Physicians.

To unblind, the requesting treating doctor should provide on the OCTOPUS website, their full name, GMC number and NHS email address where they will receive the unblinded information. The trial site PI, delegated site clinicians, OCTOPUS CI or Trial Physicians will only receive notification that the participant has been unblinded and details of the individual who has carried out the unblinding. They will not receive details of the treatment allocation.

If unblinding occurs, then the investigator(s) must document this, with the reason for unblinding, and report it to the OCTOPUS Trial team within 24 hours of the occurrence through completion of an SAE on the OCTOPUS eDC system **without unblinding the OCTOPUS Trial Team or site team to the allocation**. Treatment allocation information must be kept confidential and should be disseminated only to those individuals who must be informed for medical management of the participant.

The Trial Statistician at the MRC CTU at UCL will be notified of all emergency unblindings.

5.11.2 UNBLINDING BY THE CTU

MRC CTU at UCL staff who are not involved in the day-to-day running of the trial and the unblinded trial statisticians will be responsible for unblinding possible suspected unexpected serious adverse reactions (SUSARs) for notification to the regulatory authorities. For further details, please refer to the [section 7](#) of this protocol.

5.11.3 UNBLINDING FOLLOWING TRIAL CLOSURE

Once statistical data lock has occurred for the main analysis and no further changes will be made to the data, all participants will be unblinded. The Principal Investigator at each site will be notified in writing of the treatment allocations of all participants randomised by the site. It will be the responsibility of the Principal Investigator or delegate to inform participants of their treatment allocation, where considered appropriate.

5.12 TRIAL TREATMENT DISCONTINUATION

In consenting to the trial, participants are consenting to trial treatment in accordance with the protocol. However, a participant may stop treatment early, or have their trial treatment stopped early by clinical investigators, for any of the following reasons:

- Unacceptable toxicity or adverse event (see [section 5.6](#) for discontinuation)
- Intercurrent illness that prevents further treatment
- Any change in the participant's condition that justifies the discontinuation of treatment in the clinician's opinion
- Inadequate compliance with the protocol treatment in the judgement of the treating clinician
- Pregnancy
- Intent to become pregnant
- Withdrawal of consent for treatment by the participant
- Trial arm discontinuation as part of the MAMS design

This section refers to stopping trial treatment early and permanently, e.g. due to the reasons above. For management of pausing trial treatment due to toxicities see [section 5.6](#).

If a participant does not discontinue treatment, they will continue for up to 5 years or until their Analysis Stage completion whichever is soonest. At this point, if the participant is receiving trial treatment, a discussion will occur to determine continuation of trial treatment and its provision.

As the participant's participation in the trial is entirely voluntary, they may choose to discontinue the trial treatment at any time without penalty or loss of benefits to which they are otherwise entitled. Although the participant is not required to give a reason for discontinuing their trial treatment, a reasonable effort should be made to establish this reason while fully respecting the participant's rights.

When a participant joins OCTOPUS, they are providing consent for trial follow-up and data collection as well as trial treatment. If a participant discontinues their trial treatment, they should not be presumed to have withdrawn consent for follow up and data collection too (refer to [Section 6.8](#) for an overview of the options for withdrawing consent). Consequently, they should always be followed up in accordance with the assessment schedule, providing they are willing. Participants should be encouraged to not leave the whole trial because their data is important for the analysis even if they have stopped trial treatment.

The default position for participants who stop trial treatment early should be that they continue with face-to-face follow-up visits as per the trial assessment schedule. If this is not possible, every effort should be made to ensure these participants are followed up by telephone assessments. If a participant is considering stopping all trial follow up early, refer to [Section 6.8](#).

Participants who stop trial treatment early cannot be considered for re-randomisation unless their current trial arm is closed at the end of Analysis Stage 1.

5.13 TREATMENT DATA COLLECTION

Please refer to [section 6](#) for assessment schedules required. Investigations in this trial will use the results of data collected and processed from MRI. Other Investigations will use local assessments at site (such as blood tests and outcome assessments) as per the assessment schedule. This data will be collected in the OCTOPUS eDC system, which will be an electronic data capture (eDC) system of the MRC Clinical Trials Unit at UCL. eDC at sites must only be completed by trained personnel and who has been authorised to do so by the Principal Investigator, as recorded on the Signature and Delegation of Responsibilities Log.

Trial treatment must be recorded on the Drug Diary Card eCRF in the OCTOPUS eDC system. In addition, reasons for any dose modifications, interruptions or discontinuations of trial treatment must be documented in the appropriate eCRF. Please refer to [section 5.9](#) on compliance and adherence.

It is the responsibility of staff at participating sites to obliterate all personal identifiable data on any hospital reports, letters, etc., prior to sending to the MRC CTU. Such records should only include Trial Number, TLC and year of birth to identify the participant.

5.14 NON-TRIAL TREATMENT

5.14.1 MEDICATIONS PERMITTED

Investigators may prescribe concomitant medications or treatments deemed necessary to provide symptomatic treatment except for those medications identified as “absolutely not permitted” in [section 5.14.2](#). Care should be taken with medication identified as ‘use with caution’ in [section 5.14.3](#).

Participants can also continue their SOC as determined by the participant’s treating NHS neurologist (please refer to [section 5.3](#)).

5.14.2 NOT PERMITTED

For the current IMPs as per this version of the protocol, the participants are not permitted to take any of the below listed medications in [Table 7](#) and for which IMP (trial treatment) this is indicated for:

Table 7: Medications not permitted

	Not permitted due to:
Cancer medications or treatment	R/S-ALA
Excessive Alcohol (above national recommended limits)	R/S-ALA and Metformin
Insulin	R/S-ALA and Metformin
Diabetes medication	Metformin

Iodinated contrast agents*	Metformin
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*Iodinated contrast agents are not permitted whilst taking trial treatment. Treatment pause is permitted during the trial. Please refer to [section 5.6.1](#).

Participants must not be on any of the Analysis Stage 1 IMPs during the trial. This includes medications that are combined or include the IMPs as an ingredient. At randomisation (for eligibility) participants must not be on any of the Analysis Stage 1 IMPs in the 26 weeks prior to randomisation, unless if it is Alpha Lipoic Acid in combination with health supplements, including multi-vitamins, and has a dose of $\leq 100\text{mg}$, the participant must wait 7 days from the last dose before randomisation.

5.14.3 MEDICATIONS TO BE USED WITH CAUTION

The drugs listed in [Table 8](#) have been found to interact unfavourably with the OCTOPUS IMPs (please refer to the current approved SmPC and Investigator Brochure for a full list of contraindicated drugs). As this is a blinded study, caution as determined by the clinical team and their clinical judgement, must be used when using the following medication:

Table 8: Medications to be used with caution

	Caution due to
Diabetic drugs – any (excluding Insulin and metformin (see above))	R/S-ALA and Metformin
Anticholinergic drugs (e.g. atropine, tricyclic antidepressants)	R/S-ALA
NSAIDs, including selective cyclooxygenase (COX) II inhibitors, ACE inhibitors, angiotensin II receptor antagonists and diuretics, especially loop diuretics	Metformin
Medicinal products with intrinsic hyperglycaemic activity (e.g. glucocorticoids (systemic and local routes) and sympathomimetics)	Metformin
Inhibitors of Organic cation transporters (OCT) 1 such as verapamil	Metformin
Inducers of OCT1 such as rifampicin	Metformin
Inhibitors of OCT2 such as cimetidine, dolutegravir, ranolazine, trimethoprim, vandetanib, isavuconazole	Metformin
Inhibitors of both OCT1 and OCT2 such as crizotinib and olaparib	Metformin

Participants can take “with caution” medications concomitantly with trial IMPs at clinical discretion. Alternatively, investigators can decide to temporarily discontinue the IMP if the participant is going to take one of these medications for a short period of time. If a pause takes place, trial treatment can be resumed if within 24 weeks of randomisation.

It is recommended the participant should restart trial treatment at the low dose (2 capsules) for 2 weeks, and can then increase to the high dose (4 capsules) if the low dose is well tolerated.

5.14.4 TREATMENT AFTER TRIAL EVENT

Treatment will be at the discretion of the responsible NHS neurologist and MS teams.

6 ASSESSMENTS AND FOLLOW-UP

6.1 TRIAL ASSESSMENT SCHEDULE

For the Trial Assessment Schedule please refer to [Figure 1](#) at the start of this protocol.

Sites are required to nominate a treating clinician and a separate assessing clinician for OCTOPUS, with appropriate arrangements for cover in case of staff absence. Treating clinicians are responsible for assessing patient eligibility, obtaining informed consent, prescription and titration of trial treatment, reviewing participant progress, conducting the relapse assessment and monitoring and recording AEs and concomitant medications. The assessing clinicians and other team members, where applicable, are responsible for all clinical and patient reported outcomes, excluding the relapse assessment.

The screening visit and randomisation visit must be conducted in-person. Visit week 12 can be a telephone visit if bloods can be collected via GP or another phlebotomy clinic and provided to the site team. Visit week 38, week 64, week 90, week 116 and all subsequent 12-weekly urine dipstick visits should be telephone visits and if clinically required, should also be in-person visits. All other visits can only be telephone/remote visits in extenuating circumstances.

6.2 CLINICAL ASSESSMENTS

6.2.1 PHYSICAL EXAMINATION AND DEMOGRAPHY

Physical examinations will be performed according to the assessment schedule. Full physical examinations will be as per standard clinical visits. Height will be measured at screening only. Weight must be measured at screening and should only be measured at follow-up visits, if there is any significant weight loss. If so, appropriate clinical decision making should be followed.

Other physical examinations may include assessments of the head, eyes, ears, cardiovascular, GI, musculoskeletal and neurological systems. Demography will only be collected at screening and will include documentation of participant's date of birth, ethnicity and sex at birth.

6.2.2 VITAL SIGNS

Vital signs (blood pressure, pulse and temperature) will be evaluated according to the assessment schedules. Additional monitoring with assessment of vital signs is at the discretion of the Investigator as per standard clinical practice or as clinically indicated.

6.2.3 TREATMENT COMPLIANCE ASSESSMENT

Participants will be made aware of the importance of compliance with the trial protocol at randomisation and subsequent follow-up visits. Please refer to [Section 5.9](#) for compliance and adherence management.

6.2.4 CONCOMITANT MEDICATION

At each visit, a review of concomitant medication must be performed to ensure any contraindicated medications including taking any Analysis Stage 1 IMPs are not being taken. Please refer to [section 5.14](#) for details.

6.2.5 TELEPHONE ASSESSMENTS

Visit week 12 can be a telephone visit if bloods can be collected via GP or another phlebotomy clinic and provided to the site team. Week 38, week 64, week 90, week 116 and all subsequent 12-weekly urine dipstick visits should be telephone visits and if clinically required, should also be in-person visits.

All other visits can only be telephone or remote visits in extenuating circumstances. At such visits clinical history, adverse events, concomitant medications and treatment compliance will be assessed. Whilst the participant is receiving Trial Treatment (IMPs), then participants will also require safety bloods at these assessments, which can be taken via GP or other phlebotomy clinics and results provided to the site team. EDSS and relapse activity are the only clinical reported outcomes that should be assessed at a telephone visit. All participant report outcomes should also be performed.

6.3 SAFETY ASSESSMENTS

All the following assessments should be conducted and/or reviewed by the treating clinician.

6.3.1 BLOODS

Participants will be required to have the assessments listed in the assessment table in [Table 1](#) prior to or at the follow-up visit and prior to prescriptions being issued in order to assess and ensure participant safety. The tests can be completed up to 1 week prior to the treatment visit.

Additional haematology and clinical chemistry tests can also be carried out during the trial period as clinically indicated.

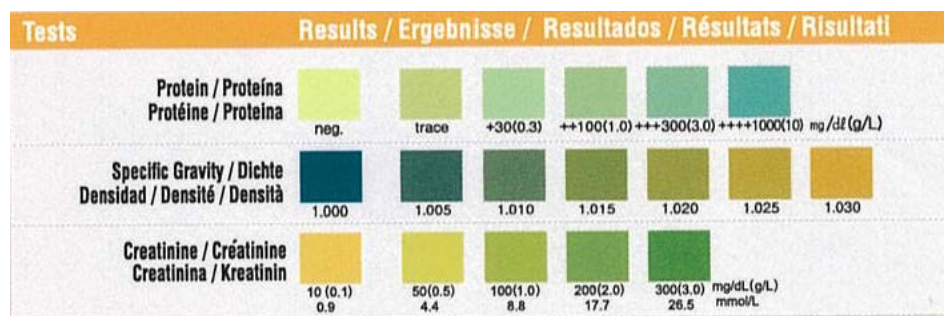
6.3.2 DIPSTICK

A urinary dipstick is required to be performed every 12 weeks whilst on treatment, due to the management and identification of proteinuria. This should be performed at the clinic at follow up visits and by the participant for the interim test between 26-weekly visits. Four test kits (reagent strip and small sterile container) and instructions should be supplied to the participants at each 26-weekly visit. Fewer kits can be provided if participant has leftover supplies from previous visits.

A standard urinary dipstick such as Bayer Multistix 10SG Reagent Strips (Bayer Corp., Diagnostics Division, Elkhart, IN, USA) can be used. The dipsticks provided to sites for participants will be the '[Home Kidney Function Urine Test Kits](http://homehealth-uk.com)' from Home Health UK (homehealth-uk.com). The dipstick is dipped into the urine sample (a mid-stream collection in a provided small sterile container) making sure all the test zones on the stick are submerged. The stick is removed, tapped to remove excess

urine and held horizontally so urine does not drip. After 60 seconds, the dipstick is held up against the colour chart provided on the instructions as per the example in [Figure 9](#) below.

Figure 9: Example of colour chart for assessing urinary dipstick



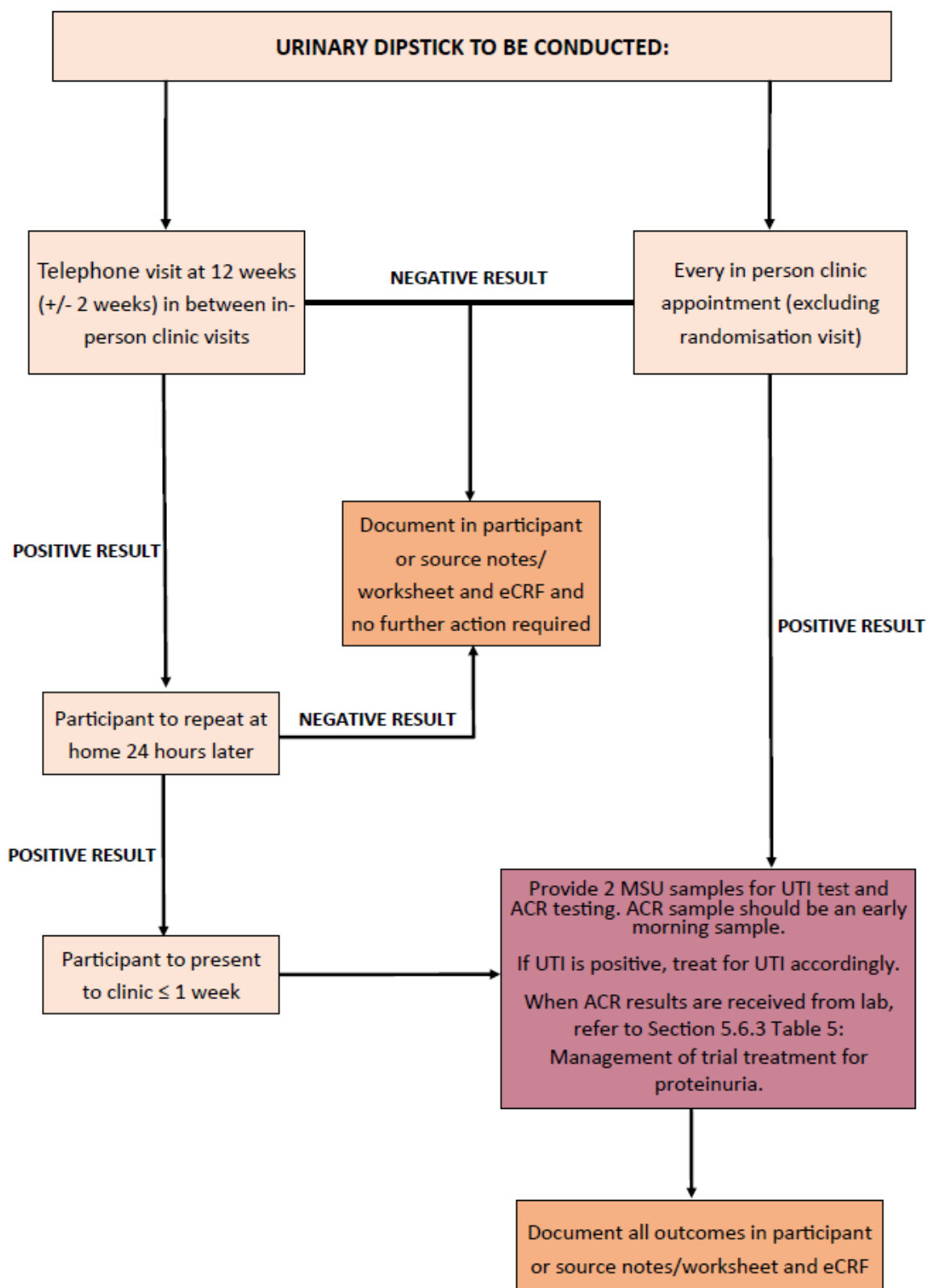
If the test is negative at an in-clinic visit, no further action is required.

The participants should report the results to the study nurse or site research team following at home 12-weekly testing. If the test is negative, no further action is required. If the test is 1+ or higher at an at-home test, it should be repeated 24 hours later. If the repeat test is negative, no further action is required.

If the test is positive at either the in-clinic visit test or the repeat home test, the participant should provide two midstream specimen of urine (MSU) samples. For at-home testing, this should be provided ≤ 1 week of the repeat home test. The sample should be tested for a urinary tract infection (UTI), as well as sending a sample to the local laboratory to measure the albumin/creatinine ratio (ACR). The MSU sample for the ACR test should be an early morning sample. The participant's IMP dose must be adjusted based on the result of the ACR in accordance to [section 5.6.3](#). Any UTIs should be treated accordingly.

All urinary dipsticks results, and if required the ACR result, must be documented in the patient or source notes/worksheets and both entered into the appropriate eCRF in the OCTOPUS eDC system. Please refer to [Figure 10](#).

Figure 10: Urinary stick management flowchart



6.3.3 PREGNANCY

For WOCBP participants, pregnancy checks prior to MRI will be performed in line with local MRI practices and this may include a urine HCG pregnancy test. This will be documented in the MRI checklist or notes. Clinical discretion should be exercised if a pregnancy test is required for WOCBP participants at follow up visits prior to any dispensing when no MRI is performed.

If a pregnancy occurs in a trial participant, it is a reportable event and female trial participants must stop trial treatment. Please refer to [section 5.12](#) and [section 7.2.2](#) for how it must be reported. A further information sheet must be provided and informed consent form completed to obtain consent to collect information and outcome of the pregnancy and health of the baby up to 30 days following the birth.

6.4 PROCEDURES FOR MRI ASSESSMENT

MRI scans will be acquired at appropriately qualified sites in Analysis Stage 1 for each participant at randomisation, week 26, week 78 and week 104 on the same MRI scanner at the same site. The site and team (PI and all assessing clinicians) must participate in the regular Quality Assurance (QA) monitoring system and ensure an acquisition has passed appropriate QA. The QA and central QC and analysis of all MRIs will be performed by UCL Queen Square Institute of Neurology, MS Unit. Please refer to [section 2.1.2](#) for scanner requirements. For details for the collection, collation and submission of MRI as well as the reporting of incidental findings, please refer to the MRI manual.

6.5 PROCEDURES FOR ASSESSING CLINICAL REPORTED OUTCOMES

All the following assessments should be conducted by the assessing clinician, with the exception of the relapse assessment which should be conducted by the treating clinician.

6.5.1 EXPANDED DISABILITY STATUS SCALE (EDSS)

The assessing investigator will perform neurological examination and calculate the functional system scores (FSS) and EDSS according to Neurostatus definitions (neurostatus.net). An EDSS Quality assurance process will be undertaken and the EDSS may only be performed by an assessor with formal Neurostatus assessment or if required deemed appropriately qualified and experienced by the PI.

6.5.2 TIMED 25 FOOT WALK (T25FW)

The T25FW is a timed 25-foot walk to test mobility and leg function performance. The participant is directed to one end of a clearly marked 25-foot course and is instructed to walk 25 feet as quickly as possible, but safely. The time is calculated from the initiation of the instruction to start and ends when the participant has reached the 25 feet mark. The task is immediately administered again by having the participant walk back the same distance. Participants may use an assistive device when carrying out this test but this must be recorded. For further detail, please refer to the Multiple sclerosis Functional Composite (MSFC) manual found at:

(http://main.nationalmssociety.org/docs/HOM/MSFC_Manual_and_Forms.pdf)

6.5.3 9-HOLE PEG TEST (9HPT)

This is a simple, timed validated test of fine motor coordination in both the dominant and non-dominant hands. The participant should be seated at a table with the 9HPT plastic apparatus. When a stopwatch is started and the participant instructed to pick up the plastic pegs, one at a time, as quickly as possible and put them into the peg holes. Once all 9 plastic pegs have been inserted, the participant should immediately remove the pegs, one at a time and replace them into the original shallow bowl. The time is recorded as that between the first peg being picked up, to the last peg being placed back into the bowl. The procedure should be carried out twice with the dominant hand and twice with the non-dominant hand. Sites must use the plastic apparatus. For further detail, please refer to the MSFC manual found at: (http://main.nationalmssociety.org/docs/HOM/MSFC_Manual_and_Forms.pdf)

6.5.4 SYMBOL DIGIT MODALITIES TEST (SDMT)

The SDMT measures information processing speed for visually presented stimuli. Participants are presented with a series of 9 symbols, each paired with a single digit in a key. When prompted, participants are asked to voice the digit associated with each symbol as quickly as possible for 90 seconds. The single outcome measure is the total number correct over the 90 second time span.

6.5.5 SLOAN LOW CONTRAST VISUAL ACUITY (SLCVA)

Sloan chart testing is a reliable, quantitative, and clinically practical measure of visual function. The Sloan flipchart consists of rows of grey letters on a white background (60 letters in total). A cardboard SLOAN flipchart will be used in OCTOPUS, not the backlit light box version.

The chart should be used with the room lights on and with the participant positioned 2 metres away from the chart. Letters are displayed in decreasing size order from the top of the chart to the bottom. The participant is asked to read the letter with both eyes (binocular vision). If the participant normally wears vision aids (e.g. glasses or contact lenses) then they should be worn during the test. Testing will be conducted at 3 different contrast levels (100%, 2.5% and 1.25%). For each of the 3 contrast levels the chart will be scored based on the number of letters correctly identified out of 60 letters.

6.5.6 RELAPSE ASSESSMENT

A relapse for OCTOPUS is defined as new or worsening neurological symptom(s) (which could be motor, sensory, balance, sphincter, visual, cognitive and fatigue) but must be:

- a) in the absence of fever, lasting for more than 24 hours
- b) preceded by a period of clinical stability of at least 4 weeks, with no other explanation other than MS.

Grade 1 and 2 relapses do not include hospitalisation or other definitions of serious and therefore should be excluded from expedited safety reporting. The severity of the relapse and the date of its occurrence, should be documented in the patient notes and on the OCTOPUS eDC system. The severity is determined by the grade as described in **Table 9** below. It should also be reported as a Serious Adverse Event (SAE).

Table 9: Grading of MS related relapses

Grade of relapse	Description of event
Grade 1	Relapse not treated with corticosteroids
Grade 2	Relapse treated with corticosteroids, but not requiring hospitalisation
Grade 3	Relapse treated with corticosteroids and requiring in-patient hospitalisation; or relapse not treated with corticosteroids but requiring in-patient hospitalisation <i>Please note: SAE forms must be completed for participants reporting a grade 3 relapse and submitted through the OCTOPUS eDC system no more than 24 hours of the investigator becoming aware of the event.</i>

6.6 PROCEDURES FOR ASSESSING PATIENT REPORTED OUTCOMES

All patient reported outcomes are required at randomisation and each subsequent in-person follow-up visit until participants stops follow-up (regardless of treatment status). Telephone visits are only allowed for scheduled in-person clinic visits in extenuating circumstances. If a telephone visit is being conducted the patient reported outcomes should be still be collected via the telephone by the study nurse or completed by the participant via links sent to them directly from the OCTOPUS eDC system (except for CSRI), for which there is no electronic version).

6.6.1 MS IMPACT SCALE-29 VERSION 2 (MSIS-29v2)

The MSIS-29v2 is a 29-item scale which assesses the impact of MS on people's health-related quality of life in terms of their physical and psychological well-being over the previous 2 weeks.

It has two subscales: a 20-item physical impact scale and a 9-item psychological impact scale, which can be combined into a total score. It is currently in its second version, which has 4-point response categories for each item: 'not at all', 'a little', 'moderately', and 'extremely'. Scores on the physical impact scale can range from 20 to 80 and on the psychological impact scale from 9 to 36. Lower scores indicate little impact of MS and higher scores indicate greater impact.

6.6.2 MS WALKING SCALE-12 VERSION 2 (MSWS-12v2)

This is a validated 12-item patient reported outcome measure on the impact of MS on the individual's walking ability over the **previous 2 weeks**.

Response categories range from 1 (not at all) to 5 (extremely). Participants are required to select one response per question. Three out of the 12 items have 3 response categories, the remaining 9 items have 5 response categories. Each item will be summed to generate a total score and transformed to a scale with a range of 0 to 100 with high scores indicating greater impact on walking.

6.6.3 MODIFIED FATIGUE IMPACT SCALE - 21 (MFIS-21)

A 21-item questionnaire which measures the impact of fatigue on cognitive (10 items), physical (9 items) and psychosocial function (2 items) in participants with MS..

6.6.4 CHALDER FATIGUE QUESTIONNAIRE (CFQ)

An 11-item questionnaire measuring the severity of physical and mental fatigue on two separate subscales. 7 items represent physical fatigue (items 1–7) and 4 represent mental fatigue (items 8–11).

6.6.5 PAIN ASSESSMENT

The pain assessment will be measured using two measures:

- **Neuropathic Pain Scale** - an 11-item questionnaire that can be completed in 3-4 minutes. Please note in OCTOPUS, item 8 will be omitted as this qualitative data is not required and will assist participant in time required to complete.
- **Single item measuring overall pain intensity** [91, 94] - this is a numerical rating scale measuring average pain intensity within the last week, with anchors at 0 and 10. It is estimated to take less than 30 seconds.

6.6.6 EQ-5D-5L

The 5-item questionnaire (assessing mobility, self-care, usual activities, pain/discomfort, and anxiety/depression) and visual analogue scale (VAS) enables calculation of quality adjusted life years (QALY) to enable health economic analyses to be performed. Each dimension assessed has 5 response scales to select from: no problems, slight problems, moderate problems, severe problems, and extreme problems.

6.6.7 CLIENT SERVICES RECEIPT INVENTORY (CSRI)

This adapted version of the CSRI questionnaire [99] collects information on health care service utilisation, paid and unpaid carer time, employment and other cost-related variables. This should be completed at each in-person follow-up visit and can be performed on a telephone follow-up in extenuating circumstances. The CSRI has been adapted to be specific to MS and tested out as part of MS-STAT II trial. This cannot be performed on the OCTOPUS eDC system and so must be completed on paper worksheets.

6.7 OTHER ASSESSMENTS

For participants who have consented to provide the optional biorepository sample collection for bioarchiving, these should be collected as per [section 10](#).

6.7.1 EQUALITY, DIVERSITY, AND INCLUSION (EDI)

Equality, diversity, and inclusion (EDI) data collection will occur at screening with some questions on the registration of interest. EDI data is being collected on behalf of the MS Society to allow the MS Society to better understand the diversity of the participants participating in MS research, in accordance with its EDI strategy. This data will not be used in the OCTOPUS analysis but aggregated data will be provided to the MS Society annually. The MS Society aims to have a research community that is equal, diverse and inclusive as possible to ensure it is best qualified to improve the lives of people affected by MS in the UK.

The EDI data will include:

- Gender
- Sexual orientation
- Ethnicity
- Caring responsibilities
- Socio-economic status

If participants do not want to provide any of this information, all questions have a 'prefer not to say' option.

6.8 EARLY STOPPING OF FOLLOW-UP, DATA COLLECTION, OR OTHER ASSESSMENTS

When a participant joins OCTOPUS, they are providing consent for trial treatment, follow-up, and data collection as well as (optionally) the collection of biosamples. If a participant wishes to discontinue participation in some aspects of OCTOPUS, it should not be presumed they wish to discontinue all of them. Instead, site staff should have a discussion with the participant exploring the situation and what options may suit the participant. These include:

- Discontinuing trial treatment (refer to [section 5.12](#))
- Discontinuing trial follow-up (see [section 6.8.1](#))
- Discontinuing consent for passive data collection (see [section 6.8.2](#))
- Discontinuing sample collections (where participant originally opted in) (refer to [section 10.1](#))

If a participant decides to discontinue some or all aspects of the trial, the OCTOPUS team should be informed of this and a discussion should be held between the site and the OCTOPUS team. This discussion is to determine the participant's situation and, if proceeding with discontinuation, what is the participant's chosen level of discontinuation, before it is reported formally to the OCTOPUS trial team.

It should be clear to the participant what aspect(s) of the trial they wish to discontinue. This should be recorded in the participant notes, and reported via the OCTOPUS eDC system.

Participants who are withdrawn due to trial arm stopping as part of the MAMS design at the end of Analysis Stage 1, can be considered for re-randomisation to an arm that is continuing in the trial. The participant must have a 6-month washout period prior to re-randomisation. No participant can be re-randomised within Analysis Stage 1.

6.8.1 DISCONTINUING TRIAL FOLLOW-UP

Participants stopping follow-up early have a negative impact on a trial's data. Participants who stop trial follow-up early will not be replaced. Data on participants who stop follow-up early will be kept and included in the analysis, so withdrawing consent can only apply to the use of participant's data from the date that their withdrawal is reported via the OCTOPUS eDC system.

If a participant does not wish to remain on trial follow-up, including telephone assessments, their decision must be respected and they will be withdrawn from future trial clinic follow-up. A participant that has formally withdrawn from OCTOPUS follow-up (except those whose arm was stopped at the end of Analysis Stage 1 for lack of efficacy) cannot be re-randomised.

However, participants may change their minds about stopping trial follow-up at any time and re-consent to participation in the trial. These cases should be discussed with the OCTOPUS team.

If participants do withdraw their consent for trial follow up as well as treatment, they can still allow for relevant data to be collected by site from their routine care (e.g. via neurologist or GP) and/or the MS Register for long-term but passive data collection. Care may return to their normal clinical care provider (such as their neurologist or GP). If the medical data collected during the participant's participation in the trial are kept for research and analysis purposes, they will be anonymised.

6.8.2 DISCONTINUING CONSENT FOR PASSIVE DATA COLLECTION

Participants may wish to withdraw their consent for long-term data collection via linkage to the MS Register and/or their routine healthcare professionals, e.g. GP or neurologist. If a participant no longer consents for their data to be collected passively to inform the analysis without them having to attend in-person or telephone follow up visits, their decision must be respected and their data will not be collected from the date of trial withdrawal.

6.9 PARTICIPANT TRANSFERS

If a participant moves from the area, every effort should be made for the participant to be seen at another participating trial site. The participant will need to sign a new consent form, and until this has been done, responsibility for the participant lies with the original site. Once this has been done, the new site will take over responsibility for the participant; and will be given access to the participant data on OCTOPUS eDC system. However if the participant was recruited in Analysis Stage 1, an effort should be made for the MRI scans to be performed at the original site. If this is not possible, the MRC CTU should be notified and the new site should perform the MRI.

6.10 LOSS TO FOLLOW-UP

Every effort should be made to follow-up participants who have been randomised. Participants should, if possible, remain under the care of a neurologist for the duration of the trial. If the care of a participant is returned to the General Practitioner, it is still the responsibility of the investigator to ensure that the follow-up data required by the protocol are collected and reported for those participants who have consented for follow-up.

Participants who have not formally withdrawn from the trial, but are unable to be contacted or located, despite the best efforts of the research team, can be considered 'lost to follow up' after 3 years have passed since the last contact with the trial team.

Participants will be asked to consent for follow-up and linkage to the MS Register prior to randomisation.

6.11 COMPLETION OF PROTOCOL FOLLOW-UP

A participant will continue follow-up (regardless of treatment) for 5 years or until their Analysis Stage completion whichever is soonest.

At this point, if the participant is receiving trial treatment, a discussion will occur to determine continuation of trial treatment and provision.

Participants who are on an arm that completes at Analysis Stage 1 and therefore does not continue to Analysis Stage 2, are able to be re-screened and considered for re randomisation to an arm that has continued into Analysis Stage 2. This can only be after a 6-month wash out period after final treatment of the treatment stopped. At this point, they will be considered a new screening participant and repeat the process described in [section 3.6](#).

Further linkage for long-term analysis for these participants may occur through the MS Register for participants who have consented for their data to be used.

7 SAFETY REPORTING

The principles of GCP require that both investigators and Sponsors follow specific procedures when notifying and reporting adverse events or reactions in clinical trials. These procedures are described in this section of the protocol. [Section 7.1](#) lists definitions, [Section 7.3](#) gives details of the investigator responsibilities and [Section 7.4](#) provides information on CTU responsibilities.

7.1 DEFINITIONS

The definitions of the EU Directive 2001/20/EC Article 2 based on the principles of GCP apply to this trial protocol. These definitions are given in [Table 10](#).

Table 10: Definitions

TERM	DEFINITION
Adverse Event (AE)	Any untoward medical occurrence in a participant or clinical trial subject to whom a medicinal product has been administered including occurrences that are not necessarily caused by or related to that product.
Adverse Reaction (AR)	Any untoward and unintended response to an investigational medicinal product related to any dose administered.
Unexpected Adverse Reaction (UAR)	An adverse reaction, the nature or severity of which is not consistent with the information about the medicinal product in question set out in the Summary of Product Characteristics (SPC) or Investigator Brochure (IB) for that product.
Serious Adverse Event (SAE) or Serious Adverse Reaction (SAR) or Suspected Unexpected Serious Adverse Reaction (SUSAR)	Respectively any adverse event, adverse reaction or unexpected adverse reaction that: <ul style="list-style-type: none">▪ Results in death▪ Is life-threatening*▪ Requires hospitalisation or prolongation of existing hospitalisation**▪ Results in persistent or significant disability or incapacity▪ Consists of a congenital anomaly or birth defect▪ Is another important medical condition***

*The term life-threatening in the definition of a serious event refers to an event in which the participant is at risk of death at the time of the event; it does not refer to an event that hypothetically might cause death if it were more severe, for example, a silent myocardial infarction.

**Hospitalisation is defined as an inpatient admission, regardless of length of stay, even if the hospitalisation is a precautionary measure for continued observation.

*** Medical judgement should be exercised in deciding whether an AE or AR is serious in other situations. The following should also be considered serious: important AEs or ARs that are not immediately life-threatening or do not result in death or hospitalisation but may jeopardise the subject or may require intervention to prevent one of the other outcomes listed in the definition above; for example, a secondary malignancy, an allergic bronchospasm requiring

intensive emergency treatment, seizures or blood dyscrasias that do not result in hospitalisation or development of drug dependency.

7.1.1 MEDICINAL PRODUCTS

An investigational medicinal product (IMP) is defined as the tested investigational medicinal product and the comparators used in the study. (EU guidance ENTR/CT 3, April 2006 revision).

Adverse reactions include any untoward or unintended response to drugs. Reactions to an IMP or comparator should be reported appropriately.

The IMPs for this trial at the time of this version of the protocol:

- Placebo
- R/S-Alpha Lipoic Acid (ALA)
- Immediate release (IR) Metformin

7.1.2 ADVERSE EVENTS

Adverse Events (AEs) include:

- An exacerbation of a pre-existing illness
- An increase in frequency or intensity of a pre-existing episodic event or condition
- A condition (even though it may have been present prior to the start of the trial) detected after trial drug administration
- Continuous persistent disease or a symptom present at randomisation that worsens following administration of the study treatment

Please note if the investigator attributes an AE solely to the participant's MS symptoms or relapse it does not need to be reported as an AE. However please note the relapse itself should be reported on the AE log.

7.1.3 ADVERSE AND DISEASE RELATED EVENTS EXEMPT FROM THE EXPEDITED REPORTING

The following events, in the context of OCTOPUS, are exempt from the expedited reporting timeframe (24 hours), but must be reported on the AE log in the OCTOPUS eDC system within 4 weeks of the investigator's knowledge of the event, if they meet the seriousness criteria.

- Medical or surgical procedures; the condition that leads to the procedure is the adverse event
- Pre-existing disease or a condition present before treatment that does not worsen
- Hospitalisations where no untoward or unintended response has occurred, e.g., elective cosmetic surgery
- Adverse events that do not meet the criteria to be considered 'serious' and deemed solely due to progression of the participant's SPMS condition
- Elective admissions (irrespective of the length of stay, e.g. 1 day admissions)

7.2 OTHER NOTABLE EVENTS

7.2.1 TOXICITIES

Lactic acidosis or glomerulonephritis are toxicities of interest for the OCTOPUS IMPs. Therefore, if participants experience these one of these two toxicities they should be reported as a notable event.

The OCTOPUS Team at MRC CTU at UCL must be notified within 24 hours of the site becoming aware of the event. Notification is via the Notable Event form in the OCTOPUS eDC system. These events may also be classed as serious and therefore if this is the case, they should be reported as notable and serious adverse events.

7.2.2 PREGNANCY

Pregnancy is not an adverse event. However, if a pregnancy occurs in a trial participant or a partner of a trial participant, it is a notable event and female trial participants must stop trial treatment please refer to [section 5.12](#).

Therefore, the OCTOPUS Team at MRC CTU at UCL must be notified within 24 hours of the site becoming aware of the event. Notification (as per [section 7.3.6](#)) is done by reporting a positive pregnancy test in the Lab Results eCRF in the OCTOPUS eDC system. If pregnancy occurs in a participant or the partner of a trial participant, consent must be obtained to collect any follow-up information on the pregnancy. All pregnancies will be followed up to collect information until 30 days following the outcome of the pregnancy, end of treatment period or end of trial regardless of the outcome.

7.3 INVESTIGATOR RESPONSIBILITIES

All events should be recorded in the participant's medical notes or worksheets and reported on the AE log on the OCTOPUS eDC system. All AEs should be reported within **the agreed timescale** of 1 week of the visit. SAEs and Notable Events should be notified to the CTU within 24 hours of the investigator becoming aware of the event via the OCTOPUS eDC system.

7.3.1 INVESTIGATOR ASSESSMENT

Adverse events will be recorded and graded according to the CTCAE v5.0, using a recognised medical term or diagnosis that accurately reflects the event. Adverse events will be assessed by the local investigator for severity, relationship to the investigational product, possible aetiologies, and whether the event meets criteria of an SAE and therefore requires expedited notification to the CTU.

7.3.2 SERIOUSNESS

When an AE or AR occurs, the investigator responsible for the care of the participant must first assess whether or not the event is serious using the definition given in [Table 10](#). If the event is serious, then an SAE Form must be reported via the OCTOPUS eDC system within 24 hours. If the event is not an SAE but meets the notable event criteria (see [section 7.2](#)) complete a Notable Event Form and submit the report within 24 hours via the same mechanism.

7.3.3 SEVERITY OR GRADING OF ADVERSE EVENTS

The severity of all AEs and/or ARs (serious and non-serious) in this trial should be graded using the toxicity gradings in NCI CTCAE V5.0.

7.3.4 CAUSALITY

The investigator must assess the causality of all serious events or reactions in relation to all the trial treatments using the definitions in [Table 11](#). There are five categories: unrelated, unlikely, possible, probable, and definitely related. If the causality assessment is unrelated or unlikely to be related, the event is classified as an SAE. If the causality is assessed as possible, probable or definitely related, then the event is classified as an SAR.

Table 11: Assigning Type of SAE Through Causality

RELATIONSHIP	DESCRIPTION	SAE TYPE
Definitely	There is clear evidence to suggest a causal relationship and other possible contributing factors can be ruled out.	SAR
Probable	There is evidence to suggest a causal relationship and the influence of other factors is unlikely.	SAR
Possible	There is some evidence to suggest a causal relationship (for example, because the event occurs within a reasonable time after administration of the trial treatment). However, the influence of other factors may have contributed to the event (for example, the participant's clinical condition, other concomitant treatments).	SAR
Unlikely	There is little evidence to suggest that there is a causal relationship (for example, the event did not occur within a reasonable time after administration of the trial treatment). There is another reasonable explanation for the event (for example, the participant's clinical condition, other concomitant treatment).	Unrelated SAE
Unrelated	There is no evidence of any causal relationship	Unrelated SAE

If an SAE is considered to be related to trial treatment and drug is stopped or the dose modified, refer to [section 5.6](#).

7.3.5 EXPECTEDNESS

The Sponsor has the overall responsibility for determination of expectedness. An unexpected adverse reaction is one not previously reported in the current approved Reference Safety Information (RSI) or one that is more frequent or more severe than previously reported. The RSI will be provided for their information to Investigators and can also be located on the OCTOPUS Website. The definition of an unexpected adverse reaction (UAR) is given in [Table 10](#). If a SAR is assessed as being unexpected, it becomes a SUSAR.

7.3.6 NOTIFICATION

The CTU should be notified of all SAEs within 24 hours of the investigator becoming aware of the event in the OCTOPUS eDC system.

All **Adverse Events** (AEs) are reportable from the time of randomisation until 4 weeks after discontinuation of trial treatment. All AEs should be recorded in the participant's medical notes and on the relevant Toxicity(AE) eCRF in the OCTOPUS eDC system.

All **Serious Adverse Events** (SAEs) are reportable from the time of randomisation until 4 weeks after discontinuation of trial treatment, with the exception of reactions i.e. related events (SARs and SUSARs), which continue to be reportable until trial arm closure.

All **Notable Events** are reportable from randomisation until trial arm closure, using the OCTOPUS eDC system.

After trial arm closure or stopping of follow-up at 5 years, any subsequent events that may be attributed to treatment should be reported to the MHRA using the yellow card system.

7.3.7 NOTIFICATION PROCEDURE

1. The SAE or NE Form must be entered into the AE log on the OCTOPUS eDC system by an investigator (named on the Signature List and Delegation of Responsibilities Log, who is responsible for the participant's care; this will be either the Principal Investigator or another medically qualified person with delegated authority for SAE reporting). Due care should be paid to the grading, causality of the event, as outlined above.

In the absence of the responsible investigator, the form should be entered by a member of the site trial team. The responsible investigator should subsequently check the SAE Form, make changes as appropriate within the OCTOPUS eDC system as soon as possible.

2. The minimum criteria required for reporting an SAE are the trial number and date of birth, name of investigator reporting, the event term, and why it is considered serious.
3. Follow-up: participants must be followed up until clinical recovery is complete and laboratory results have returned to normal or baseline, or until the event has stabilised. Follow-up should continue after completion of protocol treatment if necessary. The details of the follow-up should be entered on to the OCTOPUS eDC system.

Extra, annotated information and/or copies of test results may be requested by the OCTOPUS Trial team and/or provided separately securely via email (e.g. via Galaxkey). The participant must be identified by trial number, month and year of birth and TLC only. The participant's name should not be used on any correspondence and should be deleted from any test results.

9. Staff should follow their institution's procedure for local notification requirements.

Serious Adverse Event (SAE) and Notable Event (NE) REPORTING

**Within 24 hours of becoming aware of an SAE or NE,
please report all SAEs and Notable Events via the OCTOPUS eDC system**
If you have any issues with entering the SAE/NE or have any questions, please email
mrcctu.octopus@ucl.ac.uk

7.4 CTU RESPONSIBILITIES

Medically-qualified staff at the CTU and/or the Chief Investigator (or a medically-qualified delegate) will review all SAE reports received, code to MedDRA and perform the expectedness assessment using the approved Reference Safety Information (RSI). The causality assessment given by the local investigator at the hospital cannot be overruled. In the case of disagreement, both opinions will be provided in any subsequent reports

The CTU is undertaking the duties of trial Sponsor and is responsible for the reporting of SUSARs and other SARs to the MHRA and the research ethics committees, as appropriate. Fatal and life-threatening SUSARs must be reported to the competent authorities within 7 days of the CTU becoming aware of the event; other SUSARs must be reported within 15 days.

The CTU will also keep all investigators informed of any safety issues that arise during the course of the trial.

The CTU, as representative of the Sponsor, will submit Annual Safety Reports in the form of a Developmental Safety Update Report (DSUR) to Competent Authorities (Regulatory Authority and Ethics Committee). It will be submitted to any relevant pharmaceutical collaborator when required.

The MRC CTU at UCL will also keep all investigators informed of any safety issues that arise during the course of the trial.

8 QUALITY ASSURANCE & CONTROL

8.1 RISK ASSESSMENT

The Quality Assurance (QA) and Quality Control (QC) considerations have been based on a formal Risk Assessment, which acknowledges the risks associated with the conduct of the trial and how to address them with QA and QC processes. QA includes all the planned and systematic actions established to ensure the trial is performed and data generated, documented and/or recorded and reported in compliance with the principles of GCP and applicable regulatory requirements. QC includes the operational techniques and activities done within the QA system to verify that the requirements for quality of the trial-related activities are fulfilled. This Risk Assessment has been reviewed by the CTU's Research Governance Committee (RGC) and has led to the development of a Data Management Plan (DMP), Safety Management Plan (SMP), Pharmacovigilance Checklist, PPI Plan, SOP Deviation Tracker, Quality Management and Monitoring Plan (QMMP) and IMP Management Plan which will be separately reviewed by the Quality Management Advisory Group (QMAG).

8.2 CENTRAL MONITORING AT CTU

CTU staff will review data entered into the OCTOPUS eDC system for errors, missing data points and protocol deviations and will raise queries as appropriate.

Other essential trial issues, events and outputs will be detailed in the QMMP that is based on the trial-specific Risk Assessment.

8.3 ON-SITE MONITORING

The frequency, type and intensity for routine monitoring and the requirements for triggered monitoring will be detailed in the QMMP. This plan will also detail the procedures for review and sign-off.

8.3.1 DIRECT ACCESS TO PARTICIPANT RECORDS

Participating investigators should agree as part of their trial consent to allow trial-related monitoring, including audits, ethics committee review and regulatory inspections by providing direct access to source data and documents as required. Participants' consent for this must be obtained.

Remote or self- monitoring will be utilised through the course of the trial. Site staff may be asked to scan and send anonymised sections of a participant's medical record to the CTU for remote verification or asked to complete a form to confirm compliance with protocol procedures.

8.3.2 CONFIDENTIALITY

OCTOPUS plans to follow the principles of the UK DPA regardless of the countries where the trial is being conducted.

8.4 SOURCE DATA

The investigator and institution should maintain adequate and accurate source documents and trial records that include all pertinent observations on each of the site's trial participants. Source data are contained in source documents and are defined by EU guidelines as all information in original records that are used for the reconstruction and evaluation of the clinical trial. Source documents are the first place where the source data are recorded. OCTOPUS will provide OCTOPUS source data worksheets and sites can also include hospital records, clinical and office charts, laboratory notes, imaging, and pharmacy dispensing records.

Source data should be attributable, legible, contemporaneous, original, accurate, and complete. Changes to source data should be traceable, should not obscure the original entry, and should be explained if necessary (e.g., via an audit trail). Each data element should only have one source.

For this trial, the eCRFs will not be the source document for any data elements. However, OCTOPUS source data worksheets can be utilised.

A source data agreement will be put in place as part of the green light process with each site. This agreement will define the source documents and the data therein, together with location of these source documents and any applicable plans for transmission of source data between the site and the Sponsor/delegated institution.

The following data should all be verifiable from source documents, which may include paper notes, worksheets and electronic health records:

- Signed consent forms
- Dates of visits including dates any trial specimens were taken and processed in the laboratory
- Eligibility and screening values
- Adverse events of any grade that lead to treatment modification and adverse events judged definitely/probably/possibly related to IMP
- Severe (grade 3/4) adverse events
- Serious adverse events
- All CROMs
- All PROMs – if completed on paper, these may be scanned, electronic or paper versions of the completed questionnaires
- Dates IMP were drug dispensed and (if necessary) drugs returned
- Pharmacy or clinic IMP accountability and prescription logs.

9 STATISTICAL CONSIDERATIONS

This trial will be a multi-arm multi-stage (MAMS) platform trial that will adapt and develop with the likelihood of adding more arms as it progresses. As such, there are currently two distinct stages to the trial and a statistical analysis plan (SAP) will be produced for both Analysis Stage 1 and Analysis Stage 2 unblinded analysis and agreed by the Independent Data Monitoring Committee (IDMC) and Trial Steering Committee (TSC).

The statistical analysis will be based on all participants as randomised, irrespective of subsequent adherence with the allocated treatment (a 'treatment policy' strategy for handling non-adherence to the randomised arm). A per protocol analysis restricted to participants who received their randomised intervention as specified will also be conducted. A CONSORT diagram will be used to describe the course of participants through the trial. Baseline characteristics will be summarised by randomised group. Continuous variables will be summarised using summary statistics (mean, standard deviation, median, minimum, and maximum) by treatment group, and categorical variables will be presented using frequency distributions by treatment group.

9.1 METHOD OF RANDOMISATION

Randomisation will be performed by the PI or delegated member of the clinical team at local sites using the OCTOPUS eDC system. Each participant will be randomised using their unique participant identification number that was allocated sequentially at screening. Eligibility and consent will be verified before each participant is randomised. Trial arm allocation into the three treatment arms or SOC (1:1:1) will use minimisation with a random element, where there is a probability of allocation to the minimised group will be 0.75. The minimisation will consider these factors:

- Sex
- Age
- Baseline measure EDSS
- Use of current DMT
- PMS phenotype
- Recruiting site

Randomisation with minimisation will ensure comparability of the two trial arms on these characteristics.

DSMS-generated unique identifier bottle numbers are used to identify every bottle of trial treatment. The bottle numbers will be provided to Sharp Clinical who will ensure that trial treatment is labelled appropriately, and that the trial team and participants remain blind to treatment allocation. The drug will be dispensed at randomisation and subsequent clinic follow-up visits. A delegated member of the site team will enter the participant's unique participant identification number into DSMS, which will then provide the bottle number of the trial treatment to be dispensed. Enough trial treatment will be provided to each site to ensure availability of adequately labelled bottles for Pharmacy dispensing.

Following Analysis Stage 1, participants from any treatment group dropped at the analysis stage for reasons of limited efficacy will be given the opportunity to be 're-randomised' to any extant trial arms, providing they still meet the eligibility criteria. The randomisation method described above will still apply to those being re-randomised.

9.2 OUTCOME MEASURES

9.2.1 ANALYSIS STAGE 1 PRIMARY OUTCOME MEASURE: WHOLE BRAIN ATROPHY

Whole Brain Atrophy (SIENA technique) will be used to measure atrophy rates on MRI performed at four time points: M0 (randomisation), M6 (week 26), M18 (week 78) and M24 (week 104). SIENA provides a directly measured change in brain volume between a pair of MRI scans on the same participant. Therefore, in total there will be six measurements of whole brain atrophy for each trial participant showing change between:

- M0 and M6
- M0 and M18
- M0 and M24
- M6 and M18
- M6 and M24
- M18 and M24

Analysis will quantify atrophy rate in each arm using changes between all pairs of scans (see brief analysis plan for the model that will be used). However, if pseudoatrophy is identified in an active arm(s) (randomisation to week 26 (M0-M6) MRI), analysis will use data from the scans at M6 (week 26) and M24 (week 104) and be based only on the change between:

- M6 and M18
- M6 and M24
- M18 and M24

9.2.2 ANALYSIS STAGE 1 SECONDARY OUTCOME MEASURES: MRI

- Regional GM atrophy rate
- Cervical cord atrophy rate
- T2 lesion volume change

9.2.3 ANALYSIS STAGE 1 SECONDARY OUTCOME MEASURES: CLINICIAN AND PATIENT REPORTED OUTCOMES

The clinician-reported secondary outcome measures will be:

1. Time to initial disability progression²

² Progression must be confirmed at least 26 weeks later

2. Expanded Disability Status Scale (EDSS)
3. Timed 25 Foot Walk (T25FW)
4. 9 Hole Peg Test (9HPT)
5. Symbol Digit Modalities Test (SDMT)
6. MS Functional Composite Z score comprising of the following:
 - a. Timed 25 Foot Walk (T25FW)
 - b. 9 Hole Peg Test (9HPT)
 - c. Symbol Digit Modalities Test (SDMT)
7. Sloan Low Contrast Visual Acuity (SLCVA)
8. Relapse rate

The patient-reported secondary outcome measures will be:

1. Multiple Sclerosis Impact Scale v2 (MSIS29v2)
2. Multiple Sclerosis Walking Scale v2 (MSWSv2)
3. Fatigue (MFIS-21 and CFQ)
4. Pain Assessment (Neuropathic Pain Scale and overall pain intensity)

9.2.4 ANALYSIS STAGE 2 PRIMARY OUTCOME MEASURES

The primary outcome measure is time to initial disability progression. The initial disability progression event is finalised as positive if disability is sustained and confirmed ≥ 6 months (i.e. 26 weeks) later. This is termed confirmed disability progression (CDP).

Progression will be defined as presence of at least one of the following changes from the randomisation visit: increase in EDSS (of at least 1 point if baseline measure EDSS was < 5.5 or of at least 0.5 points if baseline measure EDSS was ≥ 5.5); $\geq 20\%$ increase in 9HPT; and $\geq 20\%$ increase in T25FW (if ambulant). Progression will be considered confirmed where progression from baseline on the same element of the composite is maintained at the next study visit at least 6 months later (e.g., two consecutive visits with $\geq 20\%$ increase in 9HPT compared to baseline). The composite will be measured at randomisation and 6-monthly thereafter until the end of the follow-up (up to a maximum of 5 years for participants included in both Analysis Stages 1 and 2). The time of the event will be from randomisation until date of the initial disability progression (if subsequently confirmed) with administrative censorship at 5 years post-randomisation.

9.2.5 ANALYSIS STAGE 2 SECONDARY OUTCOME MEASURES: CLINICIAN AND PATIENT REPORTED OUTCOMES

The clinician and patient-reported secondary outcome measures will be:

1. Expanded Disability Status Scale (EDSS)
2. Timed 25 Foot Walk (T25FW)
3. 9 Hole Peg Test (9HPT)
4. Symbol Digit Modalities Test (SDMT)
5. MS Functional Composite Z score comprising of the following:

- a. Timed 25 Foot Walk (T25FW)
 - b. 9 Hole Peg Test (9HPT)
 - c. Symbol Digit Modalities Test (SDMT)
6. Sloan Low Contrast Visual Acuity (SLCVA)
 7. Relapse rate

The patient-reported secondary outcome measures will be:

1. Multiple Sclerosis Impact Scale v2 (MSIS29v2)
2. Multiple Sclerosis Walking Scale v2 (MSWSv2)
3. Fatigue (MFIS-21 and CFQ)
4. Pain Assessment (Neuropathic Pain Scale and overall pain intensity)

The health related quality of life and resource use outcome measures will be:

1. EQ-5D-5L Health Questionnaire
2. Client Services Receipt Inventory (CSRI)

9.3 SAMPLE SIZE

9.3.1 ANALYSIS STAGE 1: R/S-ALPHA LIPOIC ACID AND METFORMIN

The sample size for analysis stage 1 evaluation of R/S-ALA and metformin has been calculated for analysis of whole brain atrophy [102]. The calculations assume an atrophy rate of 0.55% per year in the control arm and standard deviation of 0.55% per year at week 78, based on data from previous trials [18-20, 41, 103-105]. In addition, the trial is targeting a 0.15% per year reduction in the rate of whole brain atrophy, equating to a proportional reduction of 33%. Power for this analysis must be high, to minimize the risk of rejecting a genuinely active treatment at this stage. This is achieved by relaxing the alpha (i.e. accepting a higher false positive rate), which is appropriate for this first stage. To achieve 95% power, with a one-sided alpha of 0.35 acting as the threshold for a lack of benefit, 125 participants per arm are required (375 participants in total) after allowing for 11% drop-out.

Since each treatment is being compared only against the control arm and given that the selected drugs are from different mechanistic classes, we do not propose to adjust the type I error rate for multiple comparisons [106, 107]. However, allowance for multiple comparisons will be considered if later addition to the platform includes drugs of similar mechanistic action (for example, different doses or treatment combinations of drugs being used in other arms).

It is noted that there is some uncertainty around the assumption about standard deviation and, as such, a review of emerging data from the control arm is planned, at which point the sample size calculation will be reviewed and the alpha level may be adjusted by the TMG in agreement with the

TSC and IDMC to 0.40. This will be to ensure that the 95% power can be achieved with the planned sample size.

9.3.2 ANALYSIS STAGE 2

For the final Analysis Stage 2, sample size was determined on the basis of achieving an estimated 90% power to detect a treatment effect corresponding to hazard ratio (HR) of 0.75 (25% relative reduction) at the conventional 5% significance level. This requires 281 progression events to be observed in the control arm. It is anticipated that this will be achieved by recruiting 600 participants per arm over approximately 5 years (a total of 1,200 participants, assuming one active arm passes Analysis Stage 1) and following them up for a minimum of 1.5 years (maximum 5 years) after randomisation. This number will include those recruited to Analysis Stage 1, since all participants contribute to the final analysis, and accounts for some loss to follow-up (see below).

A 25% relative reduction is a realistic treatment effect to target, which is also likely to be clinically meaningful. The sample size calculation has been made on the assumption of proportional hazards and that 50% of participants in the control arm will have a primary outcome progression event by 3 years, based on review of previous studies[18, 19, 40, 41, 103, 104]. At this progression rate a 25% relative reduction would equate to 9% absolute difference in progression by 3 years (50% control vs 41% active treatment). The calculations also assumed a degree of loss to follow-up: 5% in the first 6 months and 1% per 6 months thereafter, equating to 10% at 3 years. As noted below, the primary analysis will be undertaken using intention to treat (ITT) principles such that those who have discontinued trial treatment will still be included in the analysis. The target treatment effect of 25% relative reduction in confirmed progression is a pragmatic estimate that anticipates that some participants will not fully comply with taking trial treatment. In MS-STAT1, there was a lack of compliance with randomised treatment in approximately 20% of participants, which is similar to compliance figures from published phase 3 trials[17, 19, 20, 105]. With 80% compliance, an ITT treatment effect of 25% relative reduction would be equivalent to around a 30% relative reduction in those who fully adhere to the treatment regime.

Since each treatment is being compared only against the control arm and given that the selected drugs are from different mechanistic classes, we do not propose to adjust the type I error rate for multiple comparisons[106, 107]. However, allowance for multiple comparisons will be considered if later addition to the platform includes drugs of similar mechanistic action (for example, different doses or treatment combinations of drugs being used in other arms).

9.4 MONITORING & ANALYSES

An IDMC Charter will be drawn up that describes the membership of the IDMC, relationships with other committees, terms of reference, decision-making processes, the timing and frequency of monitoring reports and details of stopping rules for Analysis Stage 1. Please refer to [section 14](#).

9.5 ANALYSIS PLAN (BRIEF)

The analyses will be described in detail in full Statistical Analysis Plans for Analysis Stage 1 and Analysis Stage 2. The SAP will detail the statistical methods in both Analysis Stage 1 and Analysis Stage 2 used for description of demographic and baseline characteristics, assessing treatment compliance, evaluation of effectiveness of the treatments on primary and secondary outcomes, and evaluation of safety. This section summarises the main issues.

9.5.1 ANALYSIS STAGE 1

For the Analysis Stage 1 for R/S-ALA and metformin treatments, whole brain atrophy rates will be assessed as a continuous variable with pairwise comparisons of each experimental arms vs control. Data will be used on atrophy measured between pairs of MRI scans taken at randomisation, week 26 and week 74 for all participants and additionally from MRI at 104 weeks, for the participants who have reached this visit (anticipated to be approximately 50% of participants at the time of Analysis Stage 1).

Mean rates of whole brain atrophy will be analysed using the family of linear mixed models developed for the analysis of repeated direct measures of change [108] with adjustment for the minimisation variables. All participants with at least one measure of atrophy (i.e. have at least one follow-up scan) will be included. This model uses the repeated measures of whole brain volume change between each pair of scans to estimate the mean atrophy rate in each arm by fitting an interaction between treatment group and duration between each pair of MRI scans. It similarly allows for the effect of the minimisation variables on atrophy rate by including their interactions with duration. Random effects are used to account for the expected correlation structure between repeated direct measures of brain volume change from the same participant. Estimated treatment effects will be presented with confidence intervals corresponding to the alpha level at Analysis Stage 1. Based on previous trial data [102], it is anticipated that atrophy will follow a normal distribution and that the assumptions for the linear mixed model will be met. However, assumptions will be assessed using plots of model residuals and if they are materially violated non-parametric methods will be used for inference (e.g. bootstrap confidence intervals).

The analysis will focus on the 'treatment policy' estimand (an intent-to-treat analysis), with the impact of non-compliance assessed in a pre-specified sensitivity analyses that targets the 'hypothetical' estimand, where the treatment effect in the absence of non-compliance is estimated.

As for the Analysis Stage 2, full details will be pre-specified in the statistical analysis plan, including any analysis of secondary outcomes at this time.

Safety outcomes (AE, AR, SAE, SAR, SUSAR etc.) as described in [section 7](#) for each arm will be tabulated by randomised group at the Analysis Stage 1 as part of the decision made by the IDMC of whether a treatment will progress to Analysis Stage 2. However, as OCTOPUS is using repurposed established drugs, additional formal stopping rules based, for example, on SUSAR rates or toxicities are not proposed.

9.5.2 ANALYSIS STAGE 2

The primary outcome for the final (Analysis Stage 2) analysis will be analysed as a time-to-event variable, measuring time from randomisation to confirmed progression. This is defined as at least one of the following changes from randomisation (confirmed at 6 months): increase in EDSS (of at least 1 point if baseline measure EDSS was <5.5 or of at least 0.5 points if baseline measure EDSS was ≥ 5.5); $\geq 20\%$ increase in 9HPT; and $\geq 20\%$ increase in T25FW between the drug and standard of care arms. Observations will be censored for participants without an event, including for those who have withdrawn from trial where unable to continue, been lost to follow-up or have died due to causes other than MS (on the date of final/most recent follow-up visit or date of death). Death due to MS would count as a confirmed progression event as this would be an EDSS score of 10.

Standard methods for analysing time-to-event data will be employed to assess a pairwise comparison of each experimental treatment versus placebo. A Cox proportional hazards model will be used with adjustment for the minimisation factors, and HRs (with 95% confidence intervals) will be presented, along with Kaplan Meier curves. Stratification by 'randomisation availability' will be used if there were any recruits who were only available for randomisation between two arms (an active arm versus control) rather than the full set of three study arms. The assumptions underlying the Cox model will be assessed and if there is clear evidence of non-proportionality, relevant alternative methods for reporting the treatment effect, such as the difference in restricted mean survival time (RMST), will be employed. Since death from MS is included as a progression event, competing risks are not expected to be an issue in this population who have established progressive disease.

The primary analysis will be performed on an intention-to-treat (ITT) basis, including all participants according to their allocated treatment. However, sensitivity analyses will be pre-specified to assess the impact of non-compliance.

9.5.3 HEALTH ECONOMIC ANALYSIS PLAN/EVALUATIONS

9.5.3.A Cost Utility

A treatment that slows progression could represent a highly cost-effective use of NHS resources with the high costs of SPMS and very low cost of these IMPs. An economic evaluation will be conducted to calculate the mean incremental cost per quality adjusted life year (QALY) gained from the perspective of the NHS and personal social services. The incremental cost per QALY gained will be estimated for:

- a) the 'within trial' period using patient level data
- b) for the lifetime of the patient using a cohort model based approach.

The lifetime model will take the form of a Markov model using EDSS states, including an absorbing state of death, to model the progression of patients beyond the trial period. Both within-trial and lifetime analyses will include a secondary wider cost perspective that will include the cost of the impact on carers, absenteeism and out-of-pocket costs

9.5.3.B Resource Use Data

Patient resource use will be assessed using a self-complete resource use form, the Client Services Receipt Inventory (CSRI) and SAEs recorded as part of the trial. The CSRI will be modified to capture resource use most pertinent to SPMS and will be administered at randomisation and 26-weekly

intervals asking about the previous 26 weeks. The CSRI will include primary care, specialist MS related secondary care, paid and un-paid carer time, work absenteeism and complimentary therapies.

9.5.3.C Utility and Quality Of Life Data

QALYs will be estimated, 6 monthly, using the EQ-5D-5L using the area under the curve approach [97, 101]. Utility scores will be calculated using UK-specific tariffs and adjusting for baseline differences in patients in the trial arms if necessary. In addition, given current uncertainties regarding the appropriateness of the EQ-5D-5L for people with SPMS [109], the MSIS-29v2[76], a condition-specific measure will be considered for estimating QALYs through methods available in the literature[110].

9.5.3.D Within-Trial Analysis

The within-trial economic evaluation will estimate cost-effectiveness of the intervention compared to control for the trial period. We will estimate results as the incremental cost-effectiveness ratio where data will be drawn as far as possible from the trial. Confidence intervals for mean costs and QALYs will be calculated using a non-parametric bootstrap with replacement. The results of the non-parametric bootstrap will be presented on a cost-effectiveness plane. The bootstrap replications will be used to construct a cost-effectiveness acceptability curve, which will show the probability that the intervention is cost-effective for different values of QALY thresholds. Appropriate methods for dealing with missing trial data such as multiple imputation will be applied. Methods will be described in a detailed economic evaluation analysis plan and presented for approval by the TSC.

9.5.3.E Model Based Analysis

A model-based analysis will be undertaken to estimate costs and benefits over the lifetime horizon of the patient to capture the progression of the condition beyond the trial period. As for the within-trial analysis, the reported outcome will be the incremental cost-effectiveness ratio (ICER). The analysis will be based primarily on the trial data and will model predicted costs and QALYs according to EDSS states using a Markov model. This approach will allow the progression of the condition to be simulated through different health states over time and changes in costs and health related quality of life to be estimated. Data to populate the model will be obtained from the trial and from published sources. Utilities and transition probabilities for each EDSS defined health state will be derived from trial data and from the literature where appropriate.

Good practice guidelines for economic evaluations will be used for the analysis[110]. Long term costs and health outcomes will be discounted using discount rates recommended by NICE[111].

10 ANCILLARY STUDIES

10.1 BIOREPOSITORY

A repository of biological samples from participants will be created. Participation in the bio-repository will be optional for all participants. The purpose of the biorepository is so that biomarker, mechanistic discovery-driven studies can be conducted to evaluate for predictors of clinical endpoints including treatment response, with the ultimate goal of individualising treatment approach in MS.

The samples to be collected will include:

- 2 red-top tubes (coated, anti-coagulant-free vacutainer[®] for serum) at randomisation and 26-weekly thereafter
- 1 purple top tube (EDTA vacutainer[®] for DNA/plasma), at any one single time point throughout the study
- 1 purple top tube (EDTA vacutainer[®] for DNA/plasma) at randomisation and 26 weekly thereafter

One purple top tube that will be for DNA extraction will be shipped immediately to the Welsh Neuroscience Research Tissue Bank (WNRTB) in Cardiff, Wales, UK. All other samples will be stored locally at site short-term. They will be shipped on a regular basis for long term storage within a central repository within the Welsh Neuroscience Research Tissue Bank, in Cardiff, Wales, UK.

Participants will be allowed to opt-out of the collection of their biosamples for the biorepository. The option to opt out will be included in the informed consent and participant information sheet.

Participants who originally opt-in to having their biosamples collected for the biorepository can withdraw their consent for future sample collection, sample sharing, and use at any time, without penalty or loss of benefits to which they are otherwise entitled. If a participant does decide to withdraw this consent, the OCTOPUS team should be informed of this and a discussion should be held between the site and the OCTOPUS team. The withdrawal of consent will only apply to future collection, sharing, and use, not retrospectively, due to the difficulty in tracking down and removing samples and relevant data.

Further details on collection, transport and storage will be provided in the Biobank manual of operations.

Funding for 120 participants at the randomisation visit, week 26, week 52 and week 78 has been confirmed. Further funding will be sourced for the remainder of the timepoints and for additional participants.

10.2 BIOREPOSITORY GOVERNANCE

The OCTOPUS biorepository will be governed by the OCTOPUS TMG until the end of trial, as defined in [section 11.5.3](#). After the end of the trial, the governance and ownership of the biorepository will be transferred to the WNRTB. After trial completion the biorepository will be open to the general research community. Proposals for use will be reviewed by the TMG and Trial Steering Committee (TSC) and prioritised given the finite nature of the specimens. At the conclusion of the review process, three outcomes for specimen use requests are possible:

1. Approval. However, even after a specimen use committee approval, the release of biospecimens may be withheld for programmatic considerations.
2. Re-evaluation. This intermediate category is for well-written applications but for which a) there is unclear significance with respect to the priorities set forth, or b) there are other potentially addressable issues raised by the committee. Applicants will be provided the opportunity to respond to concerns raised by the committee. The application may be re-submitted or, at the recommendation of a committee member, re-addressed by the committee at future review the committee will make a final decision after one or, at most two, re-submissions.
3. Disapproval. The proposal for use is rejected.

Unless exempted by the TMG, funding must be provided by the requesting investigator for preparation and shipping of samples and, if relevant, for extraction of corresponding clinical data. Failure to provide funding within an agreed-upon time frame may result in revocation of the approval. Sharing of the results obtained from the measures conducted under approved biospecimen use requests will be required within an agreed-upon time frame. Failure to conduct the proposed studies within an agreed-upon time frame will lead to the requirement to return the samples and revocation of the approval.

11 REGULATORY & ETHICAL ISSUES

11.1 COMPLIANCE

11.1.1 REGULATORY COMPLIANCE

OCTOPUS will be conducted in compliance with the approved protocol, the Declaration of Helsinki 1996, the principles of Good Clinical Practice (GCP) as laid down by the ICH topic E6 (R2), Commission Clinical Trials Directive 2005/28/EC* with the implementation in national legislation in the UK by Statutory Instrument 2004/1031 and subsequent amendments, the UK Data Protection Act 2018 (DPA number: Z6364106), and the UK Policy Framework for Health and Social Care Research.

11.1.2 SITE COMPLIANCE

An agreement will be in place between the site and the CTU, setting out respective roles and responsibilities (see [Section 2](#)).

All sites will inform the OCTOPUS Team as soon as they are aware of a possible serious breach of compliance, so that the Trials Unit can report this breach if necessary within 7 days as per the UK regulatory requirements. For the purposes of this regulation, a 'serious breach' is one that is likely to affect to a significant degree either:

- The safety or physical or mental integrity of the participants in the trial
- The scientific value of the trial

11.1.3 DATA COLLECTION & RETENTION (ARCHIVING)

Worksheets (used as source data for eCRFs), clinical notes and administrative documentation should be kept in a secure location (for example, locked filing cabinets in a room with restricted access) and archived for a minimum of 25 years after the end of the trial. During this period, all data should be accessible, with suitable notice, to the competent or equivalent authorities, the Sponsor, MRC CTU at UCL and other relevant parties in accordance with the applicable regulations. The data may be subject to an audit by the competent authorities. Medical files of trial participants should be retained in accordance with the maximum period of time permitted by the hospital, institution or private practice.

11.2 ETHICAL CONDUCT

11.2.1 ETHICAL CONSIDERATIONS

- Participants are required to attend for additional visits to their normal standard of care. This is for safety and trial conduct. Participants will be seen 5 times in first year and twice yearly thereafter compared to once per year or less in standard care.
- For safety and trial conduct, participants will have regular blood tests and 4 MRI scans (primary outcome of Analysis Stage 1), which is over and above standard care.
- Use of placebo and when and/or whether its use would be revealed. The trial is placebo controlled and can be seen as receiving no drug by participants. This could lead to reduced compliance. It will be confirmed to all participants they will also be receiving their current care

standard. This will be expanded in the PIS. After the final Analysis Stage 2, it would be appropriate to reveal the arm the participants were randomised to.

- Washout period after trial treatment will be 26 weeks to avoid any residual biological activity. After washout (if appropriate) a participant can be re-randomised into the trial.
- The IMP are re-purposed with excellent safety records. The possible side-effects and mitigations are describe in [section 5.6](#).
- Participants will be reimbursed for travel expenses (up to £40 per visit)
- The collection of sensitive or personal samples will not occur without informed consented and samples will be pseudo-anonymised
- Publication of data and feedback of overall results (not individual results) to participants
- Coincidental findings: blood tests may uncover some other previously unknown condition. If these are uncovered by the trial, these will be communicated back to their Primary Care physician if felt appropriate.
- Coincidental findings: MRI may uncover some other previously unknown condition. These will be communicated back to the participant's local team and managed as per local processes.

Steps that have been taken to minimise these issues should be included within the Risk Assessment and other Quality Management Documents. Any issues raised here should be included in the participant information sheet.

11.2.2 FAVOURABLE ETHICAL OPINION

Following Main REC approval and Health Research Authority (in England) approvals and before initiation of the trial at each clinical site, the protocol, all informed consent forms, and information materials to be given to the prospective participant will be submitted to each Trust's Research and Development (R&D) office. In Wales, Scotland and Northern Ireland, the R&D office will be asked to give approval. In England, the R&D office will be asked to confirm capacity and capability. Any further substantial amendments will be submitted and approved by the Main REC and HRA.

If further sites in non-UK countries do participate in later stages, the national ethics requirements for those countries will also be required.

OCTOPUS has been developed with Patient and Public Involvement (PPI) to ensure that its design is feasible and acceptable to potential participants, and to ensure its outcomes and potential impact are relevant to the population who may benefit from its results. PPI also helps to ensure transparency and accountability throughout this research. PPI activity will continue for the duration of the study, including dissemination of study results.

The rights of the participant to refuse to participate in the trial without giving a reason must be respected. After the participant has entered into the trial, the clinician must remain free to give alternative treatment to that specified in the protocol, at any stage, if he/she feels it to be in the best interest of the participant. The reason for doing so, however, should be recorded; the participant will remain within the trial for the purpose of follow-up and for data analysis by the treatment option to

which they have been allocated. Similarly, the participant must remain free to change their mind at any time about the protocol treatment and trial follow-up without giving a reason and without prejudicing his/her further treatment.

11.3 COMPETENT AUTHORITY APPROVALS

This version of the protocol has been submitted and reviewed by the MHRA in the UK, prior to protocol release (see CTA number on front cover). If further sites in non-UK countries do participate in later stages, the national competent authority in those countries will review the current OCTOPUS protocol.

This is a Clinical Trial of an Investigational Medicinal Product (IMP) as defined by the EU Directive 2001/20/EC. Therefore, for this version of the protocol a CTA is required in the UK.

The EudraCT number for the trial is 2021-003034-37.

The progress of the trial and safety issues will be reported to the MHRA in accordance with local requirements and practices in a timely manner. Safety reports, including expedited reporting and SUSARS will be submitted to the competent authority in accordance with each authority's requirements in a timely manner.

11.4 OTHER APPROVALS

The protocol will be submitted by those delegated to do so to the relevant R&D department of each participating site or to other local departments for approval as required in each country. A copy of the C&C (or other relevant approval as above) and of the PIS and Consent Form (CF) on local headed paper should be forwarded to the CTU before participant are entered.

11.5 TRIAL CLOSURE

11.5.1 CLOSURE OF ARMS INCLUDING AT ANALYSIS STAGE 1

At Analysis Stage 1, a decision will be made to determine which arms will proceed into Analysis Stage 2. Applicable arms will close if it is decided to no longer proceed with them. Therefore in this case or for the closure of other arms, all participants in the applicable arm(s) will be notified to stop taking any trial treatment, and complete a final follow-up visit at which they will discuss the decision and potential options for re-randomisation (allowed 26 weeks post last dose of trial treatment). No further requirement for safety reporting is required following arm closure for participants on that arm. Any subsequent events that may be attributed to trial treatment should be reported to the MHRA using the yellow card system.

Further linkage for long-term analysis for these participants may occur through the MS Register for participants who have consented for their data to be used.

11.5.2 END OF ANALYSIS STAGE 2

At the end of Analysis Stage 2, all participants in any remaining arms will be notified of the trial's decisions and have complete their final trial follow-up visit, at which there will be a discussion on their future treatment. This will be their final trial follow-up visit and no further safety reporting is required. Any subsequent events that may be attributed to trial treatment should be reported to the MHRA using the yellow card system.

11.5.3 END OF TRIAL DEFINITION

The OCTOPUS end of trial definition is when all arms are closed and all the data entered into the OCTOPUS eDC system, and once the database is checked and locked. Closure will be notified to MHRA, main ethics and each R&D department according to local applicable laws and regulations.

12 INDEMNITY

The sponsor of the trial is the University College London (UCL). OCTOPUS is co-ordinated by the MRC CTU at UCL.

UCL holds insurance against claims from participants for injury caused by their participation in this clinical trial. Participants may be able to claim compensation if they can prove that UCL has been negligent. However, as this clinical trial is being carried out in a hospital, the hospital continues to have a duty of care to the participant of the clinical trial.

UCL does not accept liability for any breach in the hospital's duty of care, or any negligence on the part of hospital employees. This applies whether the hospital is an NHS Trust or otherwise. Participants may also be able to claim compensation for injury caused by participation in this clinical trial without the need to prove negligence on the part of UCL or another party. Participants who sustain injury and wish to make a claim for compensation should do so in writing in the first instance to the Chief Investigator, who will pass the claim to the UCL's Insurers, via the UCL office.

Hospitals selected to participate in OCTOPUS must provide clinical negligence insurance cover for harm caused by their employees and a copy of the relevant insurance policy or summary can be provided on request.

13 FINANCE

OCTOPUS (Optimal Clinical Trials Platform for Progressive Multiple Sclerosis) is funded by UK MS Society (reference 135) and UCL.

All Trial treatment (or IMPs) will be provided. Participants will be reimbursed for trial travel expenses. Sites will also receive payments for the MRI scans acquisition costs and to cover other research activity costs. This will be documented in the non-commercial model agreement (mCTA) that will be in place between UCL and each participating site.

OCTOPUS is included in the UKCRN portfolio and support will be available for participating UK centres in the usual way.

14 OVERSIGHT & TRIAL COMMITTEES

There are a number of committees involved with the oversight of OCTOPUS. These committees are detailed below, and the relationship between them expressed in [Figure 11](#).

14.1 TRIAL MANAGEMENT GROUP (TMG)

A TMG has been formed comprising the Chief Investigator, other lead investigators (clinical and non-clinical) and members of the MRC Clinical Trials Unit (CTU) OCTOPUS Team, PPI contributors and a representative of the funder, UK MS Society. The membership of the TMG may be expanded if other groups of trialists wish to participate. It will also be amended during the trial if other circumstances require e.g. retirement.

The Trial Management Team (TMT) will perform the day-to-day management of the trial. The TMG will be responsible for the operational oversight and management of the trial. A TMG will meet by teleconference approximately monthly and in person if needed. The full details can be found in the TMG Charter.

The TMG has a number of TMG sub-groups, each comprising of specific members of the TMG, MRC CTU at UCL, field experts and other OCTOPUS clinicians and site staff. The groups are all chaired by TMG members and report directly into the TMG.

- The **Recruitment and Retention Group** provide expert oversight of recruitment and retention. This includes set-up and oversight of the MS Register and input from MS Society PPI forums where required.
- The **MRI Group** coordinates the collection, assessment and storage of MRI scans by UCL Queen Square Institute of Neurology, MS Unit.
- The **Treatment Advisory Committee (TAC)** are responsible for recommending treatments and related dosing to enter the OCTOPUS.
- The **Statistical Group** co-ordinates the statistical input and analysis for the trial.
- The **Biofluids and Biomarker Group** inputs and provides expert oversight of relevant translational aspects of the trial, associated sub-studies and future projects.

14.2 TRIAL STEERING COMMITTEE (TSC)

The Trial Steering Committee (TSC) has membership from the TMG plus independent members, including the Chair and PPI contributors. The role of the TSC is to provide overall supervision for the trial and provide advice through its independent Chair. The ultimate decision for the continuation of the trial lies with the TSC. Further details of TSC functioning are presented in the TSC Charter.

14.3 (INDEPENDENT) DATA MONITORING COMMITTEE (IDMC)

An Independent Data Monitoring Committee (IDMC) will be formed. The IDMC will be the only group who sees the confidential, accumulating data for the trial. Reports to the IDMC will be produced by the CTU statisticians. The IDMC will meet within 6 months after the trial opening; the frequency of meetings will be dictated in the IDMC charter. The IDMC will consider data using the statistical analysis plan (see [section 9.5](#)) and will advise the TSC. The IDMC can recommend premature closure or reporting of the trial, or that recruitment to any research arm be discontinued. Further details of IDMC functioning and the procedures for analysis and monitoring are provided in the IDMC Charter.

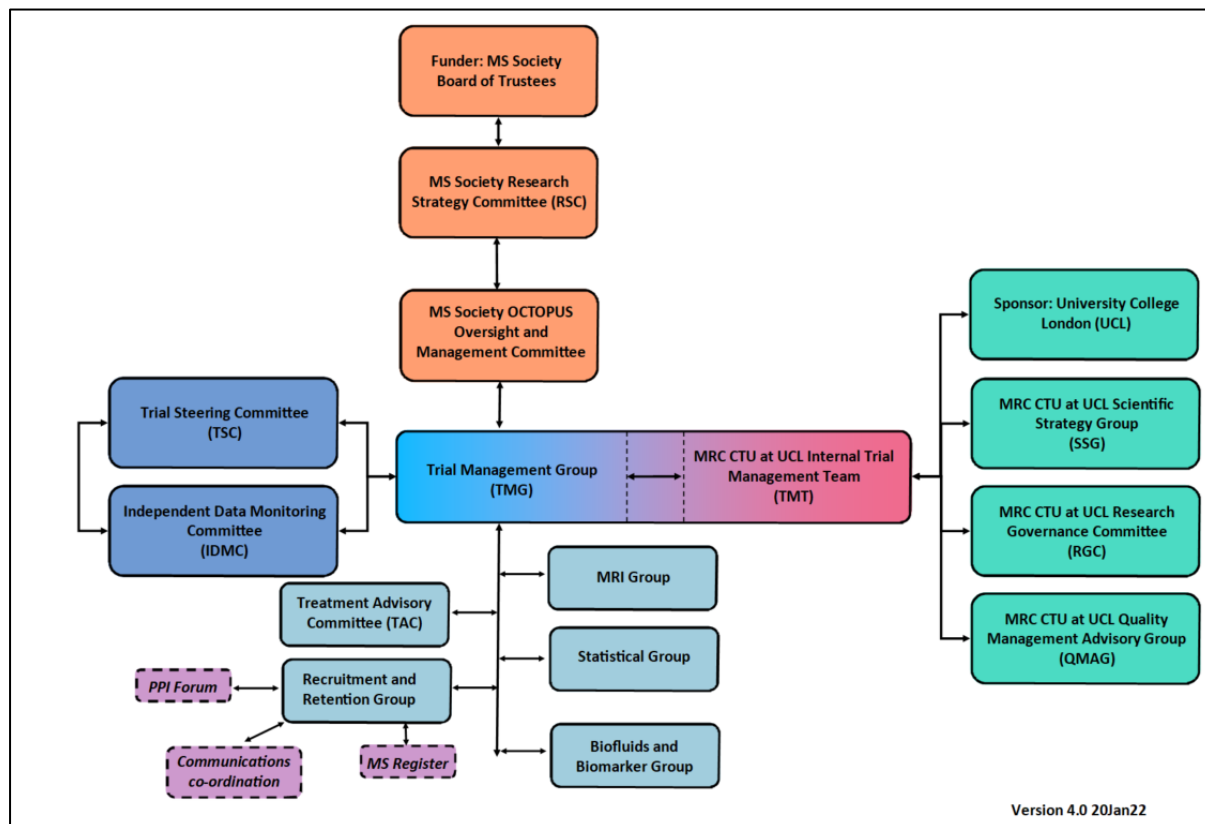
14.4 ROLE OF STUDY SPONSOR

University College London is the sponsor of OCTOPUS. It is the employer of the staff coordinating the trial at the MRC CTU at UCL. The MRC CTU at UCL is delegated Sponsor responsibilities for the trial.

14.5 MRC CTU AT UCL INTERNAL GROUPS

MRC CTU at UCL requires a number of internal working groups to run a platform protocol. These internal groups assist the TMT (or OCTOPUS Team) in the operation of OCTOPUS, providing guidance on scientific strategies of research and publication, research governance in regulatory information and protocol review and the management of research quality within OCTOPUS.

Figure 11: Relationship of trial committees



15 PATIENT AND PUBLIC INVOLVEMENT

Patient and Public Involvement (PPI) in research is defined by INVOLVE (an advisory group established by the NIHR) as research being carried out ‘with’ or ‘by’ members of the public rather than ‘to’, ‘about’ or ‘for’ them. INVOLVE intends ‘public’ to include participants, potential participants, carers and other users of health and social care services, as well as people from organisations that represent people who use services. In some cases, this may include involvement of a trial’s participants in guidance or oversight of a trial.

People affected by MS have been actively involved since the earliest study concept meeting in 2018, participating in sub groups considering the trial design, means of recruitment and communication and the selection of treatments. Focus groups led by the UK MS Society were also held with PwPMS throughout the UK to understand their views on the same topics. These consultations have led directly to:

- the wide inclusion criteria with respect to disability and age
- to the selection of a composite disability measurement score to take account of People with MS (PwPMS) who are wheelchair users and need to preserve arm and hand function for as long as possible
- to the option to allow participants who initially receive an ineffective treatment to be re-randomised to the trial following an appropriate wash-out period and
- to a website for PwPMS to register their interest in participating in the trial

The UK MS Society has been an integral partner throughout the study concept development, is a full member of key trial committees, provided seed funding for trial development work, approved the co-applicants study proposal and is the majority funder for the Octopus trial.

15.1 POTENTIAL IMPACT OF PPI

Involving people affected by MS has strengthened the quality and relevance of the design and will continue to impact the management of OCTOPUS. PwMS and their care givers offer unique insights from their lived experience that enhance the expert knowledge of our clinicians and researchers.

PPI is an essential component of all aspects of the research process, and has already been embedded in the preparatory work for OCTOPUS. Beginning at the development of the hypothesis, through the grant application process to design of the protocol. PPI has ensured that when applying for the funding the opinions of PwMS have been forefront of project.

PPI ensures that PwMS are made aware of the OCTOPUS trial. It ensures that recruitment is timely; news about the trial progress is given to appropriate forums; dissemination of research findings; and implementation of those findings into clinical practice.

15.2 PATIENT AND PUBLIC INVOLVEMENT ADVISORY GROUPS

OCTOPUS has have a number of panels, oversight committees and TMG working groups associated with it as described in the previous section (see [Figure 11](#)). There is active involvement of people affected by MS in each group, where appropriate.

One person who is personally affected by MS is a co-applicant on the programme grant and a member of the Trial Management Group and has been involved from the start of the project. A further three people affected by MS form part of the Treatment Advisory Committee (TAC).

Further PPI members who are affected by MS will sit on the following committee and TMG working groups:

- Trial Steering Committee (TSC)
- MRI Group
- Biofluids/Biomarker Group

There is also a specific PPI Forum for OCTOPUS set up by the UK MS Society. The forum has regular scheduled meetings and ad-hoc meetings as issues arise that it would be useful to discuss with the group.

15.3 IDENTIFYING PPI CONTRIBUTORS

PPI members are identified through the MS Society's Research Network. Role descriptions for these groups were developed and are advertised in an email to Research Network members when positions become available. Interested members are asked to apply to the roles by answering a few questions about their motivations, experience and any relevant skills they feel they can bring to the role. The Public Involvement Manager at the MS Society recruits to the role based on the applications whilst ensuring the group is diverse in terms of type of MS, gender, ethnicity and location.

All PPI members are supported by the MS Society Public Involvement Manager, a member of the OCTOPUS team at the MRC CTU at UCL, and the UCL QSMSC Manager. These individuals help to steer the PPI work for OCTOPUS and retain oversight of the PPI activity across the working groups to ensure consistency of quality and joined up thinking.

The OCTOPUS team aims at a minimum of six people affected by MS as members of the TSC, MRI Group and Biofluids and Biomarker Group.

PwMS choose which of the TMG working groups they would like to sit on and advise and assist the working groups by representing the MS community in discussions. These individuals will also be responsible for designing and developing the PPI activity directly related to their respective working groups.

To ensure that members feel supported in their positions in the working groups, it is proposed that the PPI Forum members meet regularly by videoconference.

15.4 PROTOCOL DESIGN AND STUDY SETUP

Four members of the MS Society's Research Network helped to shape the PPI strategy. These members were involved in the planning and running of three workshops that took place in 2019 in Edinburgh, Sheffield and London. The aim of the workshops was to hear what PwMS thought about the trial design. The topics covered included:

- Communication methods, in particular using a wide range of routes to raise awareness of research and recruitment.
- Clarity of information, especially during the consent process with regards to time commitment to the trial, trial design, potential side effects of treatments and explanations on the reasons for stopping treatments early.
- Incentives to participation, including receiving regular feedback and communication from the trial team and peer support from other participants.
- Barriers to participation including: logistical challenges of attending trial visits; duration of commitment to the trial; the possibility of receiving the standard of care arm for an extended period of time; and the possibility of being assigned to a treatment just before an analysis decision.
- Outcome measures, including acceptability of blood tests, and MRIs the importance of measuring hidden symptoms such as fatigue; and use of technology.

15.5 PPI IN THE ONGOING RUNNING OF STUDY

Please refer to [section 15.2](#) for information on PPI in the ongoing running of OCTOPUS.

15.6 INTERPRETING AND PLANNING DISSEMINATION OF STUDY RESULTS

The MS Society PPI Forum play a key role in communicating the results of the study. The group will help to ensure that OCTOPUS participants are kept up-to-date, by helping to plan and draft newsletters and website updates. The Forum also help to identify the key messages that are important to communicate with a wider audience of people affected by MS, making sure that the language used is appropriate and helping to identify ways to reach different audiences.

15.7 REPORTING AND EVALUATING IMPACT OF PPI

Feedback from people affected by MS, who are involved will be sought throughout OCTOPUS. This will include, reflecting on how they have found their involvement, if there are ways it could be more effective, if they would like further training or support and what impact they feel it is having.

OCTOPUS will include details of their PPI activities and the impact in the main publications coming out of the trial.

16 PUBLICATION AND DISSEMINATION OF RESULTS

The results for each stage the OCTOPUS Trial Programme will be analysed separately when appropriate and according to pre-defined criteria developed from the MAMS design. The results from the OCTOPUS will be published in peer-reviewed journals, as well as being presented at national and/or international conferences, when appropriate and possible. Individual groups and clinicians must not publish data concerning their participants that are directly relevant to questions posed by the study until the TMG has published its report. The TMG will form the basis of the Writing Committee and will advise on the nature of all publications. Any release, of efficacy or safety data, presentation or publication will be agreed with the TSC according to the terms of their charter.

There are expected to be a number of resulting publications and the authorship will vary for each. Individual authors will include relevant members of the TMG and collaborators, as well as high-recruiting Investigators. All participating sites and corresponding PIs and co-PIs in the relevant cohort will be acknowledged in all relevant publications, along with members of the IDMC and TSC.

With the manuscript, a full list of sites and the number of participants recruited will be provided. In the presentations, this list of sites will also be shown. The term “the OCTOPUS investigators” will clearly be stated and relevant names included in the presentation credits.

Results from the interim analyses will be available to the IDMC at various times. There are 3 scenarios that we need to consider:

1. If there is evidence of overwhelming efficacy of a research arm compared to control, the IDMC may release these results to the TSC. The IDMC and TSC may also indicate that the design of the trial might need to be altered. If the TSC confirm this recommendation then the results will be presented widely and published in an appropriate journal as soon as possible.
2. The IDMC may recommend stopping further recruitment to an arm(s) because of a lack of activity, safety or feasibility. If the TSC confirm this recommendation, these results will be presented widely and published in a journal as soon as possible.
3. The IDMC may recommend continued accrual to all research arms. If the TSC confirm this, then we shall write and publish a short paper summarising the fact that the research arms have been approved to go forward to the next stage of trial

17 DATA AND/OR SAMPLE SHARING

Data will be shared according to the CTU's controlled access approach and Data Sharing SOP, based on the following principles:

- No data should be released that would compromise an ongoing trial or study.
- There must be a strong scientific or other legitimate rationale for the data to be used for the requested purpose.
- Investigators who have invested time and effort into developing a trial or study should have a period of exclusivity in which to pursue their aims with the data, before key trial data are made available to other researchers.
- The resources required to process requests should not be under-estimated, particularly successful requests, which lead to preparing data for release. Therefore, adequate resources must be available in order to comply in a timely manner or at all, and the scientific aims of the study must justify the use of such resources.
- Data exchange complies with Information Governance and Data Security Policies in all of the relevant countries.

Data will be available for sharing following each analysis such as Analysis Stage 1 analysis for arms that do not continue. Researchers wishing to access OCTOPUS data should contact the Trial Management Group which will act as the "Data Re-Use Committee" in the first instance.

18 PROTOCOL AMENDMENTS

Please check with the OCTOPUS Trial Team or the OCTOPUS website to confirm the most recent version of the OCTOPUS protocols, appendices and associated documents.

Please note version 1.0; dated 03-Aug-2022 was not approved for use and was amended following comments from the Research Ethics Committee, MHRA and HRA. Therefore version 2.0; 11-Oct-2022 was the first approved protocol version.

Summary of changes between v2.0 and V3.0

In addition to correction of typos and grammatical errors, the following was updated:

- Updated MRC CTU at UCL contacts and TMG members
- Summary table - Addition of analysis stage 1 exploratory analysis
- Amendments to assessment table
 - Addition of haematology (FBC), Biochemistry (Bilirubin, LFTs (ALP plus AST or ALT)), potassium and sodium to screening and safety tests
 - Clarification that [C] is at PI discretion and should be strongly considered but not mandatory based on clinical opinion.
 - Amendment that pregnancy checks (removing pregnancy test) for WOCBP must be performed prior to all MRIs following local MRI practices and guidelines.
 - Alcohol assessments now carried out at baseline and as per clinical discretion throughout trial.
- Abbreviation additions of DSMS (Drug Supply Management System), PRLs (Paramagnetic Rim Lesions), SWI (Susceptibility weighted images) and TLC (three letter code)
- Lay summary - Updated Figure 3 inserted
- Section 1.9 - addition Exploratory Analysis: Paramagnetic Rim Lesions
- Section 3.2 - Removal of Participant Exclusion Criteria 3: Rare hereditary problems of galactose intolerance or glucose galactose malabsorption as moved to metformin specific criteria (in Metformin drug appendix)
- Section 3.6 - Addition of sentences to Section 3.6 Screening Procedures & Pre-randomisation investigations for PIS location on website, how obtain participant identification number and TC and clarifying all GPs and neurologists should be informed of participation involvement.
- Section 4 Randomisation - Removal of sentence for manual randomisation
- In section 5.2 Products, the wording has been clarified including confirmation that IMPs to be kept out of direct sunlight and the use of the Drug Supply Management System (DSMS)
- In section 5.5 Dispensing and Storage: clarification of use of DSMS
- In section 5.6 – confirmed *maximum dose for the remainder of the trial* will be achieved at 24 weeks and removal of sentence “no further escalations can be performed”.
- In section 5.6.1 Renal impairment – correction that all participants should pause for 24 hours prior to iodinated contrast agents and correction restart trial treatment only after eGFR has been confirmed $>50\text{ml min}/1.73\text{m}^2$ (not $30\text{ml min}/1.73\text{m}^2$).
- In section 5.6.2 Gastrointestinal table 4: clarification of wording for dose modifications for gastrointestinal toxicity
- In section 5.6.3 Table 5 Management of trial treatment for proteinuria - updated to include both units for ACR.

- In section 5.6.4 Table 6 Vitamin B12 Deficiency - Addition of >200pg/ml as units and addition of sentence: If $\leq 200\text{ng/l}$ (200 pg/ml) (148pmol/l) after 9 months post initial test, discontinue trial treatment.
- In section 5.7 – clarification on pregnancy testing and checks prior to MRI scans.
- In section 5.8 Accountability and unused drugs/devices addition and clarification of wording use of the treatment log and diary cards
- In section 5.9 Compliance and Adherence clarification and rewording of the section including addition of wording on use of the electronic diary card
- Section 5.10 Handling cases of trial treatment overdose – clarification of wording to confirm if accidental overdose, participants can restart treatment, whereas for deliberate overdose treatment should stop.
- Section 5.14.3 Medications to be used with caution addition of ‘investigator brochure’ and clarification of requirements to pause or stop medications of caution.
- Section 6.2.4 Concomitant Medication addition of wording: At each visit, a review of concomitant medication must be performed to ensure any contraindicated medications including taking any Analysis Stage 1 IMPs are not being taken.
- Section 6.3 Safety Assessments addition of wording to provide specific instructions performing for the urinary dipstick and addition of the applicable colour chart.
- Section 6.3.3 Pregnancy - clarification on pregnancy testing and checks prior to MRI scans.
- Section 6.6 Procedures for assessing patient reported outcomes – clarification of wording for collection of patient reported outcomes for telephone visits and removal of the wording “The following assessments should be facilitated by the assessing clinician and/or an appropriate trial team member.”
- Sections 6.6.3 Modified Fatigue Impact Scale -21 (MFIS-21), Section 6.6.4 Chalder Fatigue Questionnaire (CFQ); Section 6.6.5 Pain Assessment and Section 6.6.6 EQ-5D-5L - removal of the wording “This should be completed at each in person follow up visit and or online via participate if participant happy to do so. This can be performed on a telephone follow up using the worksheet in extenuating circumstances”.
- Section 9.1 Method of Randomisation clarification of the generation of the bottle numbers and to who and where they are supplied.
- Section 16 Publication and Dissemination of Results – revision of the wording for when results of interim analyses will be available and scenarios requiring consideration.
- Addition of metformin specific exclusion criteria: rare hereditary problems of galactose intolerance or glucose-galactose malabsorption
- Clarification of units in R/S-Alpha lipoic acid specific exclusion eligibility criteria – Urinary dipstick for proteinuria 1+ or higher and albumin/creatinine ratio (ACR) $>300\text{mg/g}$ or \geq equal to 34mg/mol

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APPENDIX 1: ACCEPTABLE METHODS OF CONTRACEPTION

OCTOPUS female participants who are WOCBP must agree to use an acceptable method of contraception while taking trial treatment and for 12 weeks after the last dose of trial treatment. For WOCBP participants, pregnancy checks prior to MRI will be performed, in line with local MRI practices and this may include a urine HCG pregnancy test. This will be documented in the MRI checklist or notes following local MRI practices. Clinical discretion should be exercised if a pregnancy test is required for WOCBP participants at follow up visits with when no MRI is performed, prior to any dispensing.

For the purpose of OCTOPUS, a woman is considered of childbearing potential (WOCBP), i.e. fertile, following menarche and until becoming post-menopausal unless permanently sterile. Permanent sterilisation methods include hysterectomy, bilateral salpingectomy and bilateral oophorectomy.

A postmenopausal state is defined as no menses for 12 months without an alternative medical cause. A high follicle stimulating hormone (FSH) level in the postmenopausal range may be used to confirm a post-menopausal state in women not using hormonal contraception or hormonal replacement therapy. However, in the absence of 12 months of amenorrhea, a single FSH measurement is insufficient.

OCTOPUS male participants must agree to use acceptable method of contraception during sexual contact with a woman of childbearing potential (WOCBP) while taking trial treatment, during dose interruptions and for at least 12 weeks after the last dose of treatment. Partners of male participants are encouraged to also use acceptable methods of contraception. This is due to evidence of a potential link between metformin use in males and birth defects in offspring. This will be reassessed when any future trial treatments are added to OCTOPUS[112-115].

The acceptable contraception precautions that should and should not be used are listed below:

ACCEPTABLE METHODS OF CONTRACEPTIVES

1. Combined (oestrogen and progestogen containing) hormonal contraception associated with inhibition of ovulation which can be oral, intravaginal or transdermal
2. Progestogen-only hormonal contraception associated with inhibition of ovulation which can be oral, injectable or implantable
3. Intrauterine device (IUD)
4. Intrauterine hormone-releasing system (IUS)
5. cap, diaphragm or sponge with spermicide **
6. male or female condom with or without spermicide**
7. Vasectomised or vasectomised sexual partner - this is a highly effective birth control method provided that partner is the sole sexual partner of the WOCBP trial participant and that the vasectomised partner has received medical assessment of the surgical success.
8. Bilateral tubal occlusion
9. True heterosexual abstinence (i.e. not just stopping intercourse for the duration of the trial)

** Ideally a barrier method should be used in combination with options 1-6.

UNACCEPTABLE CONTRACEPTION THEREFORE INCLUDES:

- Progestogen-only oral hormonal contraception, where inhibition of ovulation is not the primary mode of action
- Fertility awareness methods
- Periodic abstinence (calendar, symptothermal, post-ovulation methods)
- Withdrawal (coitus interruptus)
- Spermicides only
- Lactational amenorrhoea method (LAM)

OTHER CONSIDERATIONS

- A urine HCG pregnancy test is required for WOCBP as part of screening and at clinical discretion prior to treatment dispensing. It may also be performed as part of local MRI practice in pre-MRI pregnancy checks.
- If a pregnancy occurs in a trial participant or a partner of a trial participant, it is a reportable event and female trial participants must stop trial treatment please refer to Protocol [section 5.12](#) and [section 7.2.2](#) for how it is must be reported.
- Acceptable methods of contraception should be discussed before randomisation. At follow-up visits clinicians should ensure participants are continuing to use or take appropriate precautions, and clinical discretion should be exercised if pregnancy tests are required prior to dispensing. Participants should be made aware of the availability of emergency “post-coital” contraception if there is an indication for it (for example missing IUD threads or a late injection).
- Gastro-intestinal side effects: diarrhoea is unlikely to affect oral contraceptive absorption unless cholera-like. Vomiting within 3 hours of taking oral contraception does pose a risk equivalent to a missed pill and participants should follow the guidelines for a missed pill. Neither diarrhoea nor vomiting will affect non-oral routes for hormones.