OCTOPUS

Optimal Clinical Trials Platform for Progressive Multiple Sclerosis

Version: 9.0

Date: 25-Feb-2026

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: DocuSigned by: Jeremy Chataway 8DC8C197DECD4B7...

Date: 25-Feb-2026

Name: Mahesh Parmar

Role: Director of MRC CTU at UCL

Signature: Signed by: Mahesh Parmar F1E2FB8B947644A...

Date: 25-Feb-2026

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 Drug 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.

In Australia, OCTOPUS has been named;

- PLATYPUS (Australian extension of the OCTOPUS trial)

Australian sites will comply with the OCTOPUS protocol, Drug appendices and a Country Specific Appendix (CSA).

Outside the UK, a CSA is to be read in conjunction with the current approved version of the OCTOPUS trial protocol and provides additional information about trial conduct specifically in the country i.e. Australia, and therefore it supersedes entirely or partially the corresponding chapters in the protocol.

COMPLIANCE

For UK sites, this trial will adhere to the conditions and principles of GCP as outlined in the Medicines for Human Use (Clinical Trials) Regulations 2004 (SI 2004/1031), as amended.

For sites in the EU/EEA, this trial will adhere to the GCP requirements as outlined in the EU Clinical Trials Regulation No. 536/ 2014 and implementing acts in the relevant country(ies).

For sites outside the UK and EU/EEA, this trial will adhere to the GCP requirements as applicable and shall comply with all their local laws and statutes applicable to the performance of clinical trials and research. See section 11 for more information.
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 and in the UK as outlined in the UK by Statutory Instrument in the Medicines for Human Use (Clinical Trials) Regulations 2004 (SI 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.
Sites outside the UK will adhere to the GCP requirements as applicable and shall comply with all their local laws and statutes applicable to the performance of clinical trials and research.

SPONSOR

UCL is the global 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. In Australia, the trial is funded by MS Australia and Multiple Sclerosis Society of Western Australia Inc (MSWA).

AUTHORISATIONS AND APPROVALS

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

Favourable opinion will also be obtained in all participating countries outside the UK in compliance with all local laws, statutes and requirements.

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
your local co-ordinating centre

TRIAL ADMINISTRATION

Please direct all queries to the local co-ordinating centre in the first instance (see contact details below); clinical queries will be passed to the Chief Investigator via the Trial Team.

CO-ORDINATING CENTRES

UK SITES:

MRC Clinical Trials Unit at UCL
Institute of Clinical Trials & Methodology
2nd Floor, 90 High Holborn, London, WC1V 6LJ

Email: mrcctu.octopus@ucl.ac.uk

Programme Lead:	Mahesh Parmar		
Clinical Project Manager:	Cheryl Pugh	Tel:	+44 (0)207 670 4935
Statisticians:	Matthew Burnell	Tel:	+44 (0)207 670 4889
	Rachel Burton	Tel:	+44 (0)207 670 4862
Trial Manager:	Monica Lewis	Tel:	+44 (0)203 108 5130
Trial Manager:	Farjana Haque	Tel:	+44 (0)207 670 4939
Trial Manager:	Elizabeth Brodnicki	Tel:	+44 (0)207 670 4783
Data Manager:	Brendan Murphy	Tel:	+44 (0)207 670 4784
Data Manager:	Shuchi Naik	Tel:	+44 (0)207 670 4624

AUSTRALIAN SITES:

Griffith University
170 Kessels Road
Nathan QLD 4111
Australia

Email: platypus@griffith.edu.au

Country Lead Investigator:	Simon Broadley	Tel:	+61 466 207 444
Trial Manager:	Sabrina Oishi	Tel:	+61 7 5678 0523

CHIEF INVESTIGATOR

Professor Jeremy Chataway
Queen Square Multiple Sclerosis Centre
Department of Neuroinflammation
UCL Queen Square Institute of Neurology
Faculty of Brain Sciences
University College London, London, WC1B 5EH

Tel: +44 (0)203 1087414

Email: j.chataway@ucl.ac.uk

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
Simon Broadley	Professor of Neurology	Country Lead Investigator (Australia)	Griffith University, Gold Coast QLD, Australia

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 [1]	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.**

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	9.0
Date	25-Feb-2026
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
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	**Analysis Stage 1** evaluates the effect of R/S-ALA or metformin on a rate of change on composite measure comprising whole brain atrophy, Expanded Disability Status Scale (EDSS), Timed 25 Foot Walk (T25FW) and 9 Hole Peg Test (9HPT). The analysis will take place when 375 participants have completed at least 78 weeks (18 months) of follow-up. MRI data will be included for the approximately 25 participants per arm (375 in total) who have MRI scans and data on the other outcomes will include all participants with at least one follow-up visit at the time of Stage 1 analysis (anticipated to be N=205 per arm, or 615 in total). ***Only the treatments showing sufficient promise at Analysis Stage 1 will continue to Analysis Stage 2.*** **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 approximately 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. Please refer to **Figure 2** for Recruitment and Analysis time points.

SUMMARY INFORMATION TYPE	SUMMARY DETAILS
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)	Composite measure comprising EDSS, T25FW, 9HPT, and whole brain atrophy rate as measured by the SIENA technique
Analysis Stage 1 Secondary Outcome Measure(s)	**MRI outcome measures:** 1. Whole brain atrophy rate **Clinician reported outcome measures** 1. Expanded Disability Status Scale (EDSS) 2. Timed 25 Foot Walk (T25FW) 3. 9 Hole Peg Test (9HPT) If a treatment fails to show sufficient promise at Analysis Stage 1 and is further randomisations are discontinued, then results will additionally be reported for the primary and secondary outcomes listed for Analysis Stage 2. This analysis will use the accumulated data at the time the arm is discontinued.
Analysis Stage 1 Exploratory Analysis	• Paramagnetic rim lesions (PRLs) collected at baseline only • Change in candidate serum protein biomarkers between week 0 and week 52 / 78
Analysis Stage 2 Primary Outcome Measure(s)	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). 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. Progression of disability is defined by progression on at least one of the three parameters: 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.
Analysis Stage 2 Secondary Outcome Measure(s)	**Clinician reported outcome measures** 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)

SUMMARY INFORMATION TYPE	SUMMARY DETAILS
	c. Symbol Digit Modalities Test (SDMT) 6. Sloan Low contrast visual acuity (SLCVA) 7. Relapse rate **Patient reported outcome measures** 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) **MRI outcome measures (for those recruited in Analysis Stage 1 who had MRIs - N=125 per arm)** 1. Whole brain atrophy rate 2. Regional atrophy rates 3. Cervical cord atrophy rate 4. T2 lesion volume change **Health related quality of life and resource use** 1. EQ-5D-5L Health Questionnaire 2. Client Services Receipt Inventory (CSRI)
Randomisation	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. 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. 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.
Number of Participants to be Studied	Analysis Stage 1: Analysis Stage 1: 375 (approximately 125 per arm) with MRI data and an additional 240 (80 per arm) without MRI. Therefore approximately 615 in total. Analysis Stage 2: 1200 participants (approximately 600 per arm) assuming one active arm continues (inclusive of those randomised in Analysis stage 1) Please note the number of participants will be updated for the additional arms as required
Duration	7 years for evaluation of initial interventions, assuming one continues to analysis stage 2. Please note this may increase following the addition of further arms.
Funder	UK MS Society with supportive funds from MRC CTU at UCL, MS Australia and MSWA.
Chief Investigator	Professor Jeremy Chataway

TRIAL SCHEMA

Figure 1: Trial Screening, Randomisation and Treatment

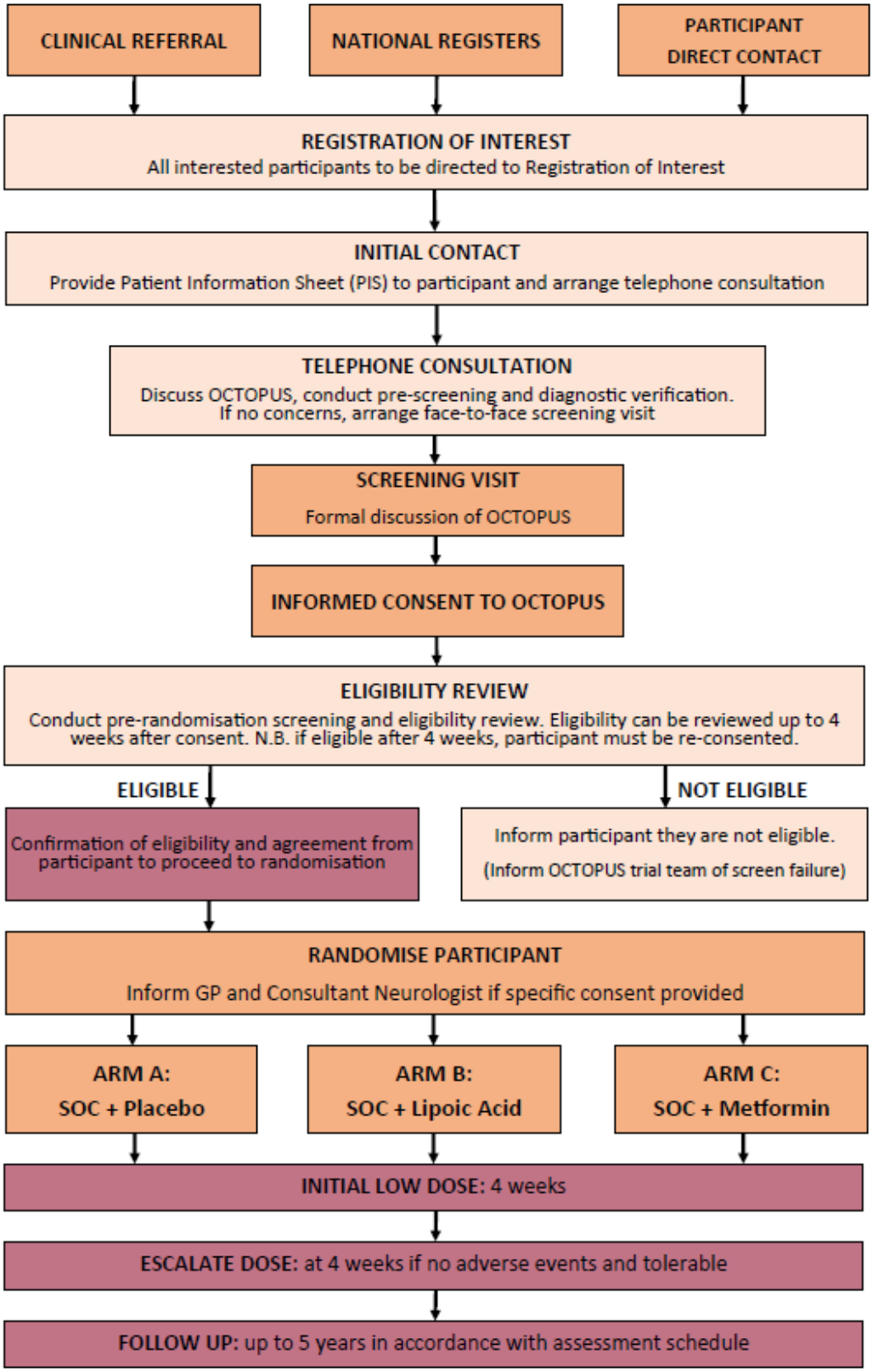
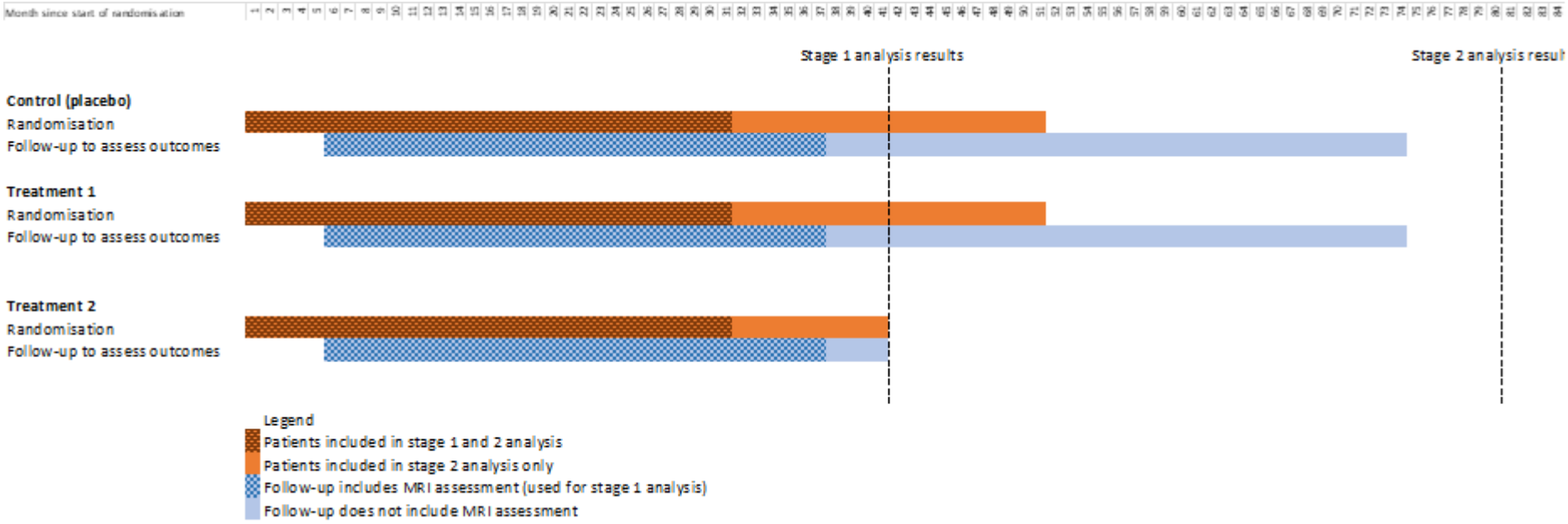


Figure 2: Recruitment and Analyses Time points



TRIAL ASSESSMENT SCHEDULE

Table 1: Trial Assessment Schedule

Week number (visit type)	-4 to 0 (Screening)†	0 (Rando-misation)	4 Dose escalation	12	26	38	52	64	78	90	104	116	Participants on treatment: every 26 weeks until 260 weeks or until trial arm closes (whichever occurs first)	Participants off treatment & in FU: 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	Phone or in person	In person	Phone	In person	Phone	In person	Phone	In person	Phone	In person and 12-weekly Phone [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 optional	x		x		x		x		x		x [C]
Dose escalation			x												x [C]
MRI Scans [M]		x [F]			X				X		x [B]				x [C]
Screening and safety tests [G]															
Haematology (FBC), & Biochemistry (Bilirubin, LFTs (ALP plus AST or ALT), potassium, sodium & albumin) ‡	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 (TSH, T4) ‡	X		x	x	x		x		x		x		x		x [C]
Vitamin B12 [H] ‡	X			x	x		x		x		x		x		x [C]
Urine Dipstick [J]	X		x	x	x	x	x	X	x	x	x	x	x (12-weekly)		x [C]
ACR ‡	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	Participants on treatment - every 26 weeks until 260 weeks or until trial arm closes (whichever occurs first)	Participants off treatment & in FU: 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 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 - [Assessor]		**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**						
1 purple top tube (EDTA vacutainer ®) for DNA extraction ‖		**x**													
1 purple top tube (EDTA vacutainer ®) for plasma collection		**x**			**x**		**x**		**x**						

Week number (visit type)	-4 to 0 (Screening)†	0 (Rando-misation)	4 (Dose escalation)	12	26	38	52	64	78	90	104	116	Participants on treatment - every 26 weeks until 260 weeks or until trial arm closes (whichever occurs first)	Participants off treatment & in FU: 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 Telephone 12-weekly [J]	In person	As required
Staff Present															
Treating clinician	X	x	x	x	x		x		x		x		x	x	x
Assessor		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 or at the week 104 visit (final MRI visit). It MUST not be after the week 104 visit. All participants recruited in Analysis Stage 1 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 for participants randomised into Analysis Stage 1, 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) for participants randomised in Analysis Stage 1. This can be before or on day of the randomisation visit but not before consent. Gadolinium is only required at this timepoint. (not applicable to participants randomised into Analysis Stage 2)

G = Not required if participant has stopped OCTOPUS Trial treatment

H = Not required if ineligible for metformin

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

K = no longer applicable.

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

M = only required for participants screened and randomised in Analysis Stage 1

* 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 biorepository. 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.

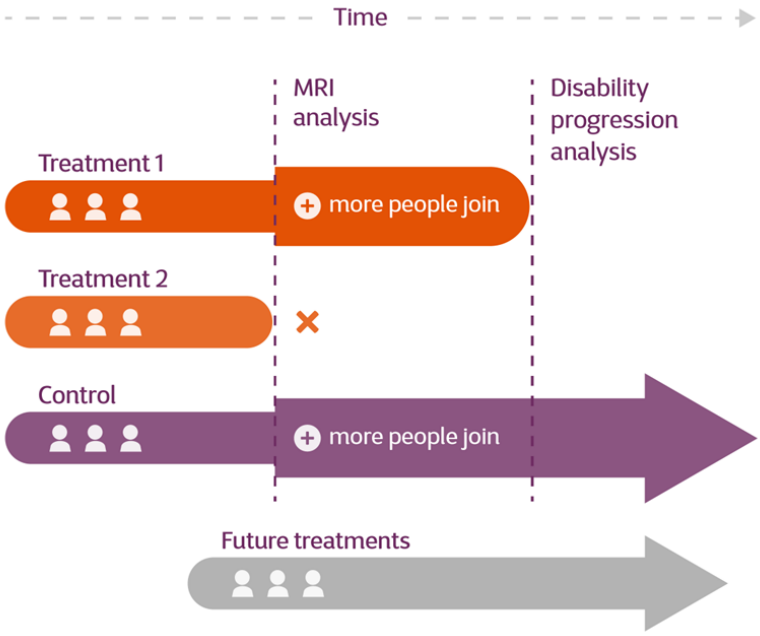
A NEW TYPE OF CLINICAL TRIAL IN MS

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”. The trial will expand to recruit in sites outside the UK. 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, the first 375 participants who are recruited in the first Analysis stage will undergo brain MRIs (four scans). Based on these scans, and assessments of disability on three clinical assessments (EDSS, 25 foot walk test, 9 hole peg test) 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 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: MS charitable organisations, neurologists and other healthcare professionals at clinics in participating sites, talks at participant groups, National Registers, PLATYPUS country coordinating centre, and a dedicated trial website. Both printed and online information can be available.

HOW WILL WE SHARE OUR RESULTS?

Participants will have regular updates on the progress of OCTOPUS through newsletters, the OCTOPUS website, the PLATYPUS country coordinating centre, and the National Registers. 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 UK MS Society, the PLATYPUS country coordinating centre, and other MS groups' websites, newsletters and social media. The study website will also include updates accessible by the general public.

CONTENTS

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
CCC	Country Coordinating centre
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

ABBREVIATION	EXPANSION
CLS	Country Lead sites
CPM	Clinical Project Manager
COX	Cyclooxygenase
CRF	Case Report Form
CROMs	Clinician Reported Outcome Measures
CSF	Cerebrospinal fluid
CSA	Country specific appendix
CSRI	Client Services Receipt Inventory
CTA	Clinical Trials Authorisation
CTCAE	See NCI CTCAE
CTU	See MRC CTU at UCL
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

ABBREVIATION	EXPANSION
ETDRS	Early Treatment Diabetic Retinopathy Study
EU	European Union
EudraCT	European Union Drug Regulatory Agency Clinical Trial
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 (or known as family doctor outside UK)
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

ABBREVIATION	EXPANSION
IMP	Investigational medicinal product
ION	Institute of Neurology
IR	Immediate Release
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
MSWA	Previously known as “Multiple Sclerosis Society of Western Australia Inc”
MSWSv2	MS Walking Scale-12 version 2

ABBREVIATION	EXPANSION
NBV	Normalised brain volume
NCI CTCAE	National Cancer Institute Common Terminology Criteria for Adverse Events
NE	Notable Event
NHS	National Health Service
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
PLATYPUS	Name of OCTOPUS extension in Australia
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

ABBREVIATION	EXPANSION
QALY	Quality adjusted life years
QC	Quality control
QMAG	Quality Management Advisory Group
QMMP	Quality Management and Monitoring Plan
QoL	Quality of life
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

ABBREVIATION	EXPANSION
SMP	Safety Management Plan
SOC	Standard of Care
SOP	Standard operating procedure
SPC	Summary of Product Characteristics
SPM	Statistical parametric mapping
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

ABBREVIATION	EXPANSION
UTI	Urinary tract infection
VAS	Visual Analogue Scale
VBM	Voxel-based morphometry
WM	White matter
WNRTB	Welsh Neuroscience Research Tissue Bank
WOCBP	Women of Child-Bearing Potential

1 BACKGROUND

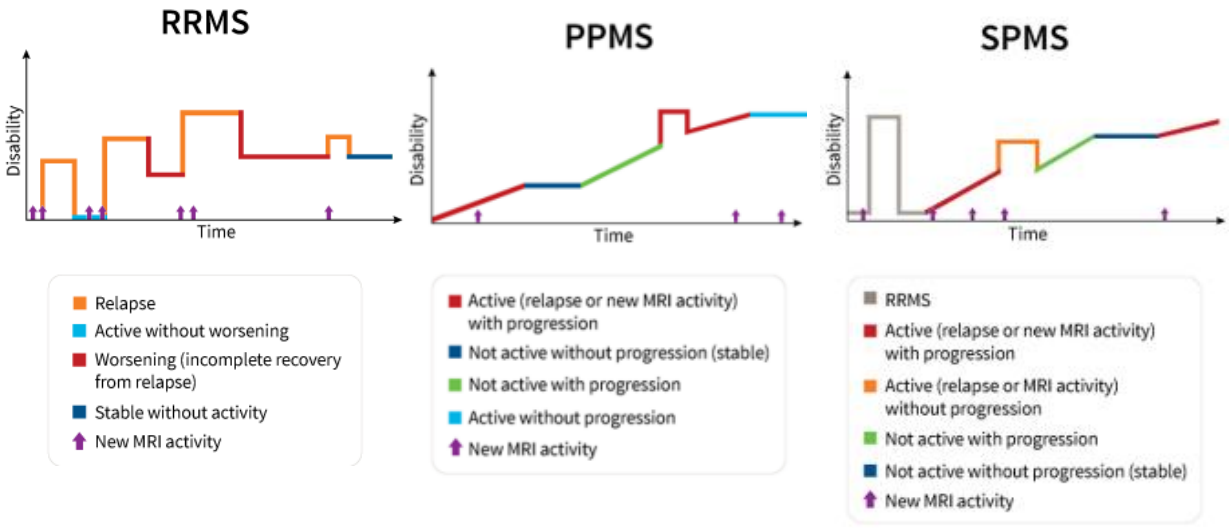
1.1 PROGRESSIVE MULTIPLE SCLEROSIS

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 [2].

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) [3]. 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 [4, 5]. 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 [4, 6, 7]. 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 [4].

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[8]. 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 [9]. Overall, healthcare costs dominate in mild disease; production losses, informal care, investments and community services dominate in more severe disease [10]. 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 [11]. 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 [12, 13]. 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 [14].

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 [15].

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 [16]. 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 [16, 17].

Since the review in 2015, four large phase 3 trials in SPMS and PPMS have reported and these are summarised in **Table 2: Summary of four phase 3 trials in PMS since 2016 [17]** [17]. In the EXPAND trial, the sphingosine 1 phosphate receptor modulator siponimod significantly reduced 3-month confirmed disability progression on EDSS in SPMS [18]. Whereas in ORATORIO, the anti-CD20 monoclonal antibody ocrelizumab significantly reduced 3-month confirmed disability progression in EDSS in PPMS [19]. Natalizumab and fingolimod did not show evidence of improvement in their primary outcome endpoints in the phase 3 trials ASCEND [20] and INFORMS [21]. 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 [17]

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 [22] and the RECOVERY trial for the treatments of COVID-19 [23]. 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

Participants who are randomised as indicated to active or control arms will have assessments every 26 weeks until 260 weeks or until trial arm closes (whichever occurs first). The first 375 participants who are randomised will have MRI based brain atrophy rate assessments at four time points up to 104 weeks in addition to the other outcome measures. Participants randomised after this will not have MRI but will be assessed on the other outcomes. Participants will be included in Analysis Stage 1 if they are randomised before the Analysis Stage 1 takes place, regardless of whether they have MRI. Analysis Stage 1 will take place once the first 375 participants have reached the 78 week (18 month) visit. At this time a decision will be made whether to continue a trial arm into further recruitment and follow-up for Analysis Stage 2 or to terminate that arm, see **Figure 2**. For further details on how this decision will be made, please refer to section 9.3.1.

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.

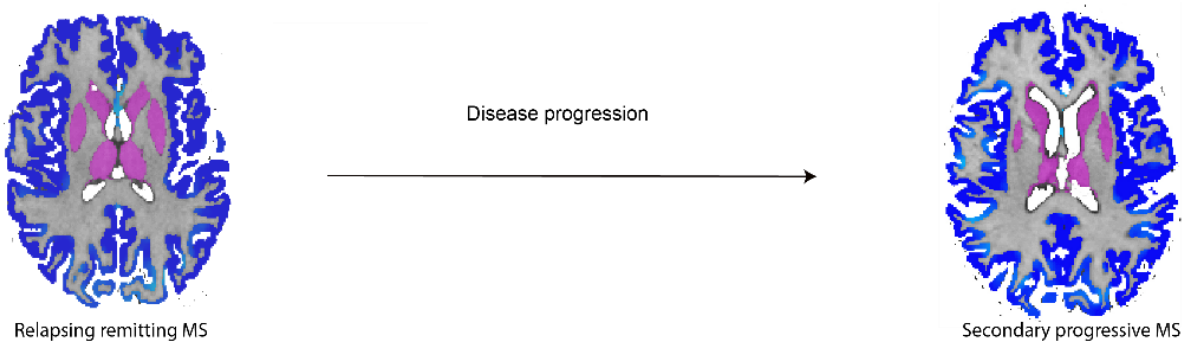
1.6 OUTCOME MEASURES

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 [24, 25].

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 [26]. Brain atrophy is part of normal ageing, but has been shown to be accelerated in MS [27]. 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 [28-30]. 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 [31, 32].

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 [26, 33, 34].

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 [25]. Structural Image Evaluation using Normalisation of Atrophy (SIENA) [35] and the brain boundary shift integral (BBSI) [36] have been used to measure atrophy or volume change in trials.

SIENA uses FSL software [37, 38] 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 [39]. The change in signal intensity at the edge points at the interface between the brain and the cerebrospinal fluid estimates the PBVC over time [35, 40].

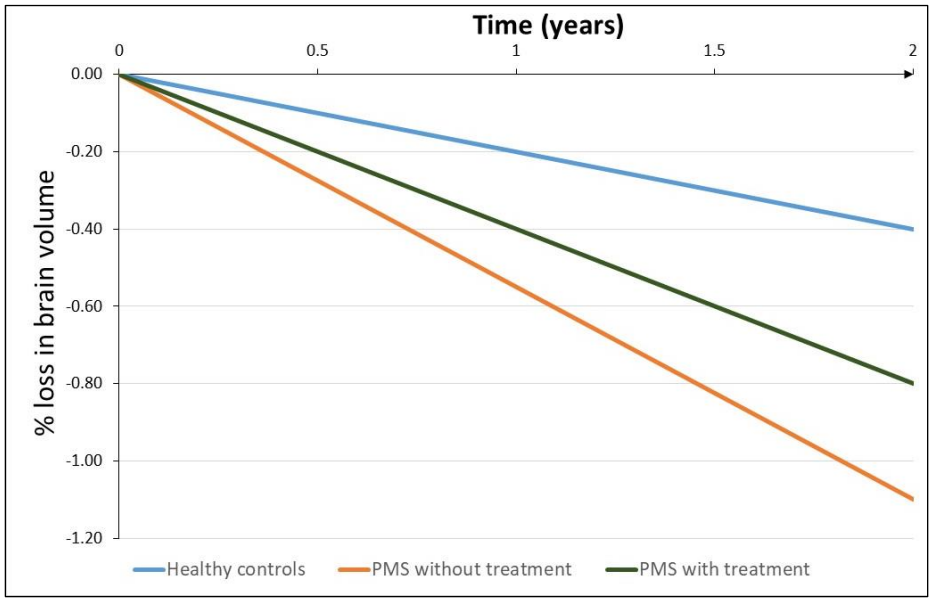
Segmentation techniques quantify regional brain areas, e.g. regional GM volumes; total GM volume, cortical grey matter (CGM), and deep grey matter (DGM) [25]. The cross-sectional version of SIENA is SIENAX. Following brain extraction as described above, with GIF, the image is registered to a standard brain template normalised for head size by using the external skull [40]. 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 to calculate whole brain atrophy for 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 [41-43] versus -0.1 to -0.3% per year for healthy controls [44].
Error! Reference source not found. is a schematic indicating average PBVC differences in controls, t hose 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 [45].

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 in Analysis Stage 1, a scan will be acquired 26 weeks after the start of treatment and at week 26 – week 104 volume change will also calculated. This will allow a sensitivity analysis of change from week 26 scan in assessment of whole brain atrophy rate.

1.6.2 Regional Atrophy

GM and subcortical atrophy are common in MS and occur in all phenotypes [26, 34, 46, 47]. 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 [46, 48]. As with whole brain atrophy, studies have shown that there is a significant anti-correlation of T2 lesion load and GM volume [49]. GM atrophy was 12 times greater in SPMS than in healthy controls in a 4 year follow-up study [46], with the lowest GM and DGM volumes [50]. PPMS has a predilection for cingulate atrophy [51]. Overall GM loss correlates more with clinical and cognitive outcome measures than WM loss [33, 34, 52]. GM volume significantly impacts the development of clinically definite MS from CIS in a 3-year cohort study [53]. 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 [50]. Regional atrophy appears to occur in different patterns in MS phenotypes and spreads dependent on disease duration and disability level in relapse-onset MS [54]. GM atrophy is therefore a useful clinical correlate in MS. Reductions in GM volume correlated with cognitive function and overall disability worsening in MS [1].

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)[5]. 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
[73] 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 [74, 75]

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) [76].

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 ≥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) [77, 78]. 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) [79].

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 [77]. The psychometric properties of the MSIS-29 have shown strong internal consistency, reproducibility and satisfaction of scaling assumptions for both components [80] and the scale has been suggested as a valuable outcome measure in intervention studies of patients with MS [81].

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[82]. 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 [83]. It is common [84], and includes both neuropathic and nociceptive pain syndromes [84, 85]. 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 [85]. Treatment, however, is often unsatisfactory, and is largely based on evidence drawn from other disorders [86, 87]. Limitations in existing

randomised trial evidence [88] were underlined by a recent Cochrane review (under review) which identified only two high quality RCTs of non-cannabinoid neuropathic pain therapies in pwMS [89].

No existing RCTs [88, 89] 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 [41]. Pain symptom measures were collected for all participants. These included overall pain severity, neuropathic pain (Neuropathic Pain Scale) [90, 91] and pain interference with function [92]. These data (under review [93]) 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 [93].

- Neuropathic Pain Scale [90], which is validated specifically in MS [91] and recommended by international guidelines to assess treatment effects[94].
- Single item measuring overall pain intensity [92, 95] - 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 ANALYSES:

1.9.1 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 [96]. 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 [41]. 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, OCTOPUS 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.

1.9.2 PROTEIN BIOMARKERS

Fluid biomarkers hold the potential to enhance pathophysiological understanding of MS. Technological advances now permit the detection of biomarkers relevant in the CNS disease, even at previously prohibitively low concentrations within the blood. This is crucial in facilitating minimally invasive sampling, that can be done conveniently (even at home in the future), at low cost, and

therefore with high temporal resolution if necessary. Several candidate biomarkers of MS disability have already emerged, including neurofilament light (NfL), glial fibrillary acid protein (GFAP), chitinase-3-like-1 (Chi3L1), CXCL13 and complement proteins. There is evidence that using combinations of blood biomarkers could offer greater utility and highlight different pathological processes than single biomarkers[97].

The OCTOPUS biorepository has collected blood samples from over 300 participants, at up to 4 timepoints: baseline (M0), Month-6 (week 26), Month-12(week 52) and Month-18 (week 78). Therefore the aim of this exploratory analysis is to measure change in candidate protein biomarkers from week 0 to weeks 52/78 follow-up in samples from OCTOPUS participants.

The exploratory analysis will:

- Use biomarker data to explore which combination of protein biomarkers optimally predicts disability outcomes.
- Explore the complementarity of fluid versus MR-imaging biomarker data in OCTOPUS Stage 1 analysis.

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 [98], which is used to assess and value the health of participants [99, 100]. 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)

This questionnaire [101] 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 Drug appendix for their background and justification for use.

2 SELECTION OF SITES & CLINICIANS

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

2.1 SITE/INVESTIGATOR INCLUSION CRITERIA

Appropriate service support (in the UK only) 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 or provided access to the OCTOPUS master file documentation for their local approvals and Sponsor 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 to 3 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 Sponsor. Sites that have previously participated in MRC CTU at UCL-coordinated trials should have a proven track record of good data return.

8. Sites participating in Analysis Stage 1 must have access to local research standard MRI with sufficient capacity to scan OCTOPUS participants. All MRI scans are subjected 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 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 Sponsor. The Sponsor 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 Investigator Site File (ISF) at the site and also in the Trial Master File (TMF) at the Sponsor office.

2.2 APPROVAL AND ACTIVATION

In the UK, 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 in the UK. Sponsor trial staff will perform this task; hence it is vital to receive full contact details for all investigators prior to their entering participants. For approval in non-UK countries, please refer to the CSA.

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 (for sites participating in Analysis Stage 1 only), 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 website (www.ms-octopus.info).

2.3 SITE MANAGEMENT

The OCTOPUS team at the MRC CTU at UCL (Sponsor) will manage the OCTOPUS recruiting sites in the UK. For details on non-UK site management please refer to the CSA.

In Analysis stage 1 only, UCL Queen Square MS Centre (QSMSC) Institute of Neurology (ION), manages the MRI acquisition set up, regular Quality Assurance (QA) monitoring systems and performs the MRI analyses, which will be reported back to the applicable country co-ordinating centre.

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. Please note that eligibility criteria only apply at the point of randomisation. If a participant no longer meets one or more of the eligibility criteria during the trial it does not trigger their withdrawal.

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 2 only**. They have been amended by substantial amendment from Analysis Stage 1 (e.g. removal of requirements for MRI) and will be amended further for addition of future arms when and as required.

3.1 PARTICIPANT CORE INCLUSION CRITERIA

1. Participants with a confirmed diagnosis of MS [5]
2. A diagnosis of Secondary Progressive MS (SPMS) or Primary Progressive MS (PPMS) [4, 5].
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 assessor
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. [Please note no longer core inclusion criteria in Analysis Stage 2 - Must have a QC-approved (as defined in MRI guide) MRI ≤ 4 weeks before randomisation]
11. [Please note no longer core inclusion criteria in Analysis Stage 2 - 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) that includes but not limited to the following:
    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
    f. Significant non-MS neurological comorbidity
    g. Hepatic impairment
3. [Please note this number is no longer core exclusion criteria: moved to **Metformin exclusion criteria only** - Rare hereditary problems of galactose intolerance or glucose-galactose]
4. Active partial or total malabsorptive disease (e.g. coeliac disease)
5. Alcohol use disorder or illicit drug use within the last 5 years (excluding cannabis for symptomatic relief)
6. Female participants that are pregnant or breast-feeding.
7. 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.
8. Use of an investigational medicinal product or investigational medical device ≤ 26 weeks before randomisation.
9. 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.
10. Male participants unwilling to desist from sperm donation during the trial and for 12 weeks after the last dose of trial treatment.
11. 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.
12. Current or previous treatment with OCTOPUS IMPs ≤ 26 weeks before randomisation. With the exception of participants taking health supplements, including multi-vitamins, that contain a dose of ≤100mg of Alpha Lipoic Acid. These participants can be randomised but must wait 7 days from the last dose before randomisation.
13. Commencement of DMT and/or fampridine (or 3,4-aminopyridine) ≤ 26 weeks before randomisation*

14. Contraindicated medications that are not permitted with OCTOPUS 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.
15. 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.
16. Previous treatment with alemtuzumab or autologous haematopoietic stem cell therapy (AHSCT) ≤ 52 weeks prior to randomisation*
17. Albumin Creatinine Ratio (ACR) result of ≥34 mg/mmol (>300 mg/g) at screening, regardless of urine dipstick results.
18. Participants with a diagnosis of diabetes mellitus.

*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 MRI component of Analysis Stage 1 is 125 participants per arm (375 participants in total). 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 4.2**.

3.6 SCREENING PROCEDURES & PRE-RANDOMISATION INVESTIGATIONS

Potential participants are identified through a variety of routes such as clinician or General Practitioner (GP) referral; direct contact between potential participants and sites; PwPMS registered on a National Register (e.g. the MS Register in the UK and MS Trial Screen in Australia) who have expressed interest in the trial (see **Figure 1: Trial Screening, Randomisation and Treatment**), or Analysis Stage 2 re-randomisation for participants whose arm was closed for lack of benefit.

All potential participants (however identified) must 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. A combination of on-site and 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 tests (including ACR and pregnancy) are classified as ineligible, these should be repeated. The repeat safety urine and 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 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 GP and neurologist informing them 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 4.3**).

Please refer to the Australian Country Specific Appendix for further information on local Australian requirements.

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 at your appropriate country co-ordinating centre.

4.3 RE-RANDOMISATION INTO OCTOPUS

Participants who are on an arm that completes at Analysis Stage 1 and therefore does not continue in Analysis Stage 2 after the decision point, are able to be re-screened and considered for re-randomisation to an arm if 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 they withdraw or 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 [1] 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 [102]. 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)

SOC is not being investigated as part of OCTOPUS and therefore is not an IMP. It is individualised for each PwPMS by their neurologist and MS teams. In the UK, 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.

For details on non-UK SOC, please refer to the CSA.

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 (minimum of 3 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) [103]
- 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 26 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 in DSMS or if required as per local SOP, on a drug accountability log as per OCTOPUS Pharmacy Manual. 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. Drug accountability will be reviewed at on-site monitoring 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 26 weeks, dose modifications can be performed to determine the appropriate dose to be tolerated by the participant. At 26 weeks, the maximum dose for the remainder of the trial will be determined 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.
45 - 59 ml/min/1.73m^2	Repeat eGFR 4 weeks post test and continue on current dose. On repeat eGFR, if result remains between 45 - 59 ml/min/1.73m^2; continue on current dose and re-test at next in-person visit.
<45 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 be confirmed as >45ml min/1.73m^2.

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	• 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	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 If on low dose, pause. then re-start after minimum of 1 week if symptoms improve. If grade 2 toxicity persists consider the following: • Pause treatment for 2 weeks, and re-start • And re-attempt a dose escalation at clinical discretion if toxicities are ≤ grade 1 if within 26 weeks of randomisation.

5.6.3 PROTEINURIA

Proteinuria might be seen with the trial treatments. If proteinuria occurs, a dose reduction to a low dose or pause may be required, as described in **Table 5** below.

Urinary dipsticks and ACRs must be performed every 12 weeks in accordance with **Table 1** (assessment schedule) to identify proteinuria. The dipstick result must be collected but follow up action is only required based on the ACR result. If dipstick (and repeat if performed) is positive, it is recommended as there may be the possibility of a UTI, the treating investigator to consider testing for a UTI and recommending treatment at clinical discretion, alongside repeating the mandatory ACR (please also see section **6.3.2** for further information).

If only a positive dipstick is identified and ACR is not performed, an ACR must be performed within 1 week of the positive dipstick. If this is not possible, participant must pause treatment until an ACR can be performed.

Table 5: Management of trial treatment for proteinuria

ACR RESULT	ACTION
≤300 mg/g (<34 mg/mmol)	Continue on trial treatment.
301 – 1950 mg/g (≥34 mg/mmol – 220 mg/mmol)	Continue at current dose and retest within 2 weeks. If ACR is raised following retest (≥34mg/mmol) immediately discontinue treatment permanently. Refer participant to local nephrology team for evaluation and include details of nephrology referral in NE (or if required SAE) report*.
≥ 1950 mg/g (>220 mg/mmol)	Stop treatment immediately and permanently. Refer participant to local nephrology team for evaluation and include details of nephrology referral in NE (or if required SAE) report*.

*Note: all cases of macroalbuminuria, nephrotic syndrome, and glomerulonephritis should also be reported as notable events (NEs). All cases of renal biopsy must be noted on the related NE and AE report.

5.6.4 VITAMIN B12 DEFICIENCY

Participants that were eligible for the metformin arm must have their vitamin B12 checked at every scheduled in-person visit (except for week 4 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
> local lab lower limit of normal (LLN)	Continue on trial treatment.
≤ local lab lower limit of normal (LLN)	Stop trial treatment for 3 months and replace vitamin B12. Re-check at 3 months and commence trial treatment if > local LLN. If ≤ local LLN at 3 months, participant remain off IMP and replace Vitamin B12 for a further 3 months and re-check. If ≤ local LLN after 9 months post initial test, discontinue trial treatment

Clinical discretion should be used when deciding whether to return to high dose IMP immediately, or to gradually escalate over 2 weeks.

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 26 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 felt appropriate, the participant 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. If no rechallenge occurs and the adverse event is causally related to the IMPs, the participant can only pause trial treatment for maximum of 12 weeks.

- Upon re-challenge, if the participant can now tolerate the low dose, then they can be escalated to the high dose.
- Upon re-challenge, if the participant is unable to tolerate low dose trial treatment or they reach over 12 weeks pausing 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 with other toxicities (not listed in sections 5.6.1 – 5.6.4).

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 capsules) or temporarily paused (0 capsules). The participant can be re-challenged with high dose trial treatment (4 capsules) within up to 4 weeks of reduction.
- 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).
- 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 capsules) for the remaining duration of the trial.

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

Please note as per stated in section 5.6, at 26 weeks the maximum dose for the remainder of the trial will be determined by the treating clinician, and therefore should be included in the decision for any rechallenge as stated above.

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

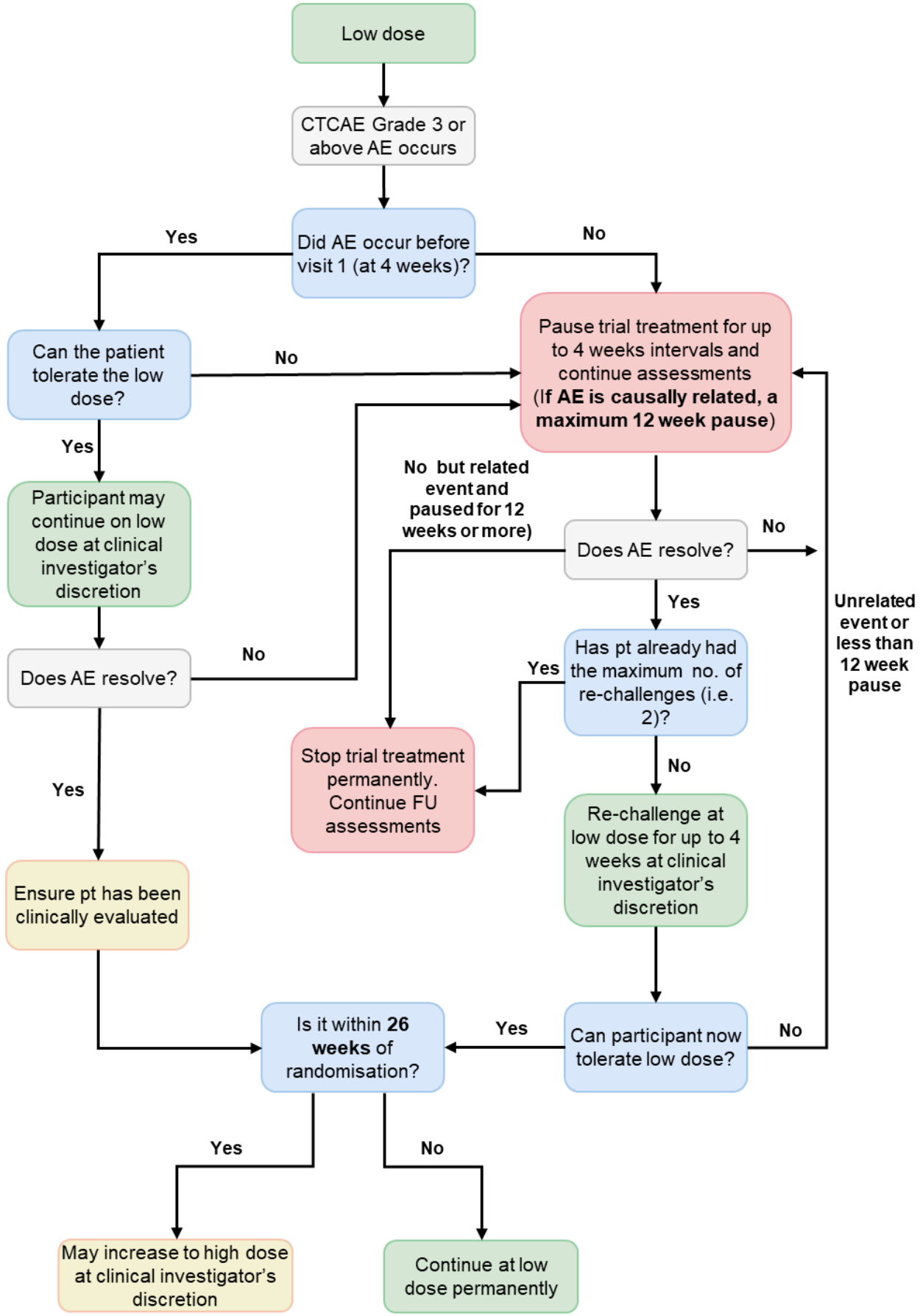
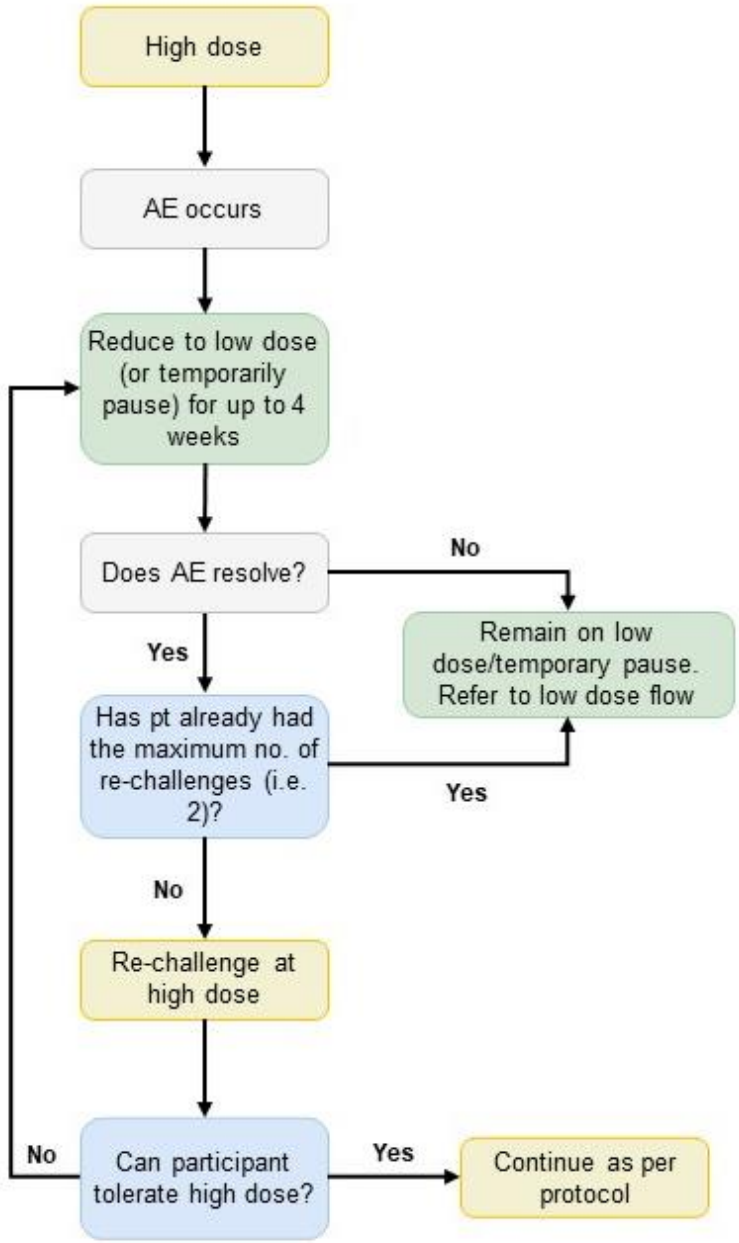


Figure 8: Treatment and dose diagram – High dose



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 screened and randomised in Analysis Stage 1, pregnancy checks prior to MRI must 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 via the OCTOPUS website. 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 in Participate, a module of the OCTOPUS eDC system. Participants will be sent a link to complete 2 days prior to their week 4 visit and 29 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

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 drug 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 or situation, 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 in the UK, the UCLH emergency number can be used to contact the OCTOPUS CI or Trial Physicians. For alternative contacts in non-UK countries, please refer to the CSA.

To unblind, the requesting treating doctor should provide on the OCTOPUS website, their full name, medical registration number and institutional email address (in the UK, this should be NHS email), 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 Sponsor within 24 hours of the occurrence through completion of an SAE on the OCTOPUS eDC system **without unblinding the Sponsor 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. Full details and guidance for unblinding are available on the OCTOPUS website.

5.11.2 Unblinding By The CTU

Sponsor 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 PI 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 PI 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 such as commencing any diabetic medication
- 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 (in Analysis Stage 1 only). 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 PI, as recorded on the Signature and Delegation of Responsibilities Log.

Trial treatment and compliance must be discussed at each in person visit and 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 Treatment log 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 Sponsor or local coordinating centre. Such records should only be sent securely, ideally via Galaxkey and include only 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 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:
OCTOPUS IMPs – R/S ALA and Metformin for any indication	R/S-ALA and Metformin
Cancer medications or treatment	R/S-ALA
Excessive Alcohol (investigator discretion)	R/S-ALA and Metformin
Diabetes medication (including Insulin used to treat diabetes (NB this does not apply to metformin see above)	R/S-ALA and Metformin
Iodinated contrast agents*	Metformin

*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 taking any of the OCTOPUS IMPs in addition to their trial treatment 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 OCTOPUS 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 ≤100mg, the participant must wait 7 days from the last dose before randomisation.

Whilst taking trial treatment, if the participant needs to commence any non-permitted medication(s) (except iodinated contrast agents) or OCTOPUS IMP, they must discontinue trial treatment for the remaining duration of the trial. The participant should remain in trial follow-up and complete all clinical assessments.

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
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. 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 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 assessor 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 assessors, who can be a doctor or appropriately trained healthcare professional, are responsible for collection of all clinical reported outcomes, excluding the relapse assessment. All assessors should be blinded to the clinical status of the participant.

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 must 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 2 weeks prior to the treatment visit. If prescriptions are issued prior to blood result availability or review due to local site procedure, appropriate procedures must be put in place to ensure participants are aware and receive written documentation of any dose modifications or treatment changes if required following review.

Additional haematology and clinical chemistry tests can also be carried out during the trial period as clinically indicated. Once participants have stopped trial treatment, bloods are not mandatory for the trial.

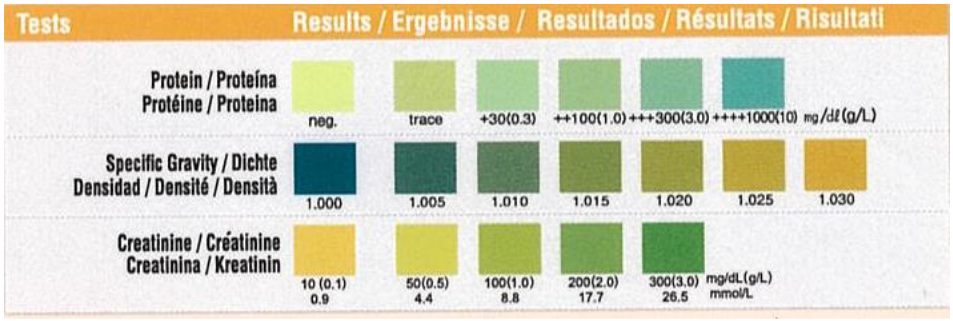
6.3.2 URINE DIPSTICK AND ACR

A urinary dipstick and ACR is required to be performed every 12 weeks whilst on trial 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 urinary dipstick test kits (reagent strip and small sterile container), an ACR collection kit (labelled sterile container and pre-paid postage material addressed to local trial site laboratory), 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. Dipsticks will be provided to sites for participants for use at

home. The dipstick is dipped into the urine sample (a mid-stream collection in a provided labelled 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

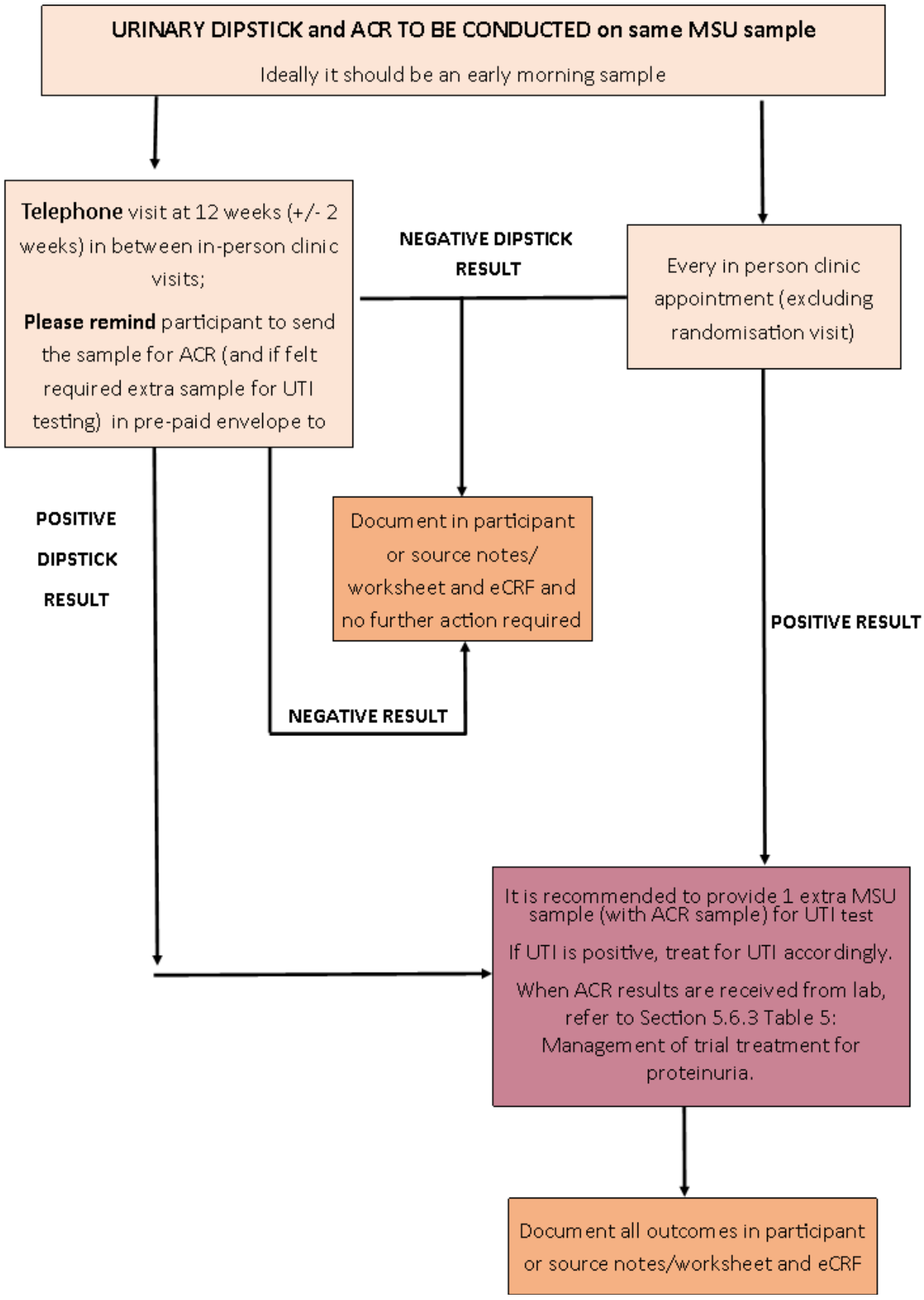


The participants should report the dipstick results to the study nurse or site research team following at home 12-weekly testing. If the dipstick is positive, it is recommended that an additional mid stream sample should be collected to check for UTIs and be treated as required according to clinical discretion.

For at-home ACR testing, the participant should use the same midstream specimen of urine collected for the dipstick, using the labelled sterile container provided. If this is not possible the ACR urine sample should be collected on the same day that the at-home dipstick test was performed. The sample should be placed in the pre-paid postage bag and box following the instructions provided and include the sample for UTI testing if required. The bag and box must be sealed securely and posted within 24 hours of collection. Once received at the local laboratory, the sample will be tested to measure the albumin/creatinine ratio (ACR) (and if required UTI).

All urinary dipsticks results and ACR results, must be documented in the patient or source notes or worksheets and both entered into the appropriate eCRF in the OCTOPUS eDC system. Please refer to **Figure 10**.

Figure 10: Urinary stick and ACR management flowchart



6.3.3 PREGNANCY

For WOCBP participants recruited in Analysis Stage 1, 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 medical 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 in all Analysis stages, 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 participating 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 assessors) 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 assessors, with the exception of the relapse assessment which should be conducted by the treating clinician.

6.5.1 EXPANDED DISABILITY STATUS SCALE (EDSS)

The assessor 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. As described in section 6.1, a treating clinician can only perform the EDSS assessment at screening as this is a component of the eligibility assessment. All other EDSS assessments throughout the trial must be conducted by an assessor.

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 medical notes and added to the AE log on the OCTOPUS eDC

system. The severity is determined by the grade as described in **Table 9** below. Grade 3 relapses should 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 *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.*

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 still be collected via the telephone by the study nurse or completed by the participant via links sent to them directly from Participate (module of the OCTOPUS eDC system). The exception to this is 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** [92, 95] - 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 [101] 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 in Participate in the OCTOPUS eDC system and so must be completed on paper worksheets and added to OCTOPUS eDC system by site teams.

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 to allow the trial and funders 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 UK MS Society annually and MS Australia. These charities aim 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.

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 National Registers 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 National Registers 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 Sponsor should be notified and the new site should perform the MRI in accordance to the criteria stipulated in section 2.1.2.

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 GP, 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 National Registers 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 National Registers 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 Sponsor responsibilities.

7.1 DEFINITIONS

The definitions for the OCTOPUS trial have been adapted from the Medicines for Human Use (Clinical Trials) Regulations 2004 (SI 2004/1031) and subsequent amendments, ICH E2A "Clinical Safety Data Management: Definitions and Standards for Expedited Reporting" and ICH GCP E6. 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: ▪ 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 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. For reporting purposes 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

The following are considered toxicities of interest for the OCTOPUS IMPS:

- Lactic acidosis
- Glomerulonephritis
    - Macroalbuminuria (defined as ACR > 34 mg/mmol to 220 mg/mmol (300-1950mg/g)
    - Nephrotic syndrome (defined as ACR > 220 mg/mmol (>1950mg/g)

If participants experience one of these above listed toxicities they should be reported as a notable event.

The Sponsor must be notified within 24 hours of the site becoming aware of the event. Notification is via the Adverse Event form in the OCTOPUS eDC system. These events may also be classed as serious and therefore if this is the case, they should 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 Sponsor 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.

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 Sponsor 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 Sponsor.

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 an Adverse 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 Sponsor should be notified of all SAEs and NEs 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 Adverse Event 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 in the UK to the MHRA using the yellow card system (or equivalent).

7.3.7 NOTIFICATION PROCEDURE

1. The SAE or NE must be entered onto 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. Note: pregnancy NEs should be reported by entering a positive pregnancy test result on the Lab eCRF. It should not be added to the AE log.

   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 Event 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 ID number, 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 Sponsor 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
your local coordinating centre

7.4 SPONSOR RESPONSIBILITIES (MRC CTU at UCL)

Medically qualified staff 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

MRC CTU is responsible for the reporting of SUSARs and other SARs in the UK 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 Sponsor becoming aware of the event; other SUSARs must be reported within 15 days.

MRC CTU will also submit the report to country coordinating centres (CCCs)/Country Lead Sites (CLSs) at least one business day before the submission deadline, to allow time for local reporting. The CCC/CLS will be responsible for forwarding SUSAR reports to their local ethics committee(s), as required, their local regulatory authority and any other organisations as identified in the agreement between the CCC and MRC CTU.

MRC CTU will submit Annual Safety Reports in the form of a Developmental Safety Update Report (DSUR) to UK Competent Authorities (Regulatory Authority and Ethics Committee) and all CCCs/CLSs. It will be submitted to any relevant pharmaceutical collaborator when required. CCCs/CLSs must forward all reports to the regulatory authority and ethics committee(s) and any other organisations as identified in the agreement between MRC CTU and the CCC/CLS in that country according to the timelines outlined in the agreement between MRC CTU and the CCC/CLS.

MRC CTU 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 MRC CTU at UCL's Research Governance Committee (RGC) who represent the Sponsor 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 SPONSOR CENTRAL MONITORING

MRC 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 Sponsor or CCC 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 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 with the exception of Patient Reported Outcomes reported via Participate, Clinical reviewer form for event reviews, adverse event MedDRA coding, and values that are derived by the OCTOPUS eDC system such as AE number. OCTOPUS source data worksheets can be utilised and is recommended to sites.

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 electronic or 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 [54].

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

The trial analyses will be split into two phases: assessment on whether treatment shows sufficient promise of benefit (Analysis Stage 1), and assessment for treatment efficacy (Analysis Stage 2). Analysis Stage 1 will determine if there is sufficient evidence of benefit for each trial treatment compared to SOC plus placebo, so that continued recruitment to and follow-up of that treatment arm in Analysis Stage 2 will be judged.

9.2.1 ANALYSIS STAGE 1 PRIMARY OUTCOME MEASURE: COMPOSITE OF EDSS, T25FW, 9HPT AND WHOLE BRAIN ATROPHY

The primary outcome for the Analysis Stage 1 is a linear combination of the rate of change of each measure in a composite outcome comprised of: Expanded Disability Status Scale (EDSS), Timed 25 Foot Walk (T25FW), 9 Hole Peg Test (9HPT) and whole Brain Atrophy. The measures that make up the composite will be standardised and linearly combined giving equal weight to each outcome measure.

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, for Analysis Stage 1 there will be up to six measurements of whole brain atrophy for each trial participant with MRI (125 per arm) showing change between:

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

EDSS, T25FW and 9HPT will be assessed from all available visits up to the time of the Analysis Stage 1, which is planned to take place once all participants have completed the M18 (week 78) visit. Therefore, data is anticipated to include measures up to M36 (week 156). These three CROMS will not be dichotomised to a disability progression outcome for Analysis Stage 1. Instead, T25FW and 9HPT will be inverted to 'speed' rather than time to reduce skew, and together with EDSS will each be standardised according to their respective random slope standard deviation. This implies a standardisation defined by the rate of change, which is the treatment effect metric.

A multivariate linear mixed model will be used to compare the rate of change on the outcome between each active trial treatment and SoC plus placebo using all available data for each measure of the composite outcome (see brief analysis plan for the model that will be used).

9.2.2 Analysis Stage 1 Secondary Outcome Measures: MRI

1. Whole brain atrophy rate

9.2.3 Analysis Stage 1 Secondary Outcome Measures: Clinician Reported Outcomes

1. Expanded Disability Status Scale (EDSS)
2. Timed 25 Foot Walk (T25FW)
3. 9 Hole Peg Test (9HPT)

The decision on whether a treatment shows sufficient evidence of benefit will be based on results for the composite outcome and its components (EDSS, T25FW, 9HPT and whole brain atrophy). If a treatment arm is discontinued then results will be presented using data accumulated up to the time of discontinuation. This will include presenting treatment effects on the full set of primary and secondary outcomes listed under Analysis Stage 2.

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); ≥ 20% increase in 9HPT; and ≥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 ≥ 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

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 MRI measures (for N=375) will be:

1. Whole brain atrophy rate
2. Regional GM atrophy rate
3. Cervical cord atrophy rate
4. T2 lesion volume change

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 required power for Analysis Stage 1 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 >90% power, the trial uses a one-sided alpha of 0.45 acting as the threshold for a lack of benefit.

The sample size for Analysis Stage 1 evaluation of R/S-ALA and metformin was originally calculated for analysis of whole brain atrophy alone [104]. Under the assumption that the atrophy rate would be 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 [19-21, 42, 105-107]) it was determined that 125 participants per arm were required (375 participants in total) to have 95% power to detect a 0.15% per year reduction in the rate of whole brain atrophy with a one-sided alpha of 0.35. This calculation allowed for 11% drop-out.

Subsequently, external data indicated that Analysis Stage 1 may be underpowered if undertaken as originally planned. Firstly, the external trial data shown in Table 12 raised a concern that the reduction in whole brain atrophy with an effective treatment may be less than 0.15% per year reduction.

Table 12: Summary of findings on CPD and whole brain atrophy from four positive phase 3 trials in PMS

Study	Mean difference in whole brain atrophy %/year (95% CI / p=value)	Hazard ratio for CDP (95% CI)
EXPAND (siponimod) [18]	0.065 (0.010 to 0.120)[108]	0.79 (0.65 to 0.95)
ORATORIO (ocrelizumab) [19]	0.10 p=0.02	0.71 (0.58 to 0.87)
HERCULES (tolebrutinib) [109]	0.039 (-0.015 to 0.097)	0.69 (0.55 to 0.88)
ORATORIO - hand (ocrelizumab) [108]	-0.002 (-0.091 to 0.087)	0.70 (0.57 to 0.86)

In addition, a planned review of emerging data on whole brain atrophy from the OCTOPUS control arm, alongside data from the MS-STAT2 trial of high dose simvastatin in patients with secondary progressive MS, indicated that the standard deviation at week 78 may be higher, 0.87% per year, than the 0.55% per year that was originally assumed. Proceeding with the original planned analysis of brain atrophy rate alone on was calculated to reach only 69% power (with one-sided alpha of 0.35) to detect a 0.10% per year reduction in the rate of whole brain atrophy at week 78, which was substantially below the target 95% power at Analysis Stage 1. It was not possible to regain 95% power by further relaxing the alpha level to 0.40.

In response to these issues, the design of the Analysis Stage 1 was revised to compare the treatments on a composite outcome, comprised of EDSS, T25FW, 9HPT and whole brain atrophy. It is planned that the Analysis Stage 1 will still be conducted when all 375 patients who received MRI have reached week 78. To calculate the power for this revised interim analysis we used the approach of Frost et al,([110]) where one first defines the required design and variance matrices for a notional 2-person trial combined with the anticipated covariance matrix for repeated measures over time and across composite outcomes. Together, these matrices are then used to derive the treatment effect variance for that “2-person trial”. This variance is then scaled for the required or proposed (when calculating power) sample size, and the calculation is then performed as usual. The differing amounts of follow-up observed at Analysis Stage 1 can be accounted for using a pattern mixture approach where for each (independent) cohort, defined by their observed data pattern, the treatment effect variance is derived as above and then combined into an overall value.

These random effect and error covariance matrices were obtained through modelling of the data from the MS-STAT2 trial. Assuming that an active treatment reduces whole brain atrophy rate by 10% per year and causes a proportionate reduction of 30% in the rate of change on the clinically reported outcome measures (EDSS, T25FW, 9HPT), then an equally-weighted (EW) linear combination of all 4 outcomes measures will give the trial 90% power to detect a benefit for the comparison of each treatment to standard of SOC plus placebo, with one-sided alpha of 0.45. The 30% proportionate rate of change for each clinically reported outcome was chosen based on the treatment effects seen in previous positive trials in PMS. The power calculation allows for 5% 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 [111, 112]. 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).

9.3.2 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. In 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). When accounting for the possibility that an effective treatment may be discontinued at the end of Stage 1, power is anticipated to be >85% for each pairwise comparison of active treatment to SOC plus placebo at the end of Analysis Stage 2.

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 [19, 20, 41, 42, 105, 106]. 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 [18, 20, 21, 107]. 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 [111, 112]. 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, rate of change on the composite measure (whole brain atrophy, EDSS, T25FW, 9HPT) will be compared in a pairwise manner between each experimental arms vs control. Data on whole brain atrophy will be from 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). Data on the clinically reported outcomes (EDSS, T25FW, 9HPT) will be from the baseline visit, week 26, and every 26 weeks thereafter. 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.

A multivariate linear mixed model will be used to compare the rate of change between active and placebo treatment arms using all available data. For the clinically reported outcomes, the model for change over time will use a random slope. This model uses the measure of the outcome at each time point to estimate the mean rate of change by including time since baseline in the model as a fixed effect. Variables can influence the mean at baseline by their inclusion as fixed effects and the mean rate of change by their inclusion as a fixed effect interacting with time since baseline. For whole brain atrophy, the model will be based on a linear mixed model for the analysis of repeated direct measures of change [113]. This model uses the repeated measures of whole brain volume change between each pair of scans and mean atrophy rate is estimated by including the duration between each pair of MRI scans as a fixed effect. Variables are allowed to influence the mean atrophy rate through their interactions with duration between MRI scans.

For each measure that makes up the composite the difference in mean rate of change between SOC and active treatment will be estimated using a fixed effect model parameter interacting treatment group with time from baseline (for EDSS, T25FW, 9HPT only) or interacting treatment group with duration between MRI scans (whole brain atrophy only). No treatment effect is included at baseline. Other fixed effects in the model will be time since baseline / duration between MRI scans, main effects for the minimisation variables Sex, Age, baseline EDSS, Use of current DMT, PMS phenotype, and site category (for EDSS, T25FW, 9HPT only), and interactions between the minimisation variables and time / duration between MRI scans.

For each outcome of the composite, the model will include participant-level random effects to account for the correlation in repeated measures over time and across outcomes. The random effects covariance matrix for the clinically reported outcomes portion of the model will include a slope and intercept for each outcome, and covariances will be estimated between all random slopes and random intercepts, both within an outcome and between outcomes. The random effects covariance matrix for

the whole brain atrophy portion of the model will have 4 random participant specific deviations for each visit, but constrained to be equal, and a random slope term. There will also be a covariance term between the whole brain atrophy random slope and each of the random effect terms for the clinically reported outcomes.

The model will provide the estimated treatment effect for each outcome, along with the variance covariance matrix for the treatment effects, allowing for correct inference of any linear combination of the 4 outcome treatment effects.

A weighted linear combination of the 4 treatment effects will be calculated as:

$$\hat{\beta} = \omega_1\hat{\beta}_{Q=1} + \omega_2\hat{\beta}_{Q=2} + \omega_3\hat{\beta}_{Q=3} + \omega_4\hat{\beta}_{Q=4}$$

with variance:

$$Var(\hat{\beta}\ ) = \sum_{qA=1}^{4}\sum_{qB=1}^{4} \omega_{qA}\omega_{qB}Cov(\hat{\beta}_{qA}, \hat{\beta}_{qB})$$

Where,
$\hat{\beta}_{Q=i}$ is the estimated difference in mean rate of change between SoC and active treatment, for the *i*th outcome measure (EDSS, T25FW, 9HPT, or whole brain atrophy)
ω_i is the weighting for the *i*th outcome

For this analysis the (equal) weights will be ¼ for all 4 outcomes. The estimated treatment effect $\hat{\beta}$ will be presented with confidence intervals corresponding to the alpha level at Analysis Stage 1. A hypothesis test will be conducted against the null that $\hat{\beta}_2$=0 with test statistic:

$$Z = \hat{\beta}/SE(\hat{\beta})$$

It is anticipated that the outcomes will approximately 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, or if the multivariate joint model fails to converge, we will use bootstrap sampling to estimate the covariance matrix of treatment effects. Bootstrap samples will be taken in a manner that reflects the clustering nature of participants' repeated measurement data. From each bootstrap sample, the 4 individual component mixed models will be separately estimated. The resulting bootstrap distribution of the treatment effects will provide the covariance matrix to enable the calculation of the variance of the weighted linear combination of the 4 treatment effects as outlined above.

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.

A sensitivity analysis will be presented that allows each treatment group to have a different rate of whole brain atrophy during the first 6 months of treatment, in order to account for any pseudoatrophy.

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); ≥20% increase in 9HPT; and ≥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 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 [99, 103]. 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 [114], the MSIS-29v2 [77], a condition-specific measure will be considered for estimating QALYs through methods available in the literature[115].

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 [115]. Long term costs and health outcomes will be discounted using discount rates recommended by NICE [116].

10 ANCILLARY STUDIES

10.1 BIOREPOSITORY

A repository of biological samples from participants has been created. Participation in the biorepository will be optional. 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.

For details of collection in non-UK countries, please refer to the country-specific appendix.

In the UK, 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 (up to and including week 78)

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.

10.2 BIOREPOSITORY GOVERNANCE

The OCTOPUS biorepository in the UK 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 in the UK, and Griffith University in Australia. 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 [54] and prioritised given the finite nature of the specimens.

For Australian biorepository samples, proposals for use will be reviewed by Griffith University on behalf of the OCTOPUS TMG. 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 (or by Griffith University for Australian samples), 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.

10.3 PROTEIN BIOMARKERS EXPLORATORY ANALYSIS

Welsh Neuroscience Research Tissue Bank (WNRTB) will use samples collected within the biorepository to conduct an exploratory analysis of change in candidate protein biomarkers during Stage 1. Samples from week 0 and weeks 52 or 78 (as available) will be used to measure annualised change in biomarkers (including NfL, GFAP, CD27 and Factor I, Vitamin D-binding protein (VDBP) and CCL27) during Analysis Stage 1 follow-up. Samples are currently held in Cardiff under the governance of the WNRTB. Serum samples will be used to measure biomarkers using a combination of Single Molecular Array (SiMoA; e.g. NfL and GFAP), ELLA immunoassay platform (e.g. VDBP, CD27), and ELISA (e.g. CCL27 and Factor I) in Cardiff, using established protocols.

Raw data on biomarker concentration will be corrected for age, sex and body mass index, and results will be converted in Z-scores to allow combination of up to 6 markers into a single model. The contribution of blood biomarker change to the modelling of interim outcomes in Analysis Stage 1 will be explored. Results will be used to inform subsequent methodology including interim analysis of future arms, as well as having relevance for clinical trials of progressive MS beyond OCTOPUS.

11 REGULATORY & ETHICAL ISSUES

11.1 COMPLIANCE

11.1.1 REGULATORY COMPLIANCE

OCTOPUS will be conducted in ALL sites in compliance with the approved protocol, the Declaration of Helsinki 1996, the UK Data Protection Act 2018 (DPA number: Z6364106). In UK sites it is also conducted with the principles of Good Clinical Practice (GCP) as outlined in the Medicines for Human Use (Clinical Trials) Regulations 2004 (SI 2004/1031), as amended and as laid down by the ICH topic E6, and the UK Policy Framework for Health and Social Care Research.

For sites outside the UK and EU/EEA, this trial will adhere to the GCP requirements as outlined in relevant legislation in the country, including ICH GCP (E6), and in Australia and New Zealand the Therapeutics Goods Administration and the NHMRC National Statement on Ethical Conduct in Human Research (2007).

11.1.2 SITE COMPLIANCE

An agreement will be in place between the site and the Sponsor/CCC, setting out respective roles and responsibilities (see **Section 2**).

All non-UK sites must provide confirmation of approval of their local institution(s).

All sites will inform the Sponsor and local CCC as soon as they are aware of a possible serious breach of compliance so that it can be reported to regulatory authorities, ethics committees and any other required organisations as required if necessary within 7 days as per the 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)

The trial TMF, including trial participant data, will be securely retained by the Sponsor for a minimum of 25 years after the end of the trial. At participating sites, 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, country coordinating centres (see CSA), 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 if recruited into Analysis Stage 1 (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 described in **section 5.6**.
- Participants will be reimbursed for travel expenses (maximum amount per visit is defined in site agreement)
- 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

For UK sites, main REC approval and Health Research Authority approvals will be obtained 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 also be submitted to each Trust's Research and Development (R&D) office for approval, and for confirmation of their capacity and capability (C&C). Any further substantial amendments will be submitted and approved by the Main REC and HRA.

For non-UK countries, 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

For UK sites, the OCTOPUS trial protocol is submitted and reviewed by the MHRA, prior to protocol release (see CTA number on front cover). For non-UK countries, the protocol is submitted to the national competent authority within those countries for review and approval.

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 and other relevant regulatory authorities 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 a 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 (or local equivalent).

Further linkage for long-term analysis for these participants may occur through the National Registers 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 (or local equivalent).

11.5.3 END OF TRIAL DEFINITION

The OCTOPUS end of trial definition is when all arms are closed, all the data is entered into the OCTOPUS eDC system, and the database is checked and locked. Closure will be notified to MHRA, main ethics and each R&D department in the UK and all other competent authorities/ethics committees as required 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.

Country coordinating centres and/or non-UK sites will be sourcing, obtaining, and managing distribution of any additional local funding for the trial outside the UK.

In Australia, the trial is funded by MS Australia and MSWA.

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 in Analysis Stage 1 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 UK participating site. In non-UK sites, an equivalent agreement will be in place and see applicable CSA for details.

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.**

Please refer to the Australian Country Specific Appendix for details on Australian oversight committees.

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, working with the country coordinating centres where relevant. 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, country coordinating centres, field experts and other OCTOPUS clinicians and site staff. The groups 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 UK MS Register, communication coordination and input from MS Society PPI forums where required.
- The **MRI Group** coordinates the collection, assessment, and storage of MRI scans in Analysis Stage 1 by UCL Queen Square Institute of Neurology, MS Unit.
- The **Treatment Advisory Committee** [1] 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.
- PLATYPUS country coordinating centre are responsible for set up and coordination of sites in Australia and work with the TMT on day to day management of the trial.

14.2 TRIAL STEERING COMMITTEE [54]

The Trial Steering Committee [54] 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.

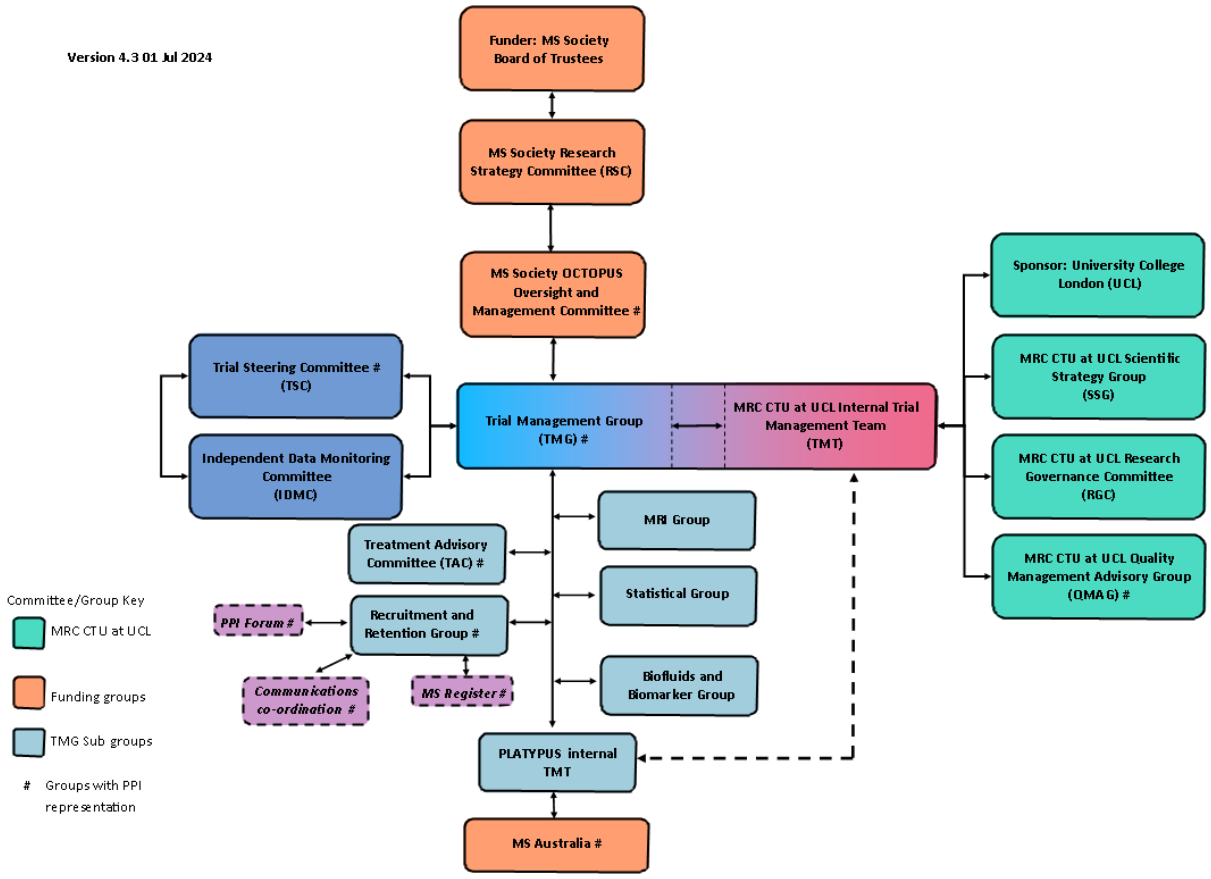
14.4 ROLE OF STUDY SPONSOR

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 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 (TMG) and has been involved from the start of the project. This is in addition to another person affect by MS who is on the TMG. A further three people affected by MS form part of the Treatment Advisory Committee [1].

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

- Trial Steering Committee [54]
- Communications sub-group
- MS Register sub-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.

A separate portfolio of PPI activity is ongoing for PLATYPUS, the Australian extension of the OCTOPUS trial. Details on Australian PPI input are documented in a local PPI Engagement Plan and CSA.

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 five people affected by MS as members of the TMG (including sub groups), TSC 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 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 Sponsor's controlled access approach and MRC CTU at UCL 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 be confirmed >50ml min/1.73m^2 (not 30ml min/1.73m^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 ≤200ng/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) >300mg/g or ≥ equal to 34mg/mmol

Summary of changes between v3.0 and V4.0

- Update to Trial team – Charlotte McGowan replaced as Trial Manager by Elizabeth Brodnicki
- Section 3.2 - Reinsertion of Participant Exclusion Criteria 3: Rare hereditary problems of galactose intolerance or glucose galactose malabsorption as previously moved to metformin specific criteria (in Metformin drug appendix)
- Update to R/S-Alpha lipoic acid specific appendix in section 2.2 the exclusion eligibility criteria clarification of units 34mg/mol should read 34mg/mmol. Therefore appendix version updated

to v4.0; 07-Sept-2023. Please note the Metformin specific appendix was not updated in this amendment and remains at v3.0.

Summary of changes between v4.0 and V5.0

In addition to correction of typos and grammatical errors, the protocol was updated to include the participation of Australian sites, and to ensure that any UK-specific references were amended accordingly. References to local Country-Specific Appendices were added where appropriate for additional information about trial conduct specifically in the country.

- Addition of Australian logos
- Inclusion of PLATYPUS (Australian extension of the OCTOPUS trial)
- Updates to compliance section to include sites outside the UK and EU/EEA
- Addition of funding bodies for PLATYPUS, the Australian extension of the OCTOPUS trial
- Updates to safety reporting contact details to make applicable for sites outside the UK
- Trial Administration and Co-ordinating Centre sections updated to include Olivia Mahoro, Aoife Nolan, and the Australian team contact details
- Simon Broadley added to the TMG member list
- MS Australia and MSWA added as funders
- Trial schema (figure 1 in protocol and drug appendices) updated to say “National Registers” instead of “MS Register”
- The trial assessment schedule was amended as follows:
    - TSH and T4 testing specified under thyroid profile tests
    - Vitamin B12 test is no longer required at week 4 visit
    - EDSS assessing clinician is now termed “EDSS assessor”
- Lay summary updated to include references to the trial activity outside the UK (i.e. PLATYPUS activity in Australia)
- GP abbreviation updated to include “(or known as family doctor outside UK)”
- PLATYPUS, Country Coordinating centre, country specific appendix and country lead sites added to abbreviation list
- Section 2.2 Approval and Activation, and section 2.3 Site Management: references to the CSA added here for non-UK sites
- Section 3.1 Participant Core Inclusion Criteria: eGFR cut off changed from eGFR ≥60ml/min/1.73m^2 to eGFR ≥65ml/min/1.73m^2
- Section 3.2 Participant Core Exclusion Criteria:
    - History of alcohol or drug use limited to within the last 5 years
    - Participation in another clinical trial of IMP of medical device ≤ 26 weeks before randomisation updated to “Use of an investigational medical product or investigational medical device ≤ 26 weeks before randomisation”
- Section 3.6:
    - Reference made to screening procedures used in Australia
    - Wording updated to state that a combination of on-site and remote monitoring of the completed consent forms will be utilised through the course of the trial
- Section 5.6 Expected Toxicities, Dose Modification & Discontinuations: the following sentence was removed “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."

- Section 5.6.1 Renal Impairment: parameters for renal impairment management were changed so that participants with eGFR of 45 – 59 ml/min/1.73m^2 must re-test within 4 weeks but can continue on current dose. If result remains 45 – 59 ml/min/1.73m^2 participants can remain on current dose but must be re-tested again at next in-person visit. Those with an eGFR <45 must permanently stop trial treatment.
- Section 5.6.3: management of proteinuria changed so that If ≥ 1000 mg/g (>113 mg/mmol), treatment must be paused until mandatory retest is completed (within 4 weeks). If retest remains ≥ 1000 mg/g (>113 mg/mmol), treatment must be stopped permanently.
- Section 5.6.4 Vitamin B12 deficiency management includes a statement confirming that it is up to clinical discretion whether to return to high dose immediately after successful B12 replacement therapy or to gradually escalate trial IMP over 2 weeks. It also highlights that a B12 test is not required at the week 4 visit
- Section 5.6.5 updated to allow for a temporary pause (not just a dose reduction) if a participant cannot tolerate high dose trial treatment
- Treatment and dose diagrams for low and high dose updated (Figure 7 and 8)
- Section 5.10 and both drug appendices: removal of the following sentence "Any dose in excess of that specified according to the protocol will constitute an overdose".
- Section 5.11.1 Emergency Unblinding section updated to make wording more generic by removing UK/NHS-specific references. Also updated to state that it can be carried out only in a medical emergency or situation
- Section 5.14.2 Medications not permitted: Definition of excessive alcohol is now as per investigator discretion.
- Section 5.14.3 Medications to be used with caution: instructions for re-starting after pause have been updated so that trial treatment can be resumed even if they are not within 24 weeks of randomisation.
- Section 6.1: more clarity on who can carry out assessments
- Section 6.2: blood tests can now be completed up to 2 weeks prior to the treatment visit (previously this was 1 week). Procedures must be in place for cases where a dose modification or treatment change is needed following blood test review.
- Specific UK provider of the urine dipstick kits removed
- Section 6.5: EDSS assessment instructions updated to include a reference to section 6.1.
- Section 6.5.6: Wording updated to clarify that the severity of grade 1 and 2 relapses should be documented in the medical notes and added to the AE log on the database. Grade 3 relapses should be reported as an SAE
- References to the Participate module of the database added to sections 5.9, 6.6, 6.6.7 and 8.4.
- Section 7.1 Safety reporting definitions updated to refer to the Medicines for Human Use (Clinical Trials) Regulations 2004 (SI 2004/1031) and subsequent amendments, ICH E2A "Clinical Safety Data Management: Definitions and Standards for Expedited Reporting" and ICH GCP E6.
- Section 7.1.3 Adverse and disease related events exempt from expedited reporting: "medical or surgical procedures; the condition that leads to the procedure is the adverse event" was moved from the bullet point list to the body of the paragraph test above

- Section 7.3.7 Notification procedure: instructions for reporting positive pregnancy test added (enter result on Lab eCRF and not on AE log).
- Minimum criteria for reporting an SAE was amended to remove date of birth
- Section 7.4 Sponsor responsibilities (MRC CTU at UCL): process for reporting outside the UK (via a country coordinating centre) added
- Section 8.4 Source Data: instances where eCRF is source data have been added
- Section 10.1 Biorepository: Reference to the CSA included for non-UK countries.
- Section 11.1 Compliance: updated wording to reference regulatory framework introduced since last amendment. Compliance wording for non-UK sites also added.
- Section 11.2.1 Ethical considerations: Travel expenses for participants changed from £40 to "maximum amount per visit is defined in site agreement"
- Section 11.2.2 Favourable ethical opinion: wording updated so it is also applicable to sites outside UK
- Section 11.3 Competent authority approvals: wording updated so it is also applicable to sites outside UK
- Section 11.5: Trial closure: wording updated so it is also applicable to sites outside UK
- Section 13 Finance: wording updated so it is also applicable to sites outside UK
- Section 14.1: Trial Management Group (TMG): wording updated to add reference to input from country coordinating centres.
- Figure 11 Relationship of trial committees scheme updated to include country coordinating centre input
- Section 15: Patient and Public Involvement: reference to Australia's PPI added
- Addition of drug manufacturers to metformin and R/S-ALA appendices
- Metformin drug appendix section 3.1: Changed "1000mg tablets" to "500mg tablets"
- R/S-ALA drug appendix section 3.1: Added clarification that 300mg capsules of R/S-ALA will be over encapsulated.

Summary of changes between v5.0 and V6.0

- Section 3.1 Participant Core Inclusion Criteria: eGFR cut off changed from eGFR ≥65ml/min/1.73m^2 to eGFR ≥60ml/min/1.73m^2

Summary of changes between v6.0 and V7.0

The main change in this protocol amendment is the removal of the QA approved MRI inclusion criteria, and the requirement for 3 follow up MRIs for those recruited in Analysis Stage 2. Some future tenses were also amended where it refers to aspects of the trial that have already been completed. A summary of all changes is provided below:

- Trial Administration: removal of data manager Christos Maniatis and replacing with Daneil Clarke
- Trial Administration: removal of trial manager Chloe Osbourne and replacing with Vanessa Vigar
- Trial Assessment Schedule: Week number (visit type) column headings updated from "On treatment" to"Participants on treatment", and "Completed treatment" to "Participants treatment & in FU"
- Trial Assessment Schedule: location of visit headings changed from "Telephone" to "Phone"

- Trial Assessment Schedule: footnotes B, D, F, and M updated to highlight that MRI is only required for participants randomised into Analysis Stage 1
- Lay Summary Background: specific reference to first Analysis Stage added to the "How will this trial be carried out" section ensuring that it is clear MRIs are only applicable to this Stage
- Abbreviations: duplicate 9HPT removed
- Section 1.6.1: reference added that use of MRI is only for Analysis Stage 1
- Section 2.1.1: GCP training requirement changed from 2 years to "2 to 3 years"
- Section 2.2: Approval and Activation - reference added to state that an MRI QA monitoring system is required for sites participating in Analysis Stage 1 only
- Section 2.3 Site Management – reference to Analysis Stage 1 added for QSMSC Institute of Neurology MRI responsibilities
- Section 3: wording updated to state that the eligibility criteria are for Analysis Stage 2 only (previously Analysis Stage 1)
- Section 3.1: Participant Core Inclusion Criteria – removal of criteria 10 and 11, and addition of a note highlighting that these are no longer core inclusion criteria in Analysis Stage 2:
    - [Please note no longer core inclusion criteria in Analysis Stage 2 - Must have a QC-approved (as defined in MRI guide) MRI ≤ 4 weeks before randomisation]
    - [Please note no longer core inclusion criteria in Analysis Stage 2 - 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)]
- Section 3.2: Participant Core Exclusion Criteria – updated wording of criteria 14 to refer to IMPs as "OCTOPUS" IMPs rather than "Analysis Stage 1" IMPs
- Section 3.6: Screening Procedures and Pre-Randomisation Investigations – updated wording to make completion of registration of interest mandatory regardless of how potential participants are identified
- Section 4.3: Re-Randomisation into OCTOPUS – added the wording "after the decision point", and added confirmation that participants who have withdrawn cannot be re-randomised if their arm hasn't closed
- Section 5.6.3: Proteinuria – Table 5 updated to remove "on repeat urinary dipstick"
- Section 5.6.3: Proteinuria – Table 5 footnote added to highlight that participants can only be re-challenged a maximum of two times
- Section 5.6.5: Other Toxicities – updated two typos ("capsule" to "capsules")
- Section 5.7: Contraception – added that only WOCBP screened and randomised in Analysis Stage 1 will require pregnancy checks prior to MRI
- Section 5.9: Compliance & Adherence – corrected typo ("a link will be sent a link" to "Participants will be sent a link") and changed timeline from "30 days" to "29 days" post all other clinic visits to complete
- Section 5.11.1: Emergency Unblinding – added sentence stating that full details and guidance for unblinding are available on the OCTOPUS website
- Section 5.13: Treatment Data Collection – added reference to Analysis Stage 1
- Section 5.14.2: Not permitted medications – changed "Analysis Stage 1 IMPs" to "OCTOPUS IMPs"
- Section 6.1: Trial Assessment Schedule – added space in third paragraph ("assessors should")
- Section 6.3.1: Bloods – Added sentence confirming that once participants have stopped trial treatment, bloods are not mandatory for the trial

- Section 6.3.3: Pregnancy – added specific reference that participants recruited in Analysis Stage 1 will require pregnancy check prior to MRIs, and clarification that pregnancies in all Analysis Stages will be reportable and must stop trial treatment
- Section 7.3.7: Notification Procedure – "The SAE or NE must entered to…" amended to "The SAE or NE must be entered onto the…"
- Section 10.2: Biorepository Governance – updated to include reference to Australian biosamples and that governance and ownership of these samples will be transferred to Griffith University (Australian National Sponsor) after the end of the trial. It was also noted that proposals for future use of Australian biosamples will be reviewed by Griffith University on behalf of the OCTOPUS TMG
- 11.2.1: Ethical Considerations – reference to Analysis Stage 1 added to second bullet point
- Section 13: Finance – reference to Analysis Stage 1 added for MRI scans acquisition costs
- Section 14.1: TMG – minor update to MRI Group description
- Section 15.3: Identifying PPI Contributors – updated wording to state that the team aims to include a minimum of five people affected by MS as members of the TMG (including subgroups), and removed reference to the MRI group in this section

Summary of changes between v7.0 and V8.0

The main change in this protocol amendment is the addition of mandatory albumin-creatinine-ratio (ACR) testing at screening and throughout the trial. This includes implementation of at-home urine sample collections for interim testing between in-person visits. A number of additional exclusion criteria have also been added to ensure the safety of potential trial participants. A summary of all changes is provided below:

- Trial Administration: addition of statistician Rachel Burton
- Trial Administration: removal of data manager Olivia Mahoro and replacing with Brendan Murphy
- Trial Administration: removal of trial manager Vanessa Vigar and replacing with Sabrina Oishi
- Trial Assessment Schedule: week number (visit type) column headings updated for consistency across pages
- Trial Assessment Schedule: prescription at week 12 updated to "optional"
- Trial Assessment Schedule: albumin added to haematology and biochemistry test list
- Trial Assessment Schedule: biorepository sample collection timepoints updated to remove collections beyond week 78
- Trial Assessment Schedule: footnotes B, F, G, J and K updated to clarify requirements around week 104 MRI and urine testing
- Section 3: Selection of Participants - clarification added to state that eligibility criteria only apply at the point of randomisation
- Section 3.2: Participant Core Exclusion Criteria –
    - addition of "significant non-MS neurological comorbidity" to criterion 2
    - updated wording of criterion 12 to refer to IMPs as "OCTOPUS" IMPs rather than "Analysis Stage 1" IMPs
    - updated wording of criterion 13 to include 3,4-aminopyridine
    - addition of criterion 16 to exclude participants that have had previous treatment with alemtuzumab or autologous haematopoietic stem cell therapy (AHSCT) ≤ 52 weeks prior to randomisation

  - addition of criterion 17 to exclude participants with an Albumin Creatinine Ratio (ACR) result of ≥34 mg/mmol (>300 mg/g) at screening, regardless of urine dipstick results
  - addition of criterion 18 to exclude participants with a diagnosis of diabetes mellitus
- Section 3.5: Co-Enrolment Guidelines – updated reference to section 4.2
- Section 3.6: Screening Procedures and Pre-Randomisation Investigations – changed "PLATYPUS Consortium Portal" to "MS Trial Screen"
- Section 3.6: Screening Procedures and Pre-Randomisation Investigations – updated wording to include reference to urine testing
- Section 3.6: Screening Procedures and Pre-Randomisation Investigations – addition of reference to the Australian Country Specific Appendix for local Australian requirements
- Section 5.4.1: Initial or Low Dose – participants must take two capsules once daily for a minimum of 3 weeks following randomisation before consideration for dose escalation
- Section 5.4.2: High Dose – updated so that the first 26 weeks (rather than 24 weeks) post randomisation will determine the participants maximum dose during the trial
- Section 5.6: Expected Toxicities, Dose Modifications & Discontinuations – updated from 24 to 26 weeks
- Section 5.6.3: Proteinuria – section updated to reflect new requirement for ACRs to be carried out every 12 weeks, alongside urine dipsticks
- Section 5.6.3: Proteinuria – Table 5 updated to reflect new ACR requirements. It also includes guidance for trial teams to refer participant to local nephrology team for evaluation if ACR result is above normal range
- Section 5.6.3: Proteinuria – Table 5 footnote added to highlight that all cases of macroalbuminuria, nephrotic syndrome, and glomerulonephritis should also be reported as notable events (NEs) and that any renal biopsy results must be noted on the related NE and AE report
- Section 5.6.4: Vitamin B12 Deficiency – Table 6 updated to refer to local lab lower limit of normal range rather than an absolute protocol cut-off range
- Section 5.6.5: Other Toxicities – guidance has been updated around managing toxicities arising when on low dose
- Section 5.6.5: Other Toxicities – Figure 7 "Treatment and dose diagram – low dose" updated to reflect updated guidance
- Section 5.12: Trial Treatment Discontinuation – addition of "commencement of any diabetic medication"
- Section 5.14.2: Medications Not Permitted – Table 7 and guidance text updated to note that diabetes medication (including insulin and metformin) are not permitted during the trial. If a participant needs to commence a non-permitted medication then they must discontinue trial treatment for the remaining duration of the trial but should remain in trial follow-up and complete all clinical assessments
- Section 5.14.3: Medications to be Used with Caution – Table 8 updated to remove diabetic drugs
- Section 6.3.2: Urine Dipstick and ACR – section updated to include at-home testing instructions for additional ACR tests required alongside urine dipstick testing
- Section 6.3.2: Urine Dipstick and ACR – Figure 10 updated to reflect new at-home ACR testing requirements

- Section 7.2.1: Toxicities – "glomerulonephritis" notable event has been expanded to define macroalbuminuria and nephrotic syndrome reporting requirements
- Section 7.2.2: Pregnancy – removal of "end of treatment period or end of trial regardless of the outcome" as pregnancies occurring during the trial will always be followed until the outcome of pregnancy has been established
- Section 10.1: Biorepository – updated to note that samples will only be collected up to and including week 78
- 11.1.3: Data Collection & Retention (Archiving) – addition of Sponsor retention requirements Section 14: Oversight & Trial Committees - addition of reference to the Australian Country Specific Appendix for local Australian oversight committees
- Section 15.2: Patient and Public Involvement Advisory Groups – updated wording describe the PPI representatives that are currently part of the TMG, communications sub-group, and MS register sub-group

Summary of changes between v8.0 and V9.0

The main change in this protocol amendment is revision of the Analysis Stage 1 primary outcome. This is in addition to clarification of an exclusion criteria and non-permitted medications and addition of biomarker exploratory analysis. A summary of all changes is provided below:

- Trial Administration: addition of statistician Farjana Haque
- Summary trial table updated due to change to the Analysis Stage 1 outcome this updated the following:
    - Definition of stages
    - Analysis Stage 1 Primary Outcome Measure(s)
    - Analysis Stage 1 Secondary Outcome Measure(s)
    - Analysis Stage 1 Exploratory Analysis
    - Analysis Stage 2 Secondary Outcome Measure(s)
    - Number of Participants to be Studied
- Corrected typos in Assessment schedule
- Update to lay summary in line with the change to Analysis Stage 1 primary outcome
- Section 1.4 Rationale for adaptive trial design and changes made
- Section 1.9.2 created for the addition of the background for the Protein Biomarkers exploratory analyses
- Section 3.2 Participant Core Exclusion Criteria – clarification to criteria 2 "Significant comorbidity (as confirmed by treating clinician) that includes but not limited to the following:" and the addition of "Hepatic" impairment" to the bullet points.
- Section 3.4 Clarification to number of participants
- Section 5.14.2 Non permitted medications – clarification added to table 7 for use of OCTOPUS IMPs and diabetic medication
- Section 6.1 clarified Participant reported outcomes are not collected by blinded assessors
- Section 9 Statistical considerations this updating the changes to Analysis Stage 1 primary outcome which updates the following subsection:
    - Section 9.2 Outcome measures
    - Section 9.3 Sample Size
    - Section 9.5.1 Analysis Stage 1 SAP
- Section 10.3 addition of the detail of the Protein biomarkers exploratory analysis

19 REFERENCES

1. Amato, M.P., et al., *Cognitive assessment and quantitative magnetic resonance metrics can help to identify benign multiple sclerosis.* Neurology, 2008. **71**(9): p. 632-8.
2. Atlas of MS, M.I.F. *https://www.atlasofms.org/map/global/epidemiology/number-of-people-with-ms*. 2021 [cited 2021 04-May-20201].
3. Polman CH, R.S., Banwell B, Clanet M, Cohen JA, Filippi M, et al., *Diagnostic criteria for multiple sclerosis: 2010 Revisions to the McDonald criteria.* Ann. Neurol. , 2011. **69**: p. 292–302.
4. Lublin, F.D., et al., *Defining the clinical course of multiple sclerosis: the 2013 revisions.* Neurology, 2014. **83**(3): p. 278-86.
5. Thompson, A.J., et al., *Diagnosis of multiple sclerosis: 2017 revisions of the McDonald criteria.* Lancet Neurol, 2018. **17**(2): p. 162-173.
6. Scalfari, A., et al., *The natural history of multiple sclerosis: a geographically based study 10: relapses and long-term disability.* Brain, 2010. **133**(Pt 7): p. 1914-29.
7. Tremlett, H., Z. Yinshan, and V. Devonshire, *Natural history of secondary-progressive multiple sclerosis.* Mult Scler, 2008. **14**(3): p. 314-24.
8. McCrone, P., et al., *Multiple sclerosis in the UK: service use, costs, quality of life and disability.* Pharmacoeconomics, 2008. **26**(10): p. 847-60.
9. Chataway, J., et al., *Secondary progressive multiple sclerosis: a systematic review of costs and health state utilities.* Current Medical Research and Opinion, 2021. **37**(6): p. 995-1004.
10. Thompson, A., et al., *New insights into the burden and costs of multiple sclerosis in Europe: Results for the United Kingdom.* Multiple Sclerosis Journal, 2017. **23**: p. 204-216.
11. Frohman, E.M., et al., *Therapeutic considerations for disease progression in multiple sclerosis: evidence, experience, and future expectations.* Arch Neurol, 2005. **62**(10): p. 1519-30.
12. Bjartmar, C., et al., *Neurological disability correlates with spinal cord axonal loss and reduced N-acetyl aspartate in chronic multiple sclerosis patients.* Ann Neurol, 2000. **48**(6): p. 893-901.
13. Compston, A. and A. Coles, *Multiple sclerosis.* Lancet, 2008. **372**(9648): p. 1502-17.
14. Barkhof, F., et al., *Imaging outcomes for neuroprotection and repair in multiple sclerosis trials.* Nat Rev Neurol, 2009. **5**(5): p. 256-66.
15. Lassmann, H., J. van Horssen, and D. Mahad, *Progressive multiple sclerosis: pathology and pathogenesis.* Nat Rev Neurol, 2012. **8**(11): p. 647-56.
16. Ontaneda, D., R.J. Fox, and J. Chataway, *Clinical trials in progressive multiple sclerosis: lessons learned and future perspectives.* Lancet Neurol, 2015. **14**(2): p. 208-23.
17. Fox, R.J. and J. Chataway, *Advancing trial design in progressive multiple sclerosis.* Mult Scler, 2017. **23**(12): p. 1573-1578.
18. Kappos L, B.-O.A., Cree BAC, et al. , *Siponimod versus placebo in secondary progressive multiple sclerosis (EXPAND): a double-blind, randomised, phase 3 study.* The Lancet, 2018. **391**: p. 1263–73.
19. Montalban, X., et al., *Ocrelizumab versus Placebo in Primary Progressive Multiple Sclerosis.* N Engl J Med, 2017. **376**(3): p. 209-220.
20. Kapoor, R., et al., *Effect of natalizumab on disease progression in secondary progressive multiple sclerosis (ASCEND): a phase 3, randomised, double-blind, placebo-controlled trial with an open-label extension.* Lancet Neurol, 2018. **17**(5): p. 405-415.
21. Lublin F, M.D., Freedman MS, et al. , *Oral fingolimod in primary progressive multiple sclerosis (INFORMS): a phase 3, randomised, double-blind, placebo-controlled trial.* The Lancet 2016. **387**: p. 1075–84.
22. Sydes, M.R., et al., *Flexible trial design in practice - stopping arms for lack-of-benefit and adding research arms mid-trial in STAMPEDE: a multi-arm multi-stage randomized controlled trial.* Trials, 2012. **13**: p. 168.

23. Oxford, U.o. *RECOVERY (Randomised Evaluation of COVID-19 Therapy*. 2021 23-Nov-2021]; Available from: https://www.recoverytrial.net/results.
24. Miller, D.H., et al., *Measurement of atrophy in multiple sclerosis: pathological basis, methodological aspects and clinical relevance.* Brain, 2002. **125**(Pt 8): p. 1676-95.
25. Jenkinson M, B.J., Chappell M, Winkler A. , *Short Introduction to the General Linear Model for Neuroimaging Analysis*. 2017: Oxford University Press.
26. Rocca, M.A., et al., *Brain MRI atrophy quantification in MS: From methods to clinical application.* Neurology, 2017. **88**(4): p. 403-413.
27. Enzinger, C., et al., *Risk factors for progression of brain atrophy in aging: six-year follow-up of normal subjects.* Neurology, 2005. **64**(10): p. 1704-11.
28. Fox, N.C. and J.M. Schott, *Imaging cerebral atrophy: normal ageing to Alzheimer's disease.* Lancet, 2004. **363**(9406): p. 392-4.
29. Moran, C., et al., *Type 2 diabetes mellitus, brain atrophy, and cognitive decline.* Neurology, 2019. **92**(8): p. e823-e830.
30. van Elderen, S.G., et al., *Progression of brain atrophy and cognitive decline in diabetes mellitus: a 3-year follow-up.* Neurology, 2010. **75**(11): p. 997-1002.
31. Sarica, A., A. Cerasa, and A. Quattrone, *The neurocognitive profile of the cerebellum in multiple sclerosis.* Int J Mol Sci, 2015. **16**(6): p. 12185-98.
32. Schoonheim, M.M., et al., *Thalamus structure and function determine severity of cognitive impairment in multiple sclerosis.* Neurology, 2015. **84**(8): p. 776-83.
33. De Stefano, N., et al., *Clinical relevance of brain volume measures in multiple sclerosis.* CNS Drugs, 2014. **28**(2): p. 147-56.
34. Honce, J.M., *Gray Matter Pathology in MS: Neuroimaging and Clinical Correlations.* Mult Scler Int, 2013. **2013**: p. 627870.
35. Smith, S.M., et al., *Normalized accurate measurement of longitudinal brain change.* J Comput Assist Tomogr, 2001. **25**(3): p. 466-75.
36. Fox, N.C., et al., *Progressive cerebral atrophy in MS: a serial study using registered, volumetric MRI.* Neurology, 2000. **54**(4): p. 807-12.
37. FMRIB. *FSL* 2000; Available from: http://www.fmrib.ox.ac.uk/fsl. .
38. Jenkinson, M., et al., *Fsl.* Neuroimage, 2012. **62**(2): p. 782-90.
39. Cardoso, M.J., et al., *Geodesic Information Flows: Spatially-Variant Graphs and Their Application to Segmentation and Fusion.* IEEE Trans Med Imaging, 2015. **34**(9): p. 1976-88.
40. Smith, S.M., et al., *Accurate, robust, and automated longitudinal and cross-sectional brain change analysis.* Neuroimage, 2002. **17**(1): p. 479-89.
41. Chataway, J., et al., *Efficacy of three neuroprotective drugs in secondary progressive multiple sclerosis (MS-SMART): a phase 2b, multiarm, double-blind, randomised placebo-controlled trial.* Lancet Neurol, 2020. **19**(3): p. 214-225.
42. Chataway, J., et al., *Effect of high-dose simvastatin on brain atrophy and disability in secondary progressive multiple sclerosis (MS-STAT): a randomised, placebo-controlled, phase 2 trial.* Lancet, 2014. **383**(9936): p. 2213-21.
43. Furby, J., et al., *A longitudinal study of MRI-detected atrophy in secondary progressive multiple sclerosis.* J Neurol, 2010. **257**(9): p. 1508-16.
44. Bermel, R.A. and R. Bakshi, *The measurement and clinical relevance of brain atrophy in multiple sclerosis.* Lancet Neurol, 2006. **5**(2): p. 158-70.
45. Chard, D. and D. Miller, *Grey matter pathology in clinically early multiple sclerosis: evidence from magnetic resonance imaging.* J Neurol Sci, 2009. **282**(1-2): p. 5-11.
46. Fisher, E., et al., *Gray matter atrophy in multiple sclerosis: a longitudinal study.* Ann Neurol, 2008. **64**(3): p. 255-65.
47. Miller, D.H., A.J. Thompson, and M. Filippi, *Magnetic resonance studies of abnormalities in the normal appearing white matter and grey matter in multiple sclerosis.* J Neurol, 2003. **250**(12): p. 1407-19.

48. Fisniku, L.K., et al., *Gray matter atrophy is related to long-term disability in multiple sclerosis.* Ann Neurol, 2008. **64**(3): p. 247-54.
49. Vrenken, H., et al., *Recommendations to improve imaging and analysis of brain lesion load and atrophy in longitudinal studies of multiple sclerosis.* J Neurol, 2013. **260**(10): p. 2458-71.
50. Eshaghi, A., et al., *Deep gray matter volume loss drives disability worsening in multiple sclerosis.* Ann Neurol, 2018. **83**(2): p. 210-222.
51. Eshaghi, A., et al., *Temporal and spatial evolution of grey matter atrophy in primary progressive multiple sclerosis.* Neuroimage, 2014. **86**: p. 257-64.
52. Zivadinov, R., et al., *Mechanisms of action of disease-modifying agents and brain volume changes in multiple sclerosis.* Neurology, 2008. **71**(2): p. 136-44.
53. Dalton, C.M., et al., *Early development of multiple sclerosis is associated with progressive grey matter atrophy in patients presenting with clinically isolated syndromes.* Brain, 2004. **127**(Pt 5): p. 1101-7.
54. Eshaghi, A., et al., *Progression of regional grey matter atrophy in multiple sclerosis.* Brain, 2018. **141**(6): p. 1665-1677.
55. Evangelou, N., et al., *Regional axonal loss in the corpus callosum correlates with cerebral white matter lesion volume and distribution in multiple sclerosis.* Brain, 2000. **123 (Pt 9)**: p. 1845-9.
56. Kearney, H., D.H. Miller, and O. Ciccarelli, *Spinal cord MRI in multiple sclerosis--diagnostic, prognostic and clinical value.* Nat Rev Neurol, 2015. **11**(6): p. 327-38.
57. Casserly, C., et al., *Spinal Cord Atrophy in Multiple Sclerosis: A Systematic Review and Meta-Analysis.* J Neuroimaging, 2018. **28**(6): p. 556-586.
58. De Stefano N, G.A., Battaglini M, Rovaris M, Sormani MP, Barkhof F, et al., *Assessing brain atrophy rates in a large population of untreated multiple sclerosis subtypes.* Neurology, 2010(74): p. 1868–1876.
59. Wheeler-Kingshott, C.A., et al., *The current state-of-the-art of spinal cord imaging: applications.* Neuroimage, 2014. **84**: p. 1082-93.
60. Horsfield, M.A., et al., *Rapid semi-automatic segmentation of the spinal cord from magnetic resonance images: application in multiple sclerosis.* Neuroimage, 2010. **50**(2): p. 446-55.
61. De Leener, B., J. Cohen-Adad, and S. Kadoury, *Automatic Segmentation of the Spinal Cord and Spinal Canal Coupled With Vertebral Labeling.* IEEE Trans Med Imaging, 2015. **34**(8): p. 1705-18.
62. De Leener, B., S. Kadoury, and J. Cohen-Adad, *Robust, accurate and fast automatic segmentation of the spinal cord.* Neuroimage, 2014. **98**: p. 528-36.
63. Moccia, M., et al., *Longitudinal spinal cord atrophy in multiple sclerosis using the generalized boundary shift integral.* Ann Neurol, 2019. **86**(5): p. 704-713.
64. Healy, B.C., et al., *Approaches to normalization of spinal cord volume: application to multiple sclerosis.* J Neuroimaging, 2012. **22**(3): p. e12-9.
65. Oh, J., et al., *Spinal cord normalization in multiple sclerosis.* J Neuroimaging, 2014. **24**(6): p. 577-584.
66. Barkhof, F., et al., *MRI monitoring of immunomodulation in relapse-onset multiple sclerosis trials.* Nat Rev Neurol, 2011. **8**(1): p. 13-21.
67. Tur, C., et al., *Assessing treatment outcomes in multiple sclerosis trials and in the clinical setting.* Nat Rev Neurol, 2018. **14**(2): p. 75-93.
68. Meyer-Moock, S., et al., *Systematic literature review and validity evaluation of the Expanded Disability Status Scale (EDSS) and the Multiple Sclerosis Functional Composite (MSFC) in patients with multiple sclerosis.* BMC Neurol, 2014. **14**: p. 58.
69. Lechner-Scott, J., et al., *Can the Expanded Disability Status Scale be assessed by telephone?* Mult Scler, 2003. **9**(2): p. 154-9.
70. Langdon, D.W., et al., *Recommendations for a Brief International Cognitive Assessment for Multiple Sclerosis (BICAMS).* Mult Scler, 2012. **18**(6): p. 891-8.

71. Parmenter, B.A., et al., *Screening for cognitive impairment in multiple sclerosis using the Symbol digit Modalities Test.* Mult Scler, 2007. **13**(1): p. 52-7.
72. Van Schependom, J., et al., *The Symbol Digit Modalities Test as sentinel test for cognitive impairment in multiple sclerosis.* Eur J Neurol, 2014. **21**(9): p. 1219-25, e71-2.
73. Di Tucci, C., et al., *The role of alpha lipoic acid in female and male infertility: a systematic review.* Gynecol Endocrinol, 2021. **37**(6): p. 497-505.
74. Balcer, L.J., et al., *Contrast letter acuity as a visual component for the Multiple Sclerosis Functional Composite.* Neurology, 2003. **61**(10): p. 1367-73.
75. Balcer, L.J., et al., *Vision and vision-related outcome measures in multiple sclerosis.* Brain, 2015. **138**(Pt 1): p. 11-27.
76. Goldman, M.D., et al., *Evaluation of multiple sclerosis disability outcome measures using pooled clinical trial data.* Neurology, 2019. **93**(21): p. e1921-e1931.
77. Hobart, J. and S. Cano, *Improving the evaluation of therapeutic interventions in multiple sclerosis: the role of new psychometric methods.* Health Technol Assess, 2009. **13**(12): p. iii, ix-x, 1-177.
78. Hobart, J., et al., *The Multiple Sclerosis Impact Scale (MSIS-29): a new patient-based outcome measure.* Brain, 2001. **124**(Pt 5): p. 962-73.
79. Cohen, J.A., et al., *Disability outcome measures in multiple sclerosis clinical trials: current status and future prospects.* Lancet Neurol, 2012. **11**(5): p. 467-76.
80. Riazi, A., et al., *Multiple Sclerosis Impact Scale (MSIS-29): reliability and validity in hospital based samples.* J Neurol Neurosurg Psychiatry, 2002. **73**(6): p. 701-4.
81. McGuigan, C. and M. Hutchinson, *The multiple sclerosis impact scale (MSIS-29) is a reliable and sensitive measure.* J Neurol Neurosurg Psychiatry, 2004. **75**(2): p. 266-9.
82. Kobelt, G., D. Langdon, and L. Jonsson, *The effect of self-assessed fatigue and subjective cognitive impairment on work capacity: The case of multiple sclerosis.* Mult Scler, 2019. **25**(5): p. 740-749.
83. Heesen C, H.R., Melzig S, et al. , *Perceptions on the value of bodily functions in multiple sclerosis.* Acta neurologica Scandinavica 2018. **137**(3): p. 356-62.
84. O'Connor, A.B., et al., *Pain associated with multiple sclerosis: systematic review and proposed classification.* Pain, 2008. **137**(1): p. 96-111.
85. Foley, P.L., et al., *Prevalence and natural history of pain in adults with multiple sclerosis: systematic review and meta-analysis.* Pain, 2013. **154**(5): p. 632-642.
86. NICE. *Multiple Sclerosis in adults: management*. 2014, update November 2019 24/09/2021]; Available from: https://www.nice.org.uk/guidance/cg186
87. NICE. *Neuropathic pain in adults: pharmacological management in non-specialist settings*. 2013; updated Sept-2020 24/09/2021]; Available from: https://www.nice.org.uk/guidance/cg173
88. Jawahar, R., et al., *A systematic review of pharmacological pain management in multiple sclerosis.* Drugs, 2013. **73**(15): p. 1711-22.
89. James E, H.S., Foley P, Young CA, Tur C., *Pharmacological treatment for chronic central neuropathic pain in people with multiple sclerosis* Under Review - Cochrane Library.
90. Galer, B.S. and M.P. Jensen, *Development and preliminary validation of a pain measure specific to neuropathic pain: the Neuropathic Pain Scale.* Neurology, 1997. **48**(2): p. 332-8.
91. Rog, D.J., et al., *Validation and reliability of the Neuropathic Pain Scale (NPS) in multiple sclerosis.* Clin J Pain, 2007. **23**(6): p. 473-81.
92. CS., C., *Measurement of pain by subjective report.* Advances in Pain Research and Therapy 1989(12): p. 391-403.
93. Foley P, P.R., de Angelis F, et al., *Efficacy of Fluoxetine, Riluzole and Amiloride in treating neuropathic pain associated with Secondary Progressive Multiple Sclerosis. Pre-specified analysis of the MS-SMART double-blind randomised placebo-controlled trial.* . Under Review, 2021.

94. Dworkin, R.H., et al., *Core outcome measures for chronic pain clinical trials: IMMPACT recommendations.* Pain, 2005. **113**(1-2): p. 9-19.
95. Tan, G., et al., *Validation of the Brief Pain Inventory for chronic nonmalignant pain.* J Pain, 2004. **5**(2): p. 133-7.
96. Maggi, P., et al., *Paramagnetic Rim Lesions are Specific to Multiple Sclerosis: An International Multicenter 3T MRI Study.* Ann Neurol, 2020. **88**(5): p. 1034-1042.
97. Kodosaki, E., et al., *Combination protein biomarkers predict multiple sclerosis diagnosis and outcomes.* J Neuroinflammation, 2024. **21**(1): p. 52.
98. group, T.E., *EuroQol: a new facility for the measurement of health related quality-of-life.* Health Policy, 1990(16): p. 199-20.
99. Herdman, M., et al., *Development and preliminary testing of the new five-level version of EQ-5D (EQ-5D-5L).* Qual Life Res, 2011. **20**(10): p. 1727-36.
100. van Hout, B., et al., *Interim scoring for the EQ-5D-5L: mapping the EQ-5D-5L to EQ-5D-3L value sets.* Value Health, 2012. **15**(5): p. 708-15.
101. Beecham, J.a.K., M. , *Measuring Mental Health Needs*. 2001, Gaskell. p. 200-224.
102. Cunniffe, N., et al., *Systematic approach to selecting licensed drugs for repurposing in the treatment of progressive multiple sclerosis.* J Neurol Neurosurg Psychiatry, 2021. **92**(3): p. 295-302.
103. Devlin, N.J. and P.F. Krabbe, *The development of new research methods for the valuation of EQ-5D-5L.* Eur J Health Econ, 2013. **14 Suppl 1**: p. S1-3.
104. Leurent, B., Li, V., et al., *Multi-arm multi-stage trials for neuroprotection in progressive multiple sclerosis: outcome choice and trial design.* Neurology, 2021. **Submitted**.
105. Kapoor, R., et al., *Lamotrigine for neuroprotection in secondary progressive multiple sclerosis: a randomised, double-blind, placebo-controlled, parallel-group trial.* Lancet Neurol, 2010. **9**(7): p. 681-8.
106. Spain, R., et al., *Lipoic acid in secondary progressive MS: A randomized controlled pilot trial.* Neurol Neuroimmunol Neuroinflamm, 2017. **4**(5): p. e374.
107. Zajicek, J., et al., *Effect of dronabinol on progression in progressive multiple sclerosis (CUPID): a randomised, placebo-controlled trial.* Lancet Neurol, 2013. **12**(9): p. 857-865.
108. Giovannoni, G.e.a. *Efficacy and Safety of Ocrelizumab vs Placebo in Primary Progressive MS: Results of the Phase IIIb ORATORIO-HAND Study*. in *41st Congress of the European Committee for Treatment and Research in Multiple Sclerosis (ECTRIMS)*. 2025. Barcelona, Spain.
109. Fox, R.J., et al., *Tolebrutinib in Nonrelapsing Secondary Progressive Multiple Sclerosis.* N Engl J Med, 2025. **392**(19): p. 1883-1892.
110. Frost, C., M.G. Kenward, and N.C. Fox, *Optimizing the design of clinical trials where the outcome is a rate. Can estimating a baseline rate in a run-in period increase efficiency?* Stat Med, 2008. **27**(19): p. 3717-31.
111. Freidlin, B., Korn, EL, Gray, R. , *Multi-arm clinical trials of new agents: some design considerations.* . Clin Cancer Res, 2008. **14**: p. 4368 – 4371.
112. Howard, D.R., et al., *Recommendations on multiple testing adjustment in multi-arm trials with a shared control group.* Stat Methods Med Res, 2018. **27**(5): p. 1513-1530.
113. Frost C, K.M., Fox NC. , *The analysis of repeated 'direct' measures of change illustrated with an application in longitudinal imaging.* Stat Med., 2004. **15**(23(21)): p. 3275-86.
114. Kuspinar, A. and N.E. Mayo, *A review of the psychometric properties of generic utility measures in multiple sclerosis.* Pharmacoeconomics, 2014. **32**(8): p. 759-73.
115. Hawton, A., et al. , *Using the Multiple Sclerosis Impact Scale to Estimate Health State Utility Values: Mapping from the MSIS-29 Version 2, to the EQ-5D and the SF-6D.* Value in Health, 2012. **15**(8): p. 1084-1091.
116. NICE. *Guide to the methods of technology appraisal 2013*. 29-Jul-2018]; Available from: https://www.nice.org.uk/process/pmg9/chapter/introduction.

117. Abbasi, B., et al., *Alpha-lipoic acid improves sperm motility in infertile men after varicocelectomy: a triple-blind randomized controlled trial.* Reprod Biomed Online, 2020. **41**(6): p. 1084-1091.
118. Ibrahim, S.F., et al., *A study of the antioxidant effect of alpha lipoic acids on sperm quality.* Clinics (Sao Paulo), 2008. **63**(4): p. 545-50.
119. Wensink, M.J., et al., *Preconception Antidiabetic Drugs in Men and Birth Defects in Offspring : A Nationwide Cohort Study.* Ann Intern Med, 2022. **175**(5): p. 665-673.

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 who were screened and/or randomised in Analysis Stage 1, pregnancy checks prior to MRI must be performed, in line with local MRI practices and this may include a urine HCG pregnancy test. This must 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 [73, 117-119].

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 for participants randomised in Analysis stage 1, 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.

OCTOPUS
Optimal Clinical Trials Platform for Progressive Multiple Sclerosis

Protocol Drug Appendix: R/S-Alpha Lipoic Acid (ALA)

Version: 6.0
Date: 28-Aug-2025

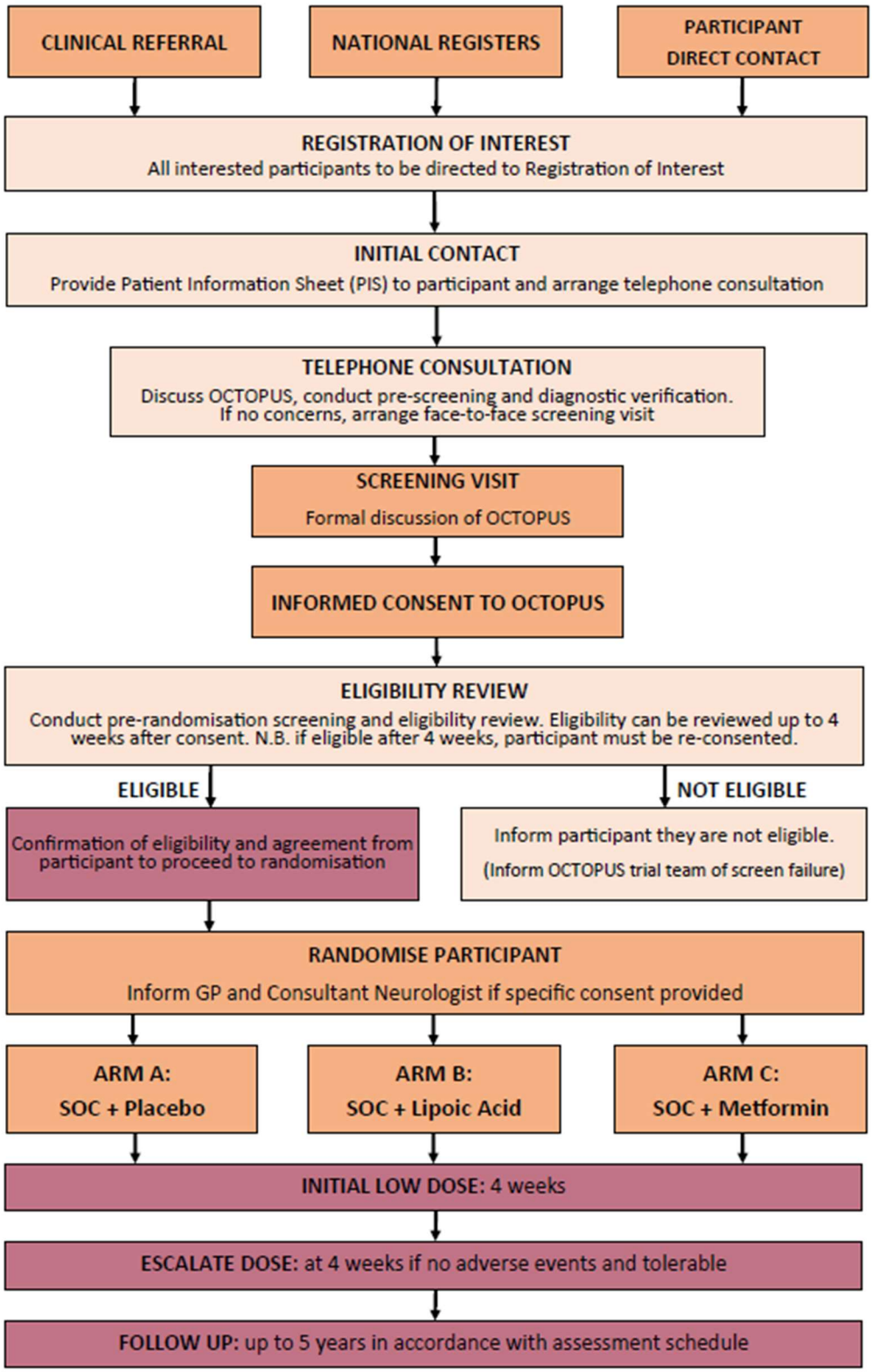
MRC CTU at UCL ID:	**ND001**
ISRCTN #:	**ISRCTN14048364**
EUDRACT #:	**2021-003034-37**
CTA #:	**CTA 20363/0445/001-0001**
MREC #:	**22/LO/0622**

Authorised by:
Name: Professor Jeremy Chataway
Role: Chief Investigator
Signature: DocuSigned by: Jeremy Chataway 8DC8C197DECD4B7...
Date: 29-Aug-2025

Name: Mahesh Parmar
Role: Director of MRC CTU at UCL
Signature: DocuSigned by: Max Parmar F1E2FB8B947644A...
Date: 01-Sep-2025

TRIAL SCHEMA

Figure 1: Trial Entry, Randomisation and Treatment: R/S-Alpha Lipoic Acid



CONTENTS

1 BACKGROUND: R/S-ALPHA LIPOIC ACID (ALA)

1.1 BACKGROUND AND MECHANISM

Alpha-lipoic acid (ALA) is an endogenous enzyme co-factor that occurs naturally in human cells. Endogenous ALA occurs as the R-enantiomer only (R-ALA); synthetic ALA may be a racemic mixture of both R- and S-enantiomers in a 1:1 ratio (R/S-ALA), or pure R-ALA alone. Essential to multiple mitochondrial enzymes [1], R-ALA is also a potent anti-oxidant, protecting mitochondria from oxidative damage and reducing excitotoxicity [2, 3]. Supplemental ALA may also have anti-inflammatory effects related to inhibition of nuclear factor-κB (NF-κB) ([4, 5], with reduced lymphocyte activity [6] and reduced toll-like receptor signalling-induced gene expression [7]. ALA is an effective treatment in EAE [8-11], and ALA is licenced in Germany for treatment of diabetic neuropathy.

1.2 RATIONALE FOR USE OF R/S-ALPHA LIPOIC ACID

ALA was selected for OCTOPUS based on evidence from both *in vivo* and *in vitro* studies that suggest it maybe anti-inflammatory, neuroprotective and has the ability to cross the blood brain barrier.

ALA is a potent antioxidant in nervous tissues [12] and in cell models of experimental autoimmune encephalomyelitis (EAE), ALA diminishes inflammatory cell migration into the brain, spinal cord and optic nerve, and inhibits macrophage/microglial activation [8-11]. The rodent MS model suggests that that infiltration of monocytes and B cells contributes to disease pathogenesis and basal migration of monocyte-enriched peripheral blood mononuclear cells (PBMCs) in RRMS subjects is significantly higher than healthy control PBMCs. George et al (2016) [13] showed that ALA treatment significantly inhibits monocyte and B cell migration in both cohorts. Salinthone et al (2010) [14] have shown that treating PBMCs from patients with progressive MS with ALA reduces IL-6 and IL-17 levels, and inhibited T cell activation and proliferation. Monocytes from racemic-ALA treated EAE mice were less migratory, and transwell assays of monocytes on rat brain endothelial cells and astrocytes in the presence of racemic-ALA reduced monocyte induced leakage of the endothelial layer suggesting protection of blood brain barrier integrity [15]

In EAE mouse models, ALA is associated with a time-dependent, rapid decrease in paralysis compared with controls and had significantly reduced inflammation, demyelination, axonal injury and infiltration of $CD3^+$ T cells and CD11b+ monocyte/macrophage cells in spinal cord [8, 15, 16].

In humans, ALA is already indicated for treating diabetes and nerve-related symptoms including peripheral neuropathy, but a recent a 2- year, randomized controlled trial of 54 patients with SPMS suggested R/S-ALA may also have a role in reducing MS progression. Spain et al in 2017 [17] demonstrated a 68% reduction in annualized percent change brain volume (PCBV) in 27 SPMS patients treated with R/S-ALA versus 24 treated with placebo and suggested a clinical benefit in that it showed an improved (but not significantly better) T25FW in the ALA group. This study also suggested favourable safety, tolerability, and compliance over 2 years.

Additional analyses from this trial cohort demonstrated possible beneficial effects of R/S-ALA on assessments of gait [18]. In a small study of acute optic neuritis (n=31), 6 weeks of R/S-ALA treatment did not reduce RNFL atrophy over 24 weeks compared to placebo.

1.3 R/S-ALPHA LIPOIC ACID DOSE JUSTIFICATION

Yadav et al in 2010 [11] found that patients with MS taking 1200 mg of R/S-ALA achieved comparable Maximum Serum Concentrations (C max in µg/ml) and area under the curve levels to those observed in mice receiving 50 mg/kg subcutaneous dose of lipoic acid, which is a highly therapeutic dose in experimental autoimmune encephalomyelitis. In the index trial [17] of R/S-ALA in Progressive MS used 600mg twice a day and so OCTOPUS will use the same dosage regimen following scientific contact with Professor Spain and will utilise this trial's monitoring schedule. Therefore R/S-ALA will be used in OCTOPUS at a dose of 600mg twice a day (high dose) with an initial low dose for first 4 weeks of 600mg once a day.

1.4 R/S-ALPHA LIPOIC ACID (ALA) TOXICITIES AND SAFETY

Preclinical data has suggested oral administration of R/S-ALA has lower risks of toxicity compared to IV routes. At high doses, the liver and kidney were the main targets of toxicity, with no evidence of carcinogenicity [19].

In September 2018, the FDA identified no reports of serious toxicity in human clinical trials or case reports. Mild gastrointestinal side effects or vertigo, however, occurred in up to 10% of patients (FDA).

Clinical trials have assessed the safety of R/S-ALA in health volunteers at doses of up to 2,400 mg/day with no reported adverse effects vs. placebo [20]. In patients with MS, doses of 1,200 mg R/S-ALA daily were well tolerated. Common adverse reactions were gastrointestinal intolerance, headache, malodorous urine, and rash [21]. R/S-ALA has favourable safety and tolerability in people with SPMS over 2 years [17]. Of 27 participants assigned to 1,200mg R/S-ALA, one patient withdrew due to prolonged nausea and vomiting which resolved following cessation of ALA; two patients took reduced doses (600mg) for the majority of the study (one due to gastritis, one due to raised ALP); one patient developed a mild vesicular rash that resolved on study completion; and 2 patients withdrew due to renal complications, not thought to be related to the ALA by a consulting nephrologist. Overall, gastrointestinal upset was significantly more common in the R/S-ALA group (14% vs 2%, p=0.007), and treatment compliance was 87% [17]. Liver and renal function will be monitored throughout follow up in accordance with the assessment schedule.

Another rare serious toxicity of R/S-ALA is that it can potentiate B12 deficiency in people with alcohol use disorder. Therefore, participants with a history of alcohol abuse will not be eligible for OCTOPUS.

A recent case series publication following two earlier phase 2 trials identified three cases (out of a combined total of 41 participants on ALA) of NELL-1 associated membranous glomerulonephropathy (MN) induced nephrotic syndrome, most likely secondary to ALA use [22]Click or tap here to enter

text.. A subsequent multi-site case series confirmed the association between MN and ALA use [23]Click or tap here to enter text.. Therefore the updated monitoring programme outlined by Spain et al. will be used NCT03161028 [17]. Therefore, in lieu of this data, renal function plus urinary albumin creatinine ratio (ACR) will be assessed at screening and monitored throughout follow up in accordance with the assessment schedule. It will be a requirement of for OCTOPUS for glomerulonephritis to be reportable as a notable event.

2 SELECTION OF PARTICIPANTS

2.1 PARTICIPANT CORE INCLUSION AND EXCLUSION CRITERIA

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 in **sections 3.1 and 3.2** in the main protocol in addition to the arm specific criteria below. If a participant is ineligible for this arm, they can be assessed for eligibility and randomised to other open arms.

2.2 R/S-ALPHA LIPOIC ACID SPECIFIC EXCLUSION ELIGIBILITY CRITERIA

In addition to the core inclusion and exclusion criteria documented in the main protocol, the following arm-specific exclusion eligibility criteria apply for the R/S-Alpha Lipoic Acid arm.

- Participants with known thiamine deficiency
- Participants with known biotin deficiency
- Participants who have undergone any bariatric surgery (including gastric bypass procedures)
- Hypersensitivity to R/S-Alpha Lipoic Acid
- Use of contraindicated medications that are not permitted with OCTOPUS IMPs (refer to section 5.14 in the main protocol). Please note a careful approach should be applied to those listed with caution. Please contact the OCTOPUS team if further advice is required.

3 TREATMENT OF PATIENTS: R/S-ALPHA LIPOIC ACID (ALA)

3.1 PRODUCT INFORMATION: R/S-ALPHA LIPOIC ACID (ALA)

- Lipoic R/S-enantiomer alpha acid (R/S-ALA) will be used in OCTOPUS.
- It is a sulphur containing vitamin like antioxidant.
- It is not a licenced product with no current UK marketing authorisation and therefore there is no PMS safety experience.
- The manufacturer and supply of R/S-ALA is Pure Encapsulations LLC.
- 300mg capsules of R/S-ALA will be over encapsulated, packaged, labelled and distributed by Sharp Clinical services and blinding will be maintained in weight and appearance.
- The half-life of alpha lipoic acid is 0.5 hours.

3.2 HANDLING CASES OF TRIAL TREATMENT OVERDOSE: R/S-ALPHA LIPOIC ACID

Measures will be taken to minimise accidental overdose of trial treatment by providing adequate education to trial participants. In the case of accidental or deliberate overdose of trial treatment, participants should be unblinded to their trial treatment (please see **section 5.10** of the main protocol) and then treated accordingly.

There is a one fatal case report of ALA overdose [24]. This was in a 14-year-old girl and estimated that 10 times the recommended dose was taken (6000mg). Multi-organ failure and death occurred. If a participant is ineligible for this arm, they can be assessed for eligibility and randomised to other open arms.

If a participant has an ALA overdose, participants should be contacted and assessed by the site team and hospital admission could be considered. The management of ALA overdoses should be as per standard clinical care by the local team. 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).

Any patient 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.

4 REFERENCES

1. Akbari, M., et al., *The effects of alpha-lipoic acid supplementation on glucose control and lipid profiles among patients with metabolic diseases: A systematic review and meta-analysis of randomized controlled trials.* Metabolism, 2018. **87**: p. 56-69.
2. Park, E., et al., *Protective Effects of Alpha-Lipoic Acid on Glutamate-Induced Cytotoxicity in C6 Glioma Cells.* Biological & Pharmaceutical Bulletin, 2019. **42**(1): p. 94-102.
3. Tang, L.H. and E. Aizenman, *Allosteric modulation of the NMDA receptor by dihydrolipoic and lipoic acid in rat cortical neurons in vitro.* Neuron, 1993. **11**(5): p. 857-63.
4. Liu, W., L.J. Shi, and S.G. Li, *The Immunomodulatory Effect of Alpha-Lipoic Acid in Autoimmune Diseases.* Biomed Res Int, 2019. **2019**: p. 8086257.
5. Sook Cho, Y.e.a., *A-Lipoic Acid Inhibits Airway Inflammation and Hyperresponsiveness in a Mouse Model of Asthma.* Journal of Allergy and Clinical Immunology, 2004. **114**(2): p. 429 - 435.
6. Waslo, C., et al., *Lipoic Acid and Other Antioxidants as Therapies for Multiple Sclerosis.* Curr Treat Options Neurol, 2019. **21**(6): p. 26.
7. Guo, J., et al., *Alpha-Lipoic Acid Alleviates Acute Inflammation and Promotes Lipid Mobilization During the Inflammatory Response in White Adipose Tissue of Mice.* Lipids, 2016. **51**(10): p. 1145-1152.
8. Marracci, G.H., et al., *Alpha lipoic acid inhibits T cell migration into the spinal cord and suppresses and treats experimental autoimmune encephalomyelitis.* J Neuroimmunol, 2002. **131**(1-2): p. 104-14.
9. Morini, M., et al., *alpha-Lipoic acid is effective in prevention and treatment of experimental autoimmune encephalomyelitis.* Journal of Neuroimmunology, 2004. **148**(1-2): p. 146-153.
10. Schreibelt, G., et al., *Lipoic acid affects cellular migration into the central nervous system and stabilizes blood-brain barrier integrity.* Journal of Immunology, 2006. **177**(4): p. 2630-2637.
11. Yadav, V., et al., *Pharmacokinetic study of lipoic acid in multiple sclerosis: comparing mice and human pharmacokinetic parameters.* Mult Scler, 2010. **16**(4): p. 387-97.
12. Nickander, K.K., et al., *Alpha-lipoic acid: antioxidant potency against lipid peroxidation of neural tissues in vitro and implications for diabetic neuropathy.* Free Radic Biol Med, 1996. **21**(5): p. 631-9.
13. George, J.D., et al., *Effects of lipoic acid on migration of human B cells and monocyte-enriched peripheral blood mononuclear cells in relapsing remitting multiple sclerosis.* J Neuroimmunol, 2018. **315**: p. 24-27.
14. Salinthone, S., et al., *Lipoic acid attenuates inflammation via cAMP and protein kinase A signaling.* PLoS One, 2010. **5**(9).

15. Schreibelt, G., et al., *Lipoic acid affects cellular migration into the central nervous system and stabilizes blood-brain barrier integrity.* J Immunol, 2006. **177**(4): p. 2630-7.
16. Morini, M., et al., *Alpha-lipoic acid is effective in prevention and treatment of experimental autoimmune encephalomyelitis.* J Neuroimmunol, 2004. **148**(1-2): p. 146-53.
17. Spain, R., et al., *Lipoic acid in secondary progressive MS: A randomized controlled pilot trial.* Neurol Neuroimmunol Neuroinflamm, 2017. **4**(5): p. e374.
18. Loy, B.D., et al., *Effects of lipoic acid on walking performance, gait, and balance in secondary progressive multiple sclerosis.* Complement Ther Med, 2018. **41**: p. 169-174.
19. *Pharmacy Compounding Advisory Committee Meeting*. 2018.
20. Shay, K.P., et al., *Alpha-lipoic acid as a dietary supplement: molecular mechanisms and therapeutic potential.* Biochim Biophys Acta, 2009. **1790**(10): p. 1149-60.
21. Yadav, V., et al., *Lipoic acid in multiple sclerosis: a pilot study.* Mult Scler, 2005. **11**(2): p. 159-65.
22. Spain, R.I., et al., *Lipoic acid supplementation associated with neural epidermal growth factor-like 1 (NELL1)-associated membranous nephropathy.* Kidney Int, 2021. **100**(6): p. 1208-1213.
23. Avasare, R.S., et al., *Characteristics and Outcomes of NELL1 Membranous Nephropathy in Lipoic Acid Users and Nonusers.* Kidney Int Rep, 2024. **9**(5): p. 1379-1386.
24. Hadzik, B., et al., *Fatal non-accidental alpha-lipoic acid intoxication in an adolescent girl.* Klin Padiatr, 2014. **226**(5): p. 292-4.

OCTOPUS
Optimal Clinical Trials Platform for Progressive Multiple Sclerosis

Protocol Drug Appendix: Metformin

Version: 5.0
Date: 28-Aug-2025

MRC CTU at UCL ID:	**ND001**
ISRCTN #:	**ISRCTN14048364**
EUDRACT #:	**2021-003034-37**
CTA #:	**CTA 20363/0445/001-0001**
MREC #:	**22/LO/0622**

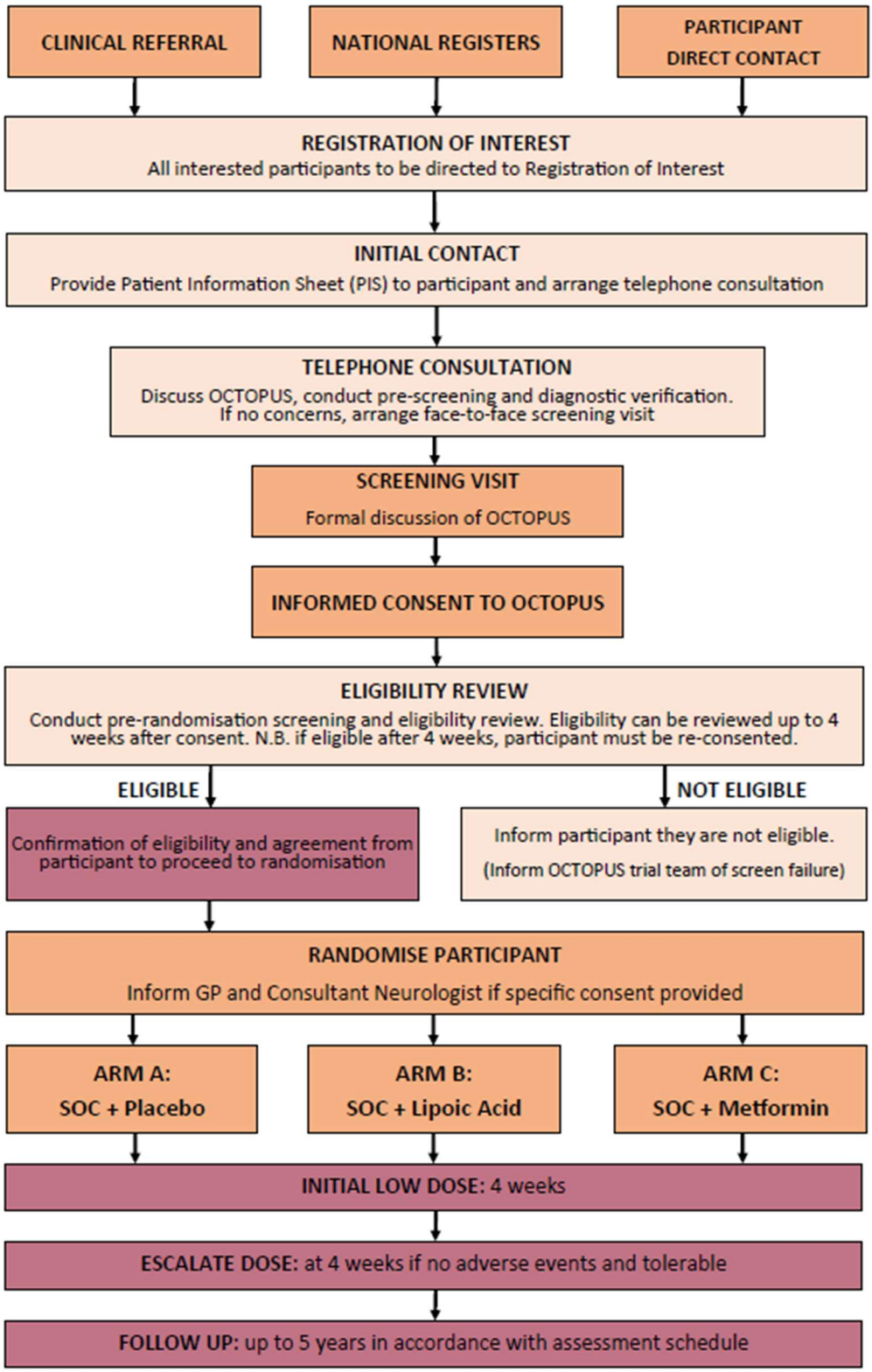
Authorised by:

Name: Professor Jeremy Chataway
Role: Chief Investigator
Signature: DocuSigned by: Jeremy Chataway 8DC8C197DECD4B7...
Date: 29-Aug-2025

Name: Mahesh Parmar
Role: Director of MRC CTU at UCL
Signature: DocuSigned by: Mahesh Parmar F1E2FB8B947644A...
Date: 01-Sep-2025

TRIAL SCHEMA

Figure 1: Trial Entry, Randomisation and Treatment: Metformin



CONTENTS

1 BACKGROUND: METFORMIN

1.1 BACKGROUND AND MECHANISM FOR METFORMIN

Metformin is a synthetic calorie restriction mimetic, and the most commonly used medication for type II diabetes mellitus (T2DM). In T2DM its principal mechanism of active appears to be via activation of adenosine monophosphate (AMP)-activated protein kinase (AMPK), and the resulting inhibition of gluconeogenesis in the liver. It does not act directly on AMPK, instead modulating multiple intracellular pathways, including mitochondrial complex I, AMP deaminase and G3PDH activity, culminating in AMPK activation [1].

Remyelination is likely to occur through the recruitment and differentiation of oligodendrocyte precursor cells (OPCs), or from regeneration of myelin by surviving mature oligodendrocytes [2]. In MS, the efficiency of remyelination declines with age, which in part may be due to reduced efficiency of OPC differentiation [3]. In vivo and in vitro, the differentiation of aged rat OPCs into remyelinating oligodendrocytes can be enhanced either through calorie restriction or through treatment with metformin. Metformin's mechanism of action in increasing OPC differentiation is dependent upon AMPK-activity and associated with improved mitochondrial function [3].

1.2 RATIONALE FOR USE OF METFORMIN IN OCTOPUS

Metformin was selected for OCTOPUS based on evidence from both *in vivo* and *in vitro* studies that suggest a role in neuroprotection and remyelination.

In isolated rat neuronal cells [4, 5], metformin improved the viability of neuronal cells in models of ischaemia and reperfusion injury. In a separate model, metformin treatment to adult rat oligodendroglia in culture improved their differentiation response to compounds promoting remyelination [3].

Animal models have also been encouraging. In rat models, metformin has been shown to improve blood-brain barrier integrity and downregulate both inflammatory cell infiltration and inflammatory cytokine production [6]. In rat models of ischaemia and reperfusion injury, metformin was found to inhibit apoptosis [7] and in rat models of experimental autoimmune encephalomyelitis (EAE), metformin was found to restore the central nervous system (CNS) remyelination capacity in aged rats (Neumann et al 2019). Also, in EAE, metformin has also been shown to be anti-inflammatory by restricting the infiltration of mononuclear cells into the CNS and therefore downregulating pro-inflammatory cytokines [8, 9]. Recent work by Largain et al (2019) [10] suggest that metformin also has an oligoprotective effect through the AMP-activated protein kinase (AMPK)-pathway. Transmission electron microscopy and luxol fast blue staining revealed that the myelinated axons within corpus callosum of cuprizone-induced demyelination animals increased after administration of metformin. Furthermore, the biochemical analysis demonstrated that metformin ameliorated the oxidative stress induced by cuprizone.

In terms of human studies of metformin in MS, there is a singled published phase 2 trial (Negrotto et al 2016) [11]. A non-randomised open-label phase 2 study, Negrotto et al. investigated the efficacy of metformin or pioglitazone on MRI-based disease activity measures in obese people with RRMS (pwRRMS) diagnosed with metabolic syndrome. Metformin was associated with a significant reduction in the number of new/enlarging T2 or T1 gadolinium enhanced lesions, compared to a pre-treatment phase, and compared to an untreated control group matched on baseline characteristics.

More recently, the CCMR2 trial [NCT05131828 [12] has been launched. This is a phase 2A trial assessing the combination of clemastine and metformin in relapsing remitting multiple sclerosis in patients who are on DMT. The trial will last 24 weeks per participant, and the primary outcome measure is the measurement of visual evoked potentials. The rationale for the CCMR2 trial is that (as stated above) experimental models show an ability of metformin to sensitise aged stem cells to the effect of clemastine, thereby enhancing its potential to stimulate remyelination. The CCMR2 trial chose people with RRMS with the view that they would be more able to achieve remyelination and require that they be on a DMT to reduce the confounding influence of a relapse.

OCTOPUS uses a similar rationale to the CCMR2 study, but in comparison will specifically look at those patients with progressive MS, will include a more liberal entry criteria including those with a greater degree of disability, and it will follow up patients over a far longer period of time. OCTOPUS will utilise whole brain atrophy as the primary outcome measure.

1.3 METFORMIN DOSE JUSTIFICATION

The dosing regimen described draws on both the clinical experience of metformin use in diabetes, combined with data from animal models that predicts what is likely to be effective at inducing remyelination. It also allows for the same dosing regimen as ALA for blinding purposes.

Using a published, widely accepted simple practice guide for dose conversion between animals and human [13], it can be anticipated that the dose of metformin needed in humans to replicate successful animal trials. In a mouse model of EAE, metformin 20 or 50 mg/kg did not provide significant protection, but doses of 100 mg/kg (equivalent to 600mg in a 75kg human) were enough to attenuate disease [8] - restricting the infiltration of mononuclear cells into the CNS, and down-regulating the expression of proinflammatory cytokines. In a separate study, experimental, aged, rat models demonstrated remyelination comparable with young animals when given with a relatively higher metformin dosing regimen of 300mg/kg (equivalent to 3600 mg per day in a 75kg humans).

Immediate release metformin will be used in OCTOPUS at an initial lower dose of 1000mg daily (500mg twice per day), up titrated to the higher dose of 2000mg daily (1000mg twice per day). The typical initial dosing regimen for metformin in diabetes is 500mg twice daily and the maximum immediate release formulation daily dosage in humans is 2,550mg per day. We feel 2000mg per day will provide an appropriate balance of benefit versus tolerability.

1.4 METFORMIN TOXICITIES AND SAFETY

1.4.1 GASTROINTESTINAL (GI)

The most common adverse events with metformin are mild gastrointestinal (GI) toxicities (nausea, vomiting, diarrhoea, abdominal pain, loss of appetite, taste disturbance), most of which resolves spontaneously following initiation. To mitigate this, the immediate release metformin will be used as this may be associated with less frequent GI side effects [14].

1.4.2 LACTIC ACIDOSIS

A rare serious side-effect or toxicity includes lactic acidosis. This is a rare (<7 per 100,000) but serious side effect of metformin use. It most commonly occurs in the setting of acute renal impairment or acute intercurrent illness, with a resulting accumulation in metformin. Additional factors include medicinal products that can be associated with a deterioration in renal function, excessive alcohol intake, hepatic insufficiency, uncontrolled diabetes and ketosis.

Lactic acidosis may present with hyperventilation, abdominal pain, muscle cramps, paraesthesias and hypothermia followed by coma. Suspected cases constitute a medical emergency, requiring immediate cessation of metformin and urgent medical assessment. The key diagnostic investigation is a blood gas, which will demonstrate acidosis (pH<7.35), raised lactate (>5mmol/L) and an increased anion gap (>16mEq/L).

Additional rare side effects include decreased absorption of vitamin B12, which may precipitate megaloblastic anaemia, isolated reports of LFT derangement of hepatitis, idiosyncratic skin reactions (including erythema, urticaria and pruritis).

The risk of lactic acidosis on metformin can be minimised principally through the identification of participants at risk of renal impairment:

- Exclusion criteria: factors known to increase the risk of lactic acidosis (reduced eGFR, history of alcohol abuse, hepatic impairment, decompensated heart failure, history of poor diabetic control or diabetes mellitus) will preclude study enrolment.
- At screening, participant's drug histories will be reviewed to identify medication that can be associated with renal impairment (NSAIDs, ACE inhibitors, angiotensin II antagonists, diuretics). Investigating physicians may exclude a participant from the trial if they perceive concomitant medications to put the participant at high risk of deteriorating renal function. Participants will be counselled on the risk of such medications, checked at each visit and issued with alert cards.
- Monitoring of renal function with appropriate metformin dose adjustment – renal function will be monitored during the trial and metformin dose adjustments made accordingly. If renal function declines significantly, metformin should be permanently stopped. For further details, please refer to **section 5.6.1** of the main protocol).
- Participants will be advised that in the case of acute medical illness (e.g. infections, severe dehydration or other acute illnesses requiring medical attention) they should cease taking IMP and inform the trial team as soon as possible.

- Medical procedures: due to risks of associated renal impairment, metformin must be stopped prior to surgery or the administration of iodine-based contrast agents (e.g. used in CT scans). Metformin can be restarted 48 hours after any such procedure, providing the participant has resumed normal oral intake and renal function has been assessed and found to be normal.
- Additional adverse events will be mitigated against through the monitoring of FBC (to detect megaloblastic anaemia) and LFTs (hepatic abnormalities) throughout the follow up, and through clinical assessment of participants to detect dermatological reactions.

1.5 PHARMACOKINETICS

Metformin's pharmacokinetics (absorption and excretion) are modulated principally by organic cation transporters 1 and 2 (OCT1/2).

- Coadministration with OCT1 inhibitors (verapamil) – may reduce absorption, and hence efficacy
- Coadministration with OCT1 inducers (rifampicin) – may increase absorption and potential toxicity
- Coadministration with OCT2 inhibitors (cimetidine, dolutegravir, ranolazine, trimethoprim, vandetanib, isavuconazole) – may decrease renal excretion, hence potentially increasing toxicity
- Coadministration with OCT1 and OCT2 inhibitors (crizotinib, Olaparib) may reduce absorption and excretion of metformin, hence unpredictably effecting potential toxicity

Participants taking such medications will be identified at screening. Caution is advised with such medications, especially if medications that may increase potential metformin toxicity are combined with impaired renal function.

If the medications cannot be ceased prior to randomisation, the local investigator will assess the perceived risk to the participant and exclude them from the study if this is believed to be unacceptably high. Participant will be counselled on the risk of such medications and issued with alert cards.

2 SELECTION OF PARTICIPANTS

2.1 PARTICIPANT CORE INCLUSION AND EXCLUSION CRITERIA

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 in **sections 3.1 and 3.2** in the main protocol in addition to the arm specific criteria below. If a participant is ineligible for this arm, they can be assessed for eligibility and randomised to other open arms.

2.2 METFORMIN SPECIFIC EXCLUSION ELIGIBILITY CRITERIA

In addition to the core inclusion and exclusion criteria documented in the main protocol, the following arm-specific exclusion eligibility criteria apply for the metformin arm must also be met:

- HbA1c ≥48mmol/mol (equivalent to ≥6.5%)
- Vitamin B12 ≤ the local lab lower limit of normal (LLN)
- History of lactic acidosis
- Administration of intravascular iodinated contrast agents ≤ 1 week prior to randomisation
- Hypersensitivity to metformin
- Use of contraindicated medications that are not permitted with OCTOPUS IMPs (refer to **section 5.14** in the main protocol). Please note a careful approach should be applied to those listed with caution. Please contact the OCTOPUS team if further advice is required.
- Rare hereditary problems of galactose intolerance or glucose-galactose malabsorption

3 TREATMENT OF PATIENTS: METFORMIN

3.1 PRODUCT INFORMATION: METFORMIN

- Immediate Release (IR) formulation metformin hydrochloride will be used in OCTOPUS.
- It is a licenced product used in Type 2 diabetes, with a well-established safety profile. However not in this indication and without MS safety experience.
- The metformin tablets used in OCTOPUS are manufactured by Relonchem.
- 500mg tablets will be used and be over encapsulated, packaged, labelled and distributed by Sharp Clinical Services and blinding will be maintained in weight and appearance.
- The half-life of metformin is 6.5 hours.

3.2 HANDLING CASES OF TRIAL TREATMENT OVERDOSE: METFORMIN

Measures will be taken to minimise accidental overdose of trial treatment by providing adequate education to trial participants. In the case of accidental or deliberate overdose of trial treatment, participants should be unblinded to their trial treatment (please see **section 5.10** of the main protocol) and then treated accordingly.

For metformin, hypoglycaemia has not been reported even with significant metformin overdoses although lactic acidosis has occurred in such circumstances. Participants should be urgently assessed in the event of an overdose and hospital admission considered. The management of metformin overdoses should be as per standard clinical care by the local team. The most effective way to remove lactate and metformin is haemodialysis. The re-introduction of trial treatment dosing will be determined by the clinical investigator at the participating site, in consultation with the OCTOPUS team (without unblinding them).

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.

4 REFERENCES

1. An, H. and L. He, *Current understanding of metformin effect on the control of hyperglycemia in diabetes.* J Endocrinol, 2016. **228**(3): p. R97-106.
2. Franklin, R.J.M., J. Frisen, and D.A. Lyons, *Revisiting remyelination: Towards a consensus on the regeneration of CNS myelin.* Semin Cell Dev Biol, 2021. **116**: p. 3-9.
3. Neumann, B., et al., *Metformin Restores CNS Remyelination Capacity by Rejuvenating Aged Stem Cells.* Cell Stem Cell, 2019. **25**(4): p. 473-485 e8.
4. Meng, X., et al., *Metformin Protects Neurons against Oxygen-Glucose Deprivation/Reoxygenation -Induced Injury by Down-Regulating MAD2B.* Cell Physiol Biochem, 2016. **40**(3-4): p. 477-485.
5. Mielke, J.G., C. Taghibiglou, and Y.T. Wang, *Endogenous insulin signaling protects cultured neurons from oxygen-glucose deprivation-induced cell death.* Neuroscience, 2006. **143**(1): p. 165-73.
6. Liu, Y., et al., *Metformin attenuates blood-brain barrier disruption in mice following middle cerebral artery occlusion.* J Neuroinflammation, 2014. **11**: p. 177.
7. Ge, X.H., et al., *Metformin protects the brain against ischemia/reperfusion injury through PI3K/Akt1/JNK3 signaling pathways in rats.* Physiol Behav, 2017. **170**: p. 115-123.
8. Nath, N., et al., *Metformin attenuated the autoimmune disease of the central nervous system in animal models of multiple sclerosis.* J Immunol, 2009. **182**(12): p. 8005-14.
9. Sun, Y., et al., *Metformin ameliorates the development of experimental autoimmune encephalomyelitis by regulating T helper 17 and regulatory T cells in mice.* J Neuroimmunol, 2016. **292**: p. 58-67.
10. Largani, S.H.H., et al., *Oligoprotective effect of metformin through the AMPK-dependent on restoration of mitochondrial hemostasis in the cuprizone-induced multiple sclerosis model.* J Mol Histol, 2019. **50**(3): p. 263-271.
11. Negrotto, L., M.F. Farez, and J. Correale, *Immunologic Effects of Metformin and Pioglitazone Treatment on Metabolic Syndrome and Multiple Sclerosis.* JAMA Neurol, 2016. **73**(5): p. 520-8.
12. Cambridge, U.o.; Available from: https://www-neurosciences.medschl.cam.ac.uk/jones-coles-group/trials-in-cambridge/.
13. Nair, A.B. and S. Jacob, *A simple practice guide for dose conversion between animals and human.* J Basic Clin Pharm, 2016. **7**(2): p. 27-31.
14. Derosa, G., et al., *Effects of metformin extended release compared to immediate release formula on glycemic control and glycemic variability in patients with type 2 diabetes.* Drug Des Devel Ther, 2017. **11**: p. 1481-1488.

Certificate Of Completion

Envelope Id: EC968CCC-C66E-4DC8-9BA4-3BA2AD406E93
Status: Completed
Subject: Complete with Docusign: OCTOPUS Protocol v9.0 25Feb2026 combined.pdf
Source Envelope:
Document Pages: 155
Signatures: 2
Certificate Pages: 5
Initials: 0
AutoNav: Enabled
EnvelopeId Stamping: Enabled
Time Zone: (UTC) Dublin, Edinburgh, Lisbon, London

Envelope Originator:
Cheryl Pugh
90 High Holborn 2nd Floor London
London, London WC1V 6LJ
cheryl.pugh@ucl.ac.uk
IP Address: 144.82.114.217

Record Tracking

Status: Original
25 February 2026 | 12:19
Holder: Cheryl Pugh
cheryl.pugh@ucl.ac.uk
Location: DocuSign

Signer Events	Signature	Timestamp
Jeremy Chataway j.chataway@ucl.ac.uk Chief Investigator; Professor of Neurology Professor Jeremy Chataway, University College London Security Level: Email, Account Authentication (Optional), Login with SSO **Electronic Record and Signature Disclosure:** Accepted: 07 October 2022 | 05:53 ID: 05ef1727-15c5-4ec6-90eb-fc59a442d9c4	DocuSigned by: Jeremy Chataway 8DC8C197DECD4B7... Signature Adoption: Pre-selected Style Using IP Address: 5.148.112.133	Sent: 25 February 2026 | 12:21 Viewed: 25 February 2026 | 13:30 Signed: 25 February 2026 | 13:30
Mahesh Parmar m.parmar@ucl.ac.uk Director, ICTM University College London Security Level: Email, Account Authentication (Optional), Login with SSO **Electronic Record and Signature Disclosure:** Not Offered via Docusign	Signed by: Mahesh Parmar F1E2FB8B947644A... Signature Adoption: Pre-selected Style Using IP Address: 144.82.8.240	Sent: 25 February 2026 | 12:21 Viewed: 25 February 2026 | 12:33 Signed: 25 February 2026 | 12:33

In Person Signer Events	Signature	Timestamp

Editor Delivery Events	Status	Timestamp

Agent Delivery Events	Status	Timestamp

Intermediary Delivery Events	Status	Timestamp

Certified Delivery Events	Status	Timestamp

Carbon Copy Events	Status	Timestamp

Witness Events	Signature	Timestamp

Notary Events	Signature	Timestamp

Envelope Summary Events	Status	Timestamps
Envelope Sent	Hashed/Encrypted	25 February 2026 | 12:21
Certified Delivered	Security Checked	25 February 2026 | 12:33

Envelope Summary Events	Status	Timestamps
Signing Complete	Security Checked	25 February 2026 | 12:33
Completed	Security Checked	25 February 2026 | 13:30

Payment Events	Status	Timestamps

Electronic Record and Signature Disclosure

ELECTRONIC RECORD AND SIGNATURE DISCLOSURE

From time to time, MRC Clinical Trials Unit at UCL (we, us or Company) may be required by law to provide to you certain written notices or disclosures. Described below are the terms and conditions for providing to you such notices and disclosures electronically through the DocuSign system. Please read the information below carefully and thoroughly, and if you can access this information electronically to your satisfaction and agree to this Electronic Record and Signature Disclosure (ERSD), please confirm your agreement by selecting the check-box next to 'I agree to use electronic records and signatures' before clicking 'CONTINUE' within the DocuSign system.

Getting paper copies

At any time, you may request from us a paper copy of any record provided or made available electronically to you by us. You will have the ability to download and print documents we send to you through the DocuSign system during and immediately after the signing session and, if you elect to create a DocuSign account, you may access the documents for a limited period of time (usually 30 days) after such documents are first sent to you. After such time, if you wish for us to send you paper copies of any such documents from our office to you, you will be charged a $0.00 per-page fee. You may request delivery of such paper copies from us by following the procedure described below.

Withdrawing your consent

If you decide to receive notices and disclosures from us electronically, you may at any time change your mind and tell us that thereafter you want to receive required notices and disclosures only in paper format. How you must inform us of your decision to receive future notices and disclosure in paper format and withdraw your consent to receive notices and disclosures electronically is described below.

Consequences of changing your mind

If you elect to receive required notices and disclosures only in paper format, it will slow the speed at which we can complete certain steps in transactions with you and delivering services to you because we will need first to send the required notices or disclosures to you in paper format, and then wait until we receive back from you your acknowledgment of your receipt of such paper notices or disclosures. Further, you will no longer be able to use the DocuSign system to receive required notices and consents electronically from us or to sign electronically documents from us.

All notices and disclosures will be sent to you electronically

Unless you tell us otherwise in accordance with the procedures described herein, we will provide electronically to you through the DocuSign system all required notices, disclosures, authorizations, acknowledgements, and other documents that are required to be provided or made available to you during the course of our relationship with you. To reduce the chance of you inadvertently not receiving any notice or disclosure, we prefer to provide all of the required notices and disclosures to you by the same method and to the same address that you have given us. Thus, you can receive all the disclosures and notices electronically or in paper format through the paper mail delivery system. If you do not agree with this process, please let us know as described below. Please also see the paragraph immediately above that describes the consequences of your electing not to receive delivery of the notices and disclosures electronically from us.

How to contact MRC Clinical Trials Unit at UCL:

You may contact us to let us know of your changes as to how we may contact you electronically, to request paper copies of certain information from us, and to withdraw your prior consent to receive notices and disclosures electronically as follows:
To contact us by email send messages to: s.assam@ucl.ac.uk

To advise MRC Clinical Trials Unit at UCL of your new email address

To let us know of a change in your email address where we should send notices and disclosures electronically to you, you must send an email message to us at s.assam@ucl.ac.uk and in the body of such request you must state: your previous email address, your new email address. We do not require any other information from you to change your email address.

If you created a DocuSign account, you may update it with your new email address through your account preferences.

To request paper copies from MRC Clinical Trials Unit at UCL

To request delivery from us of paper copies of the notices and disclosures previously provided by us to you electronically, you must send us an email to s.assam@ucl.ac.uk and in the body of such request you must state your email address, full name, mailing address, and telephone number. We will bill you for any fees at that time, if any.

To withdraw your consent with MRC Clinical Trials Unit at UCL

To inform us that you no longer wish to receive future notices and disclosures in electronic format you may:

i. decline to sign a document from within your signing session, and on the subsequent page, select the check-box indicating you wish to withdraw your consent, or you may;

ii. send us an email to s.assam@ucl.ac.uk and in the body of such request you must state your email, full name, mailing address, and telephone number. We do not need any other information from you to withdraw consent.. The consequences of your withdrawing consent for online documents will be that transactions may take a longer time to process..

Required hardware and software

The minimum system requirements for using the DocuSign system may change over time. The current system requirements are found here: https://support.docusign.com/guides/signer-guide-signing-system-requirements.

Acknowledging your access and consent to receive and sign documents electronically

To confirm to us that you can access this information electronically, which will be similar to other electronic notices and disclosures that we will provide to you, please confirm that you have read this ERSD, and (i) that you are able to print on paper or electronically save this ERSD for your future reference and access; or (ii) that you are able to email this ERSD to an email address where you will be able to print on paper or save it for your future reference and access. Further, if you consent to receiving notices and disclosures exclusively in electronic format as described herein, then select the check-box next to 'I agree to use electronic records and signatures' before clicking 'CONTINUE' within the DocuSign system.

By selecting the check-box next to 'I agree to use electronic records and signatures', you confirm that:

- You can access and read this Electronic Record and Signature Disclosure; and
- You can print on paper this Electronic Record and Signature Disclosure, or save or send this Electronic Record and Disclosure to a location where you can print it, for future reference and access; and
- Until or unless you notify MRC Clinical Trials Unit at UCL as described above, you consent to receive exclusively through electronic means all notices, disclosures, authorizations, acknowledgements, and other documents that are required to be provided or made available to you by MRC Clinical Trials Unit at UCL during the course of your relationship with MRC Clinical Trials Unit at UCL.