Study Protocol

Full title of trial:	A double-blind, randomised, placebo-controlled single-site study of high dose simvastatin treatment for progressive multiple sclerosis: impact on vascular perfusion and oxidative damage
Short title:	MS-OPT Study: Simvastatin in Progressive Multiple Sclerosis
Version and date of protocol	Version 1.7 dated 18/10/2022
Sponsor:	University College London (UCL)
Sponsor protocol number:	16/0730
Funder:	UK Multiple Sclerosis Society, Multiple Sclerosis Trials Collaboration (MSTC)
EudraCT no:	2017-003008-30
ClinicalTrials.gov Identifier:	NCT03896217
Active imp:	Simvastatin
Placebo imp:	Gelatine tablet with added cellulose microcrystalline.
Phase of trial:	Phase II
Sites(s)	Single-site

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Protocol Version History

Version Number	Date	Protocol Update Finalised By (insert name of person):	Reasons for Update
1.0	04/10/2017	First final version	Not applicable
1.1	14/12/2017	Second Final Version	MHRA prompted clarification of data monitoring
1.2	12/01/2018	Third Final Version	HRA prompted changes to protocol
1.3	23/05/2018	Fourth Final Version	Changes to retinal component
1.4	25/10/2018	Fifth Final Version	Update to sponsor representative and clarification on drug storage; PASAT instrument removed; minor contact updates/grammar/spelling corrections to existing sections
1.5	10/04/2019	Sixth Final Version	Minor clarification on wording making clear the intention to split screening/baseline assessments across two days with randomisation occurring on day 1 of 2 after all eligibility assessments are complete. Subsequent visits may also take place over 1 or 2 days.
1.6	05/02/2020	Seventh Final Version	Revision of entry criteria: PPMS added and no upper age limit. Removal of fasting cholesterol/triglycerides Addition of ASL questionnaire at retinal visits.

			Binary disease type added to randomisation algorithm.
1.7	18/10/2022	Eighth Final Version	Revision of secondary objectives (Myelin changes instead of Glutamate concentration) in line with the MRI techniques used on the trial. MRI techniques updated in the MRI section. End of trial definition amended. IDMC removed

Signatures

The Chief Investigator and the JRO have discussed this protocol. The investigator agrees to perform the investigations and to abide by this protocol

The investigator agrees to conduct the trial in compliance with the approved protocol, EU GCP and UK Regulations for CTIMPs (SI 2004/1031; as amended), the UK Data Protection Act (2018), the Trust Information Governance Policy (or other local equivalent), the current Research Governance Framework, the Sponsor's SOPs, and other regulatory requirements as amended.

Chief investigator

Prof Richard Nicholas

Signature Date

Sponsor

Dr Nick McNally
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Signature Date

Contents

GLOSSARY OF TERMS

AE	Adverse Event
AOSLO	Adaptive Optics and Scanning Light Ophthalmoscopy
AR	Adverse Reaction
ASL	Arterial Spin Labelling
BAT	Bolus Arrival Time
BD	Twice per day
CA	Competent Authority
CBF	Cerebral Blood Flow
CCTU	Comprehensive Clinical Trials Unit
CI	Chief Investigator
CNS	Central Nervous System
CRF	Case Report Form
CRO	Contract Research Organisation
CTA	Clinical Trial Authorisation
CTIMP	Clinical Trial of Investigational Medicinal Product
CTM	Clinical Trials Manager
DI	Designated Individual
DMC	Data Monitoring Committee
DSUR	Development Safety Update Report
EAE	Experimental Autoimmune Encephalomyelitis
EC	Endothelial Cell
EC	European Commission
EDSS	Expanded Disability Status Score
EMEA	European Medicines Agency
EU	European Union
EUCTD	European Clinical Trials Directive
EudraCT	European Clinical Trials Database
EudraVIGILANCE	European database for Pharmacovigilance
FAB	Frontal Assessment Battery
GAfREC	Governance Arrangements for NHS Research Ethics

GCP	Good Clinical Practice
GMP	Good Manufacturing Practice
HPS	Heart Protection Study
HRA	Health Research Authority
IB	Investigator Brochure
ICF	Informed Consent Form
IDMC	Independent Data Monitoring Committee
IMP	Investigational Medicinal Product
IMPD	Investigational Medicinal Product Dossier
ISF	Investigator Site File
ISRCTN	International Standard Randomised
MA	Marketing Authorisation
MHRA	Medicines and Healthcare products Regulatory Agency
MRI	Magnetic Resonance Imaging
MS	Multiple Sclerosis
MS	Member state
MSFC	Multiple Sclerosis Functional Composite
MSIS-29v2	Multiple Sclerosis Impact Scale version 2
MSWSv2	Multiple Sclerosis Walking Score version 2
Main REC	Main Research Ethics Committee
NHS R&D	National Health Service Research & Development
NODDI	Neurite density and orientation dispersion imaging
OCT	Optical Coherence Tomography
OD	Once per day
PASAT	Paced Auditory Serial Addition Test
PI	Principal Investigator
PIS	Participant Information Sheet
PTI	Prenyl Transferase Inhibitor
QA	Quality Assurance
QC	Quality Control
QP	Qualified Person for release of trial drug

RCT	Randomised Control Trial
REC	Research Ethics Committee
RNFL	Retinal Nerve Fibre Layer
SAR	Serious Adverse Reaction
SAE	Serious Adverse Event
SDOCT	Spectral-domain Optical Coherence Tomography
SDV	Source Document Verification
SOP	Standard Operating Procedure
SmPC/SPC	Summary of Product Characteristics
SPMS	Secondary Progressive Multiple Sclerosis
SSA	Site Specific Assessment
SSOCT	Swept-source Optical Coherence Tomography
SUSAR	Suspected Unexpected Serious Adverse Reaction
TMF	Trial Master File
TMG	Trial Management Group
TSC	Trial Steering Committee
VBM	Voxel-Based Morphometry

1. Trial personnel

See protocol cover page for Sponsor contact details.

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2. Lay Summary

Multiple sclerosis is a neurological condition which is a common cause of disability in young people. It is thought to be an autoimmune condition, where the body's immune system begins to attack itself. The cause of MS is unknown but is thought to be a mix of genetic and environmental factors. There are treatments available for early stages of MS, but the later stage known as Secondary Progressive MS (SPMS) has no current treatment.

Statins are a safe treatment traditionally used to reduce cholesterol levels. However, statins also have other effects which could reduce the progression of SPMS, such as effects on the immune system and circulation. A recent study (Chataway et al., 2014) showed that treatment with high-dose simvastatin, a type of statin, reduced the progression of SPMS but no effect on the immune system was seen. It is possible that simvastatin does not treat the immune system but improves how the blood and blood vessels in the brain work in this disease.

The purpose of the clinical trial is to test how Simvastatin (80mg/day) may slow down disease progression in people living with Progressive Multiple Sclerosis (PMS) compared to placebo (dummy pill). Participants will receive either Simvastatin or placebo and will be asked to take 2 tablets daily, for up to 17 weeks.

2.1 Structured trial summary

Public Title	Simvastatin in Progressive Multiple Sclerosis
Scientific Title	A double-blind, randomised, placebo-controlled multi-site study of high dose simvastatin treatment for progressive multiple sclerosis: impact on vascular perfusion and oxidative damage
Countries of Recruitment	United Kingdom
Health Condition(s) or Problem(s) Studied	Progressive Multiple Sclerosis
Objectives:	The primary outcome ASL measured CBF will be compared between patients on simvastatin or placebo using multiple linear regressions at 16 weeks. Secondary objectives include: A. MRI: NODDI, myelin loss or changes, Grey matter atrophy and Number of new or enlarging T2 lesions. B. Clinical outcomes: EDSS, 25 foot timed walk, 9 hole peg test, MSIS-29v2, and MSWSv2. C. Retinal imaging parameters: vascular imaging, relative retinal vessel oxygen saturation and vessel width, non-invasive wide-field maps of both retinal (superficial and deep) and choroidal vascular plexuses, high-resolution retinal neuronal structure and SDOCT. D. Health Economic outcomes: EQ5D5L. E. Exploratory outcomes include immune parameters, and biomarkers. F. Frontal executive functioning will be assessed using the Frontal Assessment Battery (FAB) and other neuropsychological assessments (SDMT instrument).
Type of trial:	Phase II, double-blind, randomised, parallel group, single-site trial in progressive multiple sclerosis.
Trial design and methods:	40 subjects will be randomised double blind 1:1 to simvastatin or placebo. Simvastatin will be started at 40mg once daily for one month increasing to 80mg daily for a further three months with matching placebo based

	on a satisfactory safety assessment at one month. The primary outcome ASL measured CBF and BAT will be compared between patients on simvastatin or placebo using multiple linear regressions with CBF or BAT at 16 weeks as the dependent variable, and age, gender, CBT or BAT at baseline and treatment group entered as covariates.
Trial duration per participant:	Twenty-two weeks including follow-up (up to 17 weeks on treatment)
Estimated total trial duration:	Two years
Planned trial sites:	2
Total number of participants planned:	40
Main inclusion/exclusion Criteria:	**Trial Participant inclusion criteria** The following inclusion criteria must be met (answer yes) when assessing patient's eligibility onto the trial: 1. Patients must have a confirmed diagnosis of multiple sclerosis according to revised Mc Donald criteria and have entered the secondary progressive stage. (Polman et al., 2011, Lublin, 2014) or have been diagnosed with Primary Progressive MS. Steady progression rather than relapse must be the major cause of increasing disability in the preceding 2 years. Progression can be evident from either an increase of at least one point on the EDSS or clinical documentation of increasing disability. 2. EDSS 4.0 – 6.5 (inclusive). 3. Male and Females aged 18 with no upper age limit 4. Females of childbearing potential and males with partners who are of childbearing age must be willing to use an effective method of contraception (Double barrier method of birth control or True abstinence) from the time consent is signed until 6 weeks after treatment discontinuation and inform the trial team if pregnancy occurs. For the purpose of clarity, True abstinence is when this is in line with the preferred and usual lifestyle of the subject. Periodic abstinence (e.g., calendar, ovulation, symptothermal, post-ovulation methods), declaration of abstinence, withdrawal, spermicides only or lactational amenorrhoea method for the duration of a trial, are not acceptable methods of contraception. 5. Females of childbearing potential have a negative pregnancy test within 7 days prior to being

registered/randomised. Participants are considered not of child bearing potential if they are surgically sterile (i.e. they have undergone a hysterectomy, bilateral tubal ligation, or bilateral oophorectomy) or they are postmenopausal.
6. Willing and able to comply with the trial protocol (e.g. can tolerate MRI and fulfils the requirements for MRI, e.g. not fitted with pacemakers or permanent hearing aids) ability to understand and complete questionnaires
7. Willing and able to provide written informed consent
8. Willing to ingest gelatine (placebo will contain this). Participants must therefore be informed sensitive to personal beliefs.

Trial participant exclusion criteria
Patients presenting with any of the following exclusion criteria (i.e. answers yes) at screening will not be eligible to proceed with the trial:
1. Unable to give informed consent.

2. Those that have experienced a relapse or have been treated with steroids (both i.v. and oral) for multiple sclerosis relapse within 3 months of the screening visit. These patients may undergo a further screening visit once the 3 month window has expired and may be included if no steroid treatment has been administered in the intervening period. Patients on steroids for another medical condition may enter as long as the steroid prescription is not for multiple sclerosis (relapse/ progression).
3. Patient is already taking or is anticipated to be taking a statin or lomitapide for cholesterol control.
4. Any medications that unfavourably interact with statins as per Spc recommendations e.g.: fibrates, nicotinic acid, cyclosporin, azole anti-fungal preparations, macrolideantibiotics, protease inhibitors, nefazodone, verapamil, amiodarone, large amounts of grapefruit juice or alcohol abuse within 6 months.
5. The use of immunosuppressants (e.g. azathioprine, methotrexate, cyclosporin) or disease modifying treatments (avonex, rebif, betaferon, glatiramer, dimethyl fumerate, fingolimod) within the previous 6 months.
6. The use of mitoxantrone if treated within the last 12 months.
7. Patient has received treatment with alemtuzumab.
8. Use of other experimental disease modifying treatment (including research in an investigational medicinal product) within 6 months of baseline visit

9. Active Hepatic disease or known severe renal failure (creatinine clearance <30ml/min)
10. Screening levels of alanine aminotransferase (ALT), aspartate aminotransferase (AST) or creatine kinase (CK) are three times the upper limit of normal patients.
11. If the patient reports any ophthalmic conditions such as glaucoma, ocular trauma or degenerative eye disease. Cataracts are acceptable as long as they have not been advised to have surgery. No restrictions on post surgical care, unless the patient reports sight restricting capsule opacity.
12. Patient unable to tolerate or unsuitable to have baseline MRI scan (e.g. metal implants, heart pacemaker) or MRI scan not of adequate quality for analysis (e.g. too much movement artefact).
13. Females who are pregnant, planning pregnancy or breastfeeding.
14. Allergies to IMP active substance or to any excipients of IMP and placebo or other conditions that contraindicate use of galactose (eg. Hereditary galactose intolerance, Lactase deficiency, glucose-galactose malabsorption)

Statistical methodology and analysis:

Randomisation with a minimization algorithm will be used (up to a maximum of three binary variables). The study is exploratory and the number of subjects/arm is estimated based on established measures of within and between subject standard deviations using ASL, based on a large test-retest study (Petersen et al., 2010). The power calculation (N=20 subjects per arm) is based on the ability to detect a 30% change in perfusion induced by statins at 0.8 power and 5% significance level. An expected mean grey matter CBF of 40 mL/100g per min and a standard deviation per subject of 12 mL/100g per min were chosen leading to N=17 per group. Accounting for drop-outs and problems in imaging patients (e.g. motion artefacts (20%)) gives N=20 subjects per group. A hypothetical increase in CBF by 30% was estimated based on a previous paper comparing the effects of normal doses of statins on healthy volunteers (Xu et al., 2008). Any potential regression to the mean, which was not accounted for above will lead to a lower number of subjects per arm being necessary.

3. Background and Rationale

Multiple sclerosis (MS), an autoimmune condition affecting the central nervous system, is the most common cause of disability in young adults and affects over 2.3 million people worldwide. It is estimated that in the UK there are 150,000 people with MS, and about 75,000 people have secondary progressive MS (SPMS). It has an estimated global prevalence of 30 people per 100,000, although in the UK the incidence is considerably greater (Mackenzie et al., 2014). Apart from the enormous societal, psychological and emotional cost, it has been estimated that the total annual fiscal cost of MS to Europe is of the order of €14.6 billion, which increases with disability (Olesen et al., 2012).

While the cause is unknown, it is thought to result from interplay of genetic and environmental factors. Initially, focal leukocyte infiltration leads to myelin damage and, in the majority of patients, this triggers a cascade of events that lead to neuro-degeneration and long-term disability. MS presents most commonly as a relapsing and remitting (RR) disease, characterised by neurological deterioration followed by complete or incomplete recovery. Approximately 60% of those affected with RRMS enter a secondary progressive (SPMS) stage after a median interval of 10 to 15 years, where disability accumulates gradually in the absence of relapses. A smaller proportion (15%), run a progressive course from onset (primary progressive (PP) MS). The progressive, “neurodegenerative” component of MS, rather than the clinical deficit resulting from incomplete recovery from each relapse in RRMS, is the dominant cause of long-term disability. Whilst over ten therapies are now licensed for RRMS, no treatment strategies, with the exception of a recent study by our group (Chataway et al., 2014), have succeeded in slowing the progression of this later debilitating stage.

Optic neuritis, inflammation of the optic nerve, is a common event associated with MS resulting in 27% of subjects with residual visual impairment. The impact of damage arising from an inflammatory lesion in the optic nerve can be visualised using optical coherence tomography (OCT) as a reduction in both ganglion cell layer and retinal nerve fibre layer thickness (Grecescu, 2014; Huang-Link et al., 2014; Bennett et al., 2015). However it is increasingly being appreciated that a number of other inflammatory and neurodegenerative changes occur in the retina of MS patients. These retinal changes, reflecting both the disease and its level of activity, have highlighted its potential as a surrogate outcome measure to study preservation of neuronal and/or vascular structure/function after an inflammatory event or as the disease progresses (Grecescu, 2014; Huang-Link et al., 2014; Bennett et al., 2015).

During the last two decades there have been significant advances in our understanding of MS leading to treatment for the RR phase. Despite this, there has been a failure to find an effective treatment for progression and this remains a major unmet need, as highlighted by the International Progressive MS Alliance (Fox et al.,

2012). The many challenges of progressive studies including optimal design, sensitive outcomes, suitable length and subject numbers are gradually being overcome by the MS community, but as yet extending the anti-inflammatory approach that has been effective in RRMS has not borne fruit in SPMS. Indeed the failure of the recent PPMS trial using fingolimod (Lublin et al., 2016) makes the success of simvastatin in the SPMS study (Chataway et al., 2014) all the more exciting, especially as the extensive systemic immunological assessment in this latter study revealed no impact on immune status. The real success of this simvastatin phase II study may be that it initiates novel avenues of investigation driven by the wide-ranging and well-characterised effects statins have on the body as well as a prelude to a definitive phase III trial. This premise underpins our research strategy.

3.1 Preclinical data

Preclinical work has focused on the role played by the vascular barriers (the blood-brain and blood retinal barriers) in the inflammatory process and in particular how they support leukocyte traffic to the central nervous system (CNS). This research, along with that of others, led to the identification and characterisation of endothelial cell (EC) signalling processes that facilitate leukocyte diapedesis and activate pro-inflammatory responses (for review see Greenwood et al., 2011). We found that a key central regulator of the EC signalling pathway supporting leukocyte diapedesis was the small GTPase Rho, and this led us to investigate whether small GTPases could be targeted pharmacologically to reduce aberrant leukocyte migration into the brain and retina. Since small GTPases require posttranslational lipid modification (prenylation) to become functional we tested whether inhibition of Rho prenylation with prenyl transferase inhibitors (PTIs) affects lymphocyte migration. Treatment of brain endothelial cell monolayers *in vitro*, or animals induced for experimental autoimmune encephalomyelitis (EAE, the animal model of MS), resulted in inhibition of lymphocyte migration and attenuation of the disease respectively (Walters et al., 2002).

Since the isoprenoids used for post-translational prenylation of small GTPases are derived from the cholesterol synthesis pathway, we next investigated whether HMGCoA reductase inhibitors (statins) were also able to significantly inhibit Rho activity and reduce the severity of brain and retinal inflammatory disease. This research revealed that statins effectively reduced Rho prenylation and attenuated disease in experimentally induced models of MS and posterior uveitis (Greenwood et al., 2003; Gegg et al., 2005). Whilst we were able to demonstrate that one of the effects of statin treatment was to modify endothelia cell function and inhibit transendothelial migration of leukocytes, it is clear from many other experimental studies that efficacy may also be due to effects on other cell types such as immune cells (Greenwood et al., 2006; Weber et al., 2006; Greenwood and Mason, 2007).

Indeed, it is now widely recognised that statins have anti-inflammatory properties that operate independently of their cholesterol lowering effect. Accordingly, statins have

been shown to inhibit MHC class II restricted Ag presentation, attenuate antigen-presenting cell maturation and down-regulate T cell activation and proliferation. Of those T cells that proliferate, statins induce a shift from a proinflammatory Th1 to a regulatory Th2 phenotype. In addition, statins block adhesion molecule expression and their interactions, inhibit the production of chemokines and their receptors, and reduce the secretion of matrix metalloproteinases. Activation of the transcription factor NFκB, an important activator of pro-inflammatory mediators, is also inhibited by statins, alongside a concomitant upregulation of endothelial cell protective genes (Greenwood and Mason, 2007). Finally, it has been shown that endothelial nitric oxide synthase (eNOS) activity is enhanced, whilst inducible NOS (iNOS) is inhibited.

3.2 Clinical data

This remarkable pleiotropic capacity for modulating the immune system and inflammation has prompted the clinical testing of statins for the treatment of RRMS and other inflammatory diseases (Vollmer et al., 2004; Neuhaus and Hartung, 2007; Paraskevas, 2008; Yuan et al., 2012; Young and Hopkins, 2013). In one such study in 30 patients with RRMS, simvastatin (80mg) taken over 6 months reduced the number of brain lesions by 40%, although no change in disability scores was observed over this short study period (Vollmer et al., 2004). Other studies, however, have failed to demonstrate any significant clinical improvement in RRMS following statin treatment alone or in combination with other disease modifying drugs. Nevertheless, it should be noted that none of the studies so far have been sufficiently powered, rendering definitive conclusions impossible.

Whilst there is a clear-cut rationale for using statins for the treatment of RRMS, in SPMS/PPMS there is less obvious justification, as disease progression in the absence of new plaque formation is thought to be due predominantly to neurodegeneration (or neuronal loss). This results from several mechanisms, including microglia activation, chronic oxidative injury, accumulation of mitochondrial damage in axons, and age-related iron accumulation in the human brain (Mahad et al., 2015). Whereas large scale inflammatory lesions rarely occur at this stage of the disease, inflammation is prominent in progressive MS, where it is found throughout the grey and white matter, and in the meninges, with its most severe form being represented by the ectopic follicles that contribute to grey matter damage (Kutzelnigg et al., 2005; Magliozzi et al., 2007). This suggested that given their Immunomodulatory / anti-inflammatory actions, statins might still provide some benefit in SPMS/PPMS. Nonetheless, neuronal loss is regarded as the key pathological feature, which raised the question whether statins also possess neuroprotective properties. Several lines of evidence suggest this may be the case.

Firstly, statins are increasingly seen as vasculoprotective (Greenwood and Mason, 2007; Liao, 2002; Mason, 2003; Haendeler et al., 2004; Antonopoulos et al., 2012) with a capacity to improve vascular perfusion (Endres et al., 1998; Giannopoulos et al.,

2012) and maintain/enhance blood vessel function (Xu et al., 2008) thus protecting against long-term chronic hypoxic damage. This is germane given the growing evidence that dysfunctional/reduced blood flow in MS (De Keyser et al., 2008; D'Haeseleer et al., 2013; Paling et al., 2014) may predispose the tissue to damage resulting in neuronal cell dysfunction and ultimately cell death. Such beneficial effects on microvascular perfusion may be mediated through statins enhancing eNOS activation (Laufs et al., 1998) and inhibiting endothelin-1 (Mraiche et al., 2005).

Secondly, there are reports that statins may also be neuroprotective through reducing free radical damage either by improving blood flow and reducing hypoxia-mediated reactive oxygen species (ROS) production, or through direct inhibition of cytotoxic pathways. In the latter case, statins may protect neuroparenchymal cells via inhibition of iNOS in activated microglia and astrocytes (Pahan et al., 1997; van der Most et al., 2009), resulting in attenuated cytotoxic damage to neurons and oligodendrocytes. Furthermore, statins may also exert a neuroprotective effect by preventing glutamate-mediated excitotoxicity (Schmeer et al., 2006).

Together these data provided a compelling rationale for testing the potential therapeutic effect of statins in SPMS. In 2008 we therefore embarked on a two-year double-blind, controlled trial of 140 patients, randomising them to either 80mg of simvastatin or placebo. The recently published results of this trial showed that brain atrophy was reduced by over 40% alongside a similar favourable effect on two major disability outcome measures (Chataway et al., 2014). This is the first evidence of a drug having a beneficial effect on SPMS disease progression. Surprisingly, however, and contrary to expectations, we did not identify any modulation of the immune system, raising the critical question of the mechanism of statin action.

3.3 Rationale and risks/benefits

It is our hypothesis, therefore, that the neuroprotective effects of statins in SPMS are mediated by stimulating enhanced microvascular perfusion and/or by inhibition of oxidative damage/neurotoxicity. This study will test this hypothesis.

There are no current treatments for SPMS/PPMS. Given we demonstrated that simvastatin was beneficial in a phase II trial but were unable to elucidate any mechanism, it is important to try and understand the mechanism of action to develop further therapies.

We will investigate the impact of high dose simvastatin (80mg/day) on cerebral and retinal blood perfusion and vascular structure/function, brain neuroaxonal density and myelin loss or changes in PMS. In addition, various systemic parameters will be evaluated to determine the effect of high dose statin treatment on immune function, oxidative damage and vascular barrier function.

Simvastatin is being used outside of its posology and method of administration. The previous phase two trial found simvastatin was safe up to the maximum dose of 80

mg/day given as a single dose in the evening. Based on the recommendations of the SPC and previous studies, the proposed use of 80mg of Simvastatin will, therefore, be used for this study (Chataway et al, 2014).

4. Assessment and management of risk

Risk minimisation:. All symptoms will be monitored as per routine best medical practice.

The table below summarises the risks, frequencies and mitigations of the IMP.

Name of IMP	Potential risk	Risk Frequency	Risk Management
Simvastatin	Hypersensitivity	Rare	Patients with known hypersensitivity to the active substance or any of the excipients will be excluded from the trial. Patients on trial treatment phase who have an allergic reaction will, at the discretion of the treating clinician, simvastatin be discontinued.
Simvastatin	Hepatitis or Jaundice	Rare	Patient will have liver function tests performed prior to study entry and whilst on study to monitor their Hepatic function. Patients with known Hepatic failure, who consume substantial quantities of alcohol and / or have screening Liver function test > 3XULN will be excluded from the study. If patients whilst on study have LFTs > 3XULN or present with clinical symptoms of liver injury, then, at the discretion of the treating clinician, simvastatin will be discontinued (see section 14.2 for discontinuation).
Simvastatin	fatal and non fatal hepatic failure)	Very rare	Patient will have liver function tests performed prior to study entry and whilst on study to monitor their Hepatic function. Patients with known Hepatic failure, who consume substantial quantities of alcohol and/or have screening Liver function test > 3XULN will be excluded from the study. If

			patients whilst on study have LFTs > 3XULN or present with clinical symptoms of liver injury, then, at the discretion of the treating clinician, simvastatin will be discontinued.
Simvastatin	Myopathy/ Rhabdomyolysis	Rare	Simvastatin occasionally causes myopathy manifested as muscle pain, tenderness or weakness with creatine kinase (CK) above ten times the upper limit of normal (ULN). The risk of myopathy is greater in patients on simvastatin 80 mg. The risk of myopathy and rhabdomyolysis is also significantly increased by concomitant use of simvastatin with certain medications and supplements such as potent inhibitors of CYP3A4, Fibrates, grapefruit juice, Calcium Channel Blockers (see section 7.5 for full list of medications). Myopathy sometimes takes the form of rhabdomyolysis with or without acute renal failure secondary to myoglobinuria, and very rare fatalities have occurred. Patient's plasma renal function will be tested at screening and monitored whilst on study. Patients with known renal failure and or plasma potassium exceeds 5.5mmol/l or plasma sodium <125mmol/l or creatinine>130mmol/l, will be excluded. If these parameters are breached during the trial, patient will be monitored as per routine best medical practice and at the discretion of the treating clinician, simvastatin dose may be reduced or discontinued. Potassium conserving drugs and potassium supplements are also prohibited (see section 7.5). Patients who are on medications that interact with Simvastatin and increases the risk of myopathy (see list in section

			7.5) will be excluded from the study. The patient information sheet will explain the risk of myopathy, explain to patients the need to inform doctors of the medications they take and advise patients on medications/supplements they need to avoid whilst on the study. As a higher rate of myopathy has been observed in patients titrated to the 80 mg dose, Creatine Kinase (CK) will be tested at screening and monitored whilst on study. Patients who have a screening CK of > 3xULN will be excluded. If patients whilst on study have CK > 3XULN or present with clinical symptoms of myopathy, then, at the discretion of the treating clinician, simvastatin will be discontinued.
Simvastatin	Hyperglycaemia	Rare	Some evidence suggests that statins as a class raises blood glucose and in some patients at risk of future diabetes. Patients who have or are at risk of Diabetes Mellitus will be monitored both clinically and biochemically according to national guidelines for Diabetes.
Simvastatin	Interstitial lung disease (dyspnoea, non productive cough)	Not Known	If Interstitial lung disease is suspected whilst on the study, at the discretion of the treating clinician, simvastatin will be discontinued.
Simvastatin	Gastro-intesitinal disorders (diarrhoea, nausea, vomiting, pancreatitis)	Rare	Vital signs will be observed prior to study enrolment and at treatment visits to ensure significant hypotension or hypovolaemia does not occur during the trial. Patients will be advised to avoid dehydration and the volume status will be carefully monitored of the patients. The Patient information sheet will explain this risk and advise patients on avoiding dehydration.

Simvastatin	Anaemia	Rare	Full blood Count will be tested at screening and monitored whilst on study. Patients whose results show clinical significant levels will be monitored and treated at the discretion of the treating clinician as per routine best medical practice.
Simvastatin	Elevated International Normalized Ratio (INR)	Very Rare	Very rare cases of elevated INR have been reported in patients taking oral coumarin anticoagulants. Patients who are on these anticoagulants will be monitored and treated at the discretion of the treating clinician as per routine best medical practice. Recommendations outlined in the SPC will also be considered.
Simvastatin	Insomnia	Very Rare	Symptoms will be monitored and treated at the discretion of the treating clinician as per routine best medical practice.
	Cognitive / memory impairment	Very rare	There have been rare post-marketing reports of cognitive impairment (e.g. memory loss, forgetfulness, amnesia, memory impairment, confusion) associated with statin use. The reports are generally nonserious, and reversible upon statin discontinuation, with variable times to symptom onset (1 day to years) and symptom resolution (median of 3 weeks). Symptoms will be monitored and treated at the discretion of the treating clinician as per routine best medical practice.
Simvastatin	Headache, paresthsia, dizziness or peripheral neuropathy.	Rare	Symptoms will be monitored and treated at the discretion of the treating clinician as per routine best medical practice. Simvastatin has no or negligible influence on the ability to drive and use machines. However, when driving vehicles or operating machines, it should be taken into

			account that dizziness has been reported rarely in post-marketing experiences and the patient information sheet will explain this rare risk and caution.
Simvastatin	Skin and Subcutaneous disorders (e.g. rash, pruritus, alopecia)	Rare	Symptoms will be monitored and treated at the discretion of the treating clinician as per routine best medical practice.
Simvastatin	Pregnancy	Not Known	Safety in pregnant women has not been established and it is not known whether simvastatin or its metabolites are excreted in human milk. Women who are pregnant or breast feeding will be excluded. Women of Child bearing potential will need to agree to use adequate contraception and will have a urine pregnancy test to confirm they are not pregnant prior to being enrolled.

The table below summarise the risks and mitigations of all tests above standard care that are being performed:

Intervention	**Potential risk**	**Risk Management**
Venepuncture for Blood Tests	Risk of discomfort, bruising, excessive bleeding, fainting or feeling lightheaded, hematoma & infection	Venepuncture risks will be managed using standard clinical care precautions which include wearing protective clothing, hand and surface hygiene. Risks to participants from venepuncture will be managed using standard clinical care. Non clinical staff performing venepuncture will receive appropriate training. Every effort will be made to make participants feel comfortable before, during and after venepuncture by encouraging participants to relax and talking

		through any concerns they have about the procedure. Trust incident reporting will apply and be followed in the event of patient/staff needle stick injury.
MRI	MRI is generally well tolerated. There can occasionally be some discomfort and/ or claustrophobia. It is however unsafe in patients who have metal inplants or heart pacemaker. Also not recommended in patients who are pregnant.	Trial participants will have had MRI as part of the diagnostic pathway and will be familiar with it. During the scan they have real-time contact with the radiographer with any concerns and can halt the scan if needed. Patients fitted with pacemakers or permanent hearing aids are excluded because these are metal containing products and highly unsafe for MRI. Protocol excludes patients who are unable to tolerate scans. Pregnant participants will be excluded from the study and women of child bearing potential will need to have a negative urine pregnancy test.
Advanced retinal imaging inc. OCT	Patients may have some discomfort from glare induced by having their eyes dilated. There is also a small risk of eye irritation from application of the drops.	Light levels are well below recommended levels and are electronically controlled to prevent accidental over exposure Patient will be advised to bring sunglasses to protect against glare. Lights within the building are designed to account for increased light sensitivity. Irritation from the drops is mitigated by use of a sterile single use applicators.

In accordance with the MRC/DH/MHRA Joint Project Risk-adapted Approaches to the Management of Clinical Trials of Investigational Medicinal Products, this trial is categorised as:

Type B = somewhat higher than the risk of standard medical care

5. Objectives

5.1 Summary

The general aim of the study is to determine the effect high-dose Simvastatin treatment has on vascular perfusion and oxidative damage in progressive multiple sclerosis.

5.2 Hypothesis

Simvastatin reduces the progression of progressive MS by increasing vascular perfusion and reducing oxidative damage as demonstrated by measuring cerebral blood flow in people with SPMS/PPMS.

5.3 Aims

Primary: To test against placebo the efficacy and mechanism of simvastatin in progressive MS.

Secondary: To advance our understanding of the mechanisms of efficacy, and how vascular perfusion and oxidative damage is affected in progressive MS both in the presence and absence of simvastatin.

5.4 Primary objective

To establish whether simvastatin has an effect on cerebral blood flow in progressive MS over 20 weeks using arterial spin labelling MRI.

5.5 Secondary objectives

- To establish whether ASL and AOSLO measurements of blood flow are useful correlates for cerebral blood flow measurement on and off treatment. This will be supported by a questionnaire investigating factors that influence brain perfusion.
- To explore whether statin reduce the rate of brain atrophy on MRI (excluding the effect of pseudo-atrophy, which is a temporary response to the drug rather than an actual loss of tissue).
- To detect subtle changes in both normal-appearing white matter and normal-appearing grey matter using DWI and tract-based analyses.
- To determine the role of myelin loss or changes in PMS using MTV imaging as a surrogate marker of brain myelin volume.

- To examine the clinical effect of simvastatin treatment as reported by the clinician (EDSS, SDMT, MSFC inc. 9HPT and 25FTW) and patient reported outcome measures (MSIS-29v2, and MSWSv2).
- Frontal executive functioning will be assessed using the Frontal Assessment Battery (FAB).
- To collect health economic data (EQ5D5L) to inform future phase III trials
- Investigate the effect statins may have on retinal parameters such as blood flow, oxygen saturation, structure of vascular plexuses, neuronal structure and retinal layer thicknesses.

5.6 Exploratory objectives

- To investigate phenotypic immune markers in whole blood to determine effect simvastatin has on immune function
- To measure biomarkers of blood brain barrier dysfunction, vascular leakage and oxidative damage in participants treated with statins and placebo
- To investigate levels of circulating cholesterol

6. Trial design

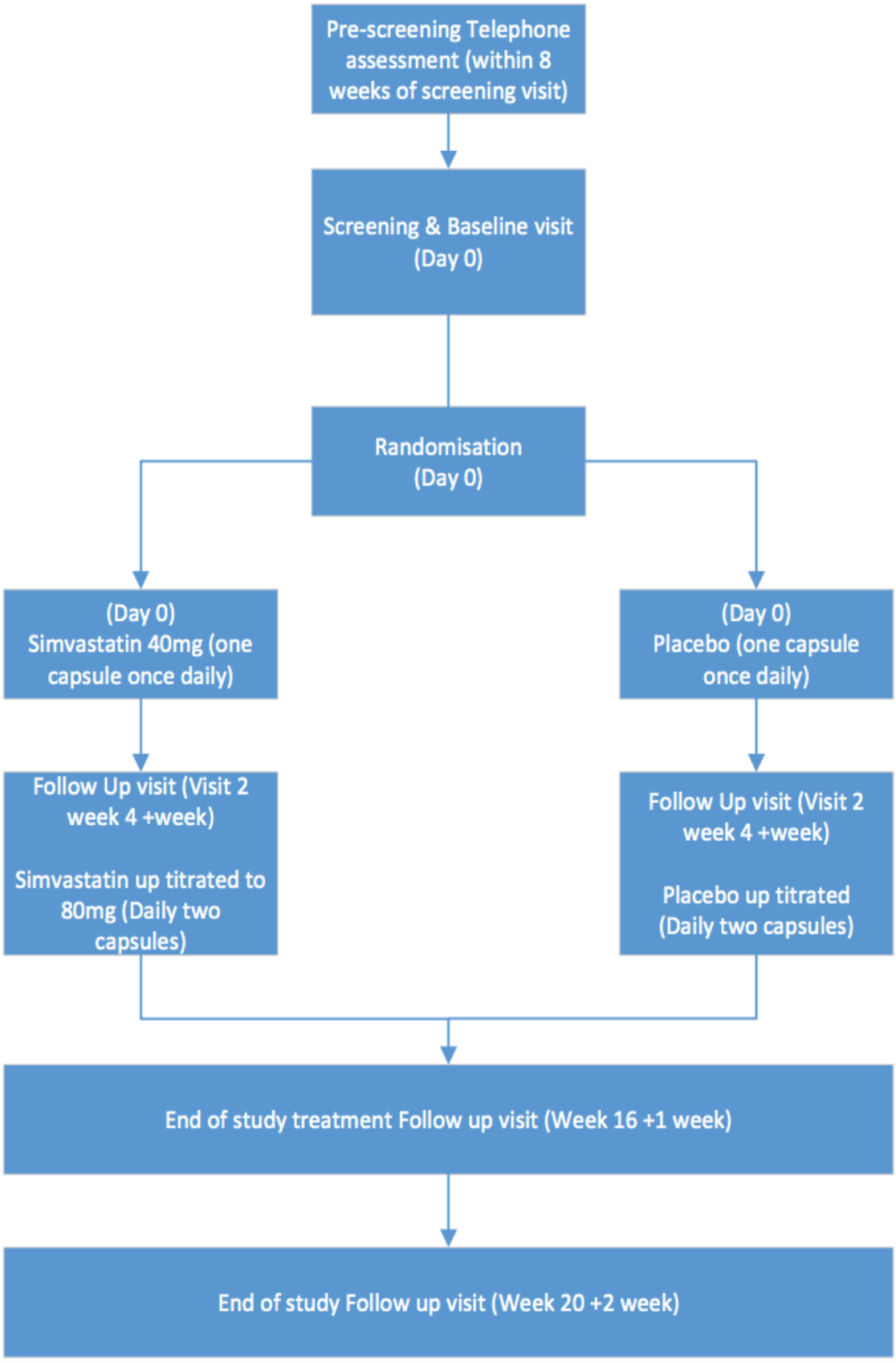
6.1 Overall design

This is a non-commercial short duration (up to 17 weeks on treatment), double-blind placebo-controlled randomised trial of high dose simvastatin versus placebo to determine the impact of simvastatin on the MS population described.

The 17 week duration is based on the tolerability of previous studies which demonstrated that this length of treatment at the given dose of 80mg Simvastatin was well tolerated. Given simvastatin has a well-established safety profile and the half-life of the simvastatin is short, patients will be followed-up until 4 weeks post-IMP administration.

The trial design will be double blinded so as to reduce any bias from the power of suggestion of which treatment the patient is receiving by both the researchers and the patient.

Figure 1: Schematic of overall trial design from recruitment to end of follow up



7. Investigational Medicinal Products and Non-Investigational Medicinal Products

7.1 Name and description of IMP(s)

Simvastatin is part of the pharmacotherapeutic group of HMG-CoA reductase inhibitors (ATC-Code: C10A A01).Simvastatin is licensed within the EU for hypercholesterolemia and cardiovascular prevention but for this trial its use will be outside its licensed indication.

After oral ingestion, simvastatin, which is an inactive lactone, is hydrolyzed in the liver to the corresponding active beta-hydroxyacid form which has a potent activity in inhibiting HMG-CoA reductase (3 hydroxy – 3 methylglutaryl CoA reductase). This enzyme catalyses the conversion of HMG-CoA to mevalonate, an early and rate-limiting step in the biosynthesis of cholesterol.

Simvastatin has been shown to reduce both normal and elevated LDL-C concentrations. LDL is formed from very-low-density protein (VLDL) and is catabolised predominantly by the high affinity LDL receptor. The mechanism of the LDL-lowering effect of simvastatin may involve both reduction of VLDL-cholesterol (VLDL-C) concentration and induction of the LDL receptor, leading to reduced production and increased catabolism of LDL-C. Apolipoprotein B also falls substantially during treatment with simvastatin. In addition, simvastatin moderately increases HDL-C and reduces plasma TG. As a result of these changes the ratios of total- to HDL-C and LDL- to HDL-C are reduced.

Following randomisation study drug will be dispensed by the site pharmacy.

Patients will be randomised to one of the following treatment arms:

- Oral Simvastatin 40mg daily (one tablet in the evening) for 4 weeks and then at week 4 up titrated to 80mg daily (two tablets in the evening)
  or
- Matched Placebo (one tablet in the evening) for 4 weeks and then at week 4 up titrated to two tablets daily in the evening.

For dose modification, please see section 10.2.

For treatment stopping rules, please see section 14.2.

The blinding will be achieved by over-encapsulation of Simvastatin and producing an matched placebo. Commercial simvastatin will be used which have marketing authorisations within the EU, encompassing a variety of brands that can be used. Further details on the sourcing and manufacturing arrangements is given in section 7.2.

7.2 Source of IMP, Manufacture, Distribution and Storage

The over-encapsulation of Simvastatin, manufacture of the placebo and QP release of both will be done by a third party manufacturer holding a MIA IMP in conformance with EU GMP. Mode Pharma will source Simvastatin and ingredients for placebo and will over encapsulate the Simvastatin and matching placebo.

ModePharma will issue the Simvastatin and placebo tablets in child-resistant tamper-evident containers of 220 tablets per container. Each will be labelled in a blinded fashion labelled “Simvastatin or Placebo” along with a unique randomisation number. ModePharma will conduct the final QP release and ship supplies to the site pharmacy using temperature loggers to monitor temperature during transfer.

As each participant in the trial attends their visit for issue of their medication, the site pharmacist will issue the total amount of tablets to end of study of the trial medication according to the patients’ clinical trial randomisation number . The participant will be advised to uptitrate at Visit 2 to 80mg from 40mg (issued at baseline).

Sourcing of the IMP(s) is also discussed in the Summary of Drug Arrangements/IMP management plan.

7.3 Storage and handling of IMP(s) at site

All IMP aspects of the trial at participating sites are the responsibility of the PI, who may delegate this duty to the local pharmacist or other appropriately trained personnel. The delegation of duties must be recorded on the Staff Signature and Delegation of Tasks.

Storage and handling of the IMP will be completed in accordance with the relevant IMPD or Investigator Brochure and summary of drug arrangements.

Do not store the trial drug above 30°C. Store in the original container, in order to protect from light. All active and placebo drugs will be packaged and QP released by the third party manufacturer in High-density polyethylene (HDPE) Bottles containing an identical allocation of tablets.

Labelling will be blinded and carried out in accordance with EU GMP. In order to maintain blinding, bottles will be labelled with numbers predetermined by a code list supplied by Sealed Envelope which will correspond to the treatment allocation. Shelf-life and storage conditions will be monitored.

7.4 NAME AND DESCRIPTION OF EACH NIMP

Patients will have their pupils dilated using one drop each of phenylephrine (2.5%) and tropicamide (1%) before imaging. This is done for each patient in clinic and Moorfields tracks uses.

The host site are responsible for maintaining a system which allows adequate reconstruction of NIMP movements; there should be a procedure that permits recording which participants received which NIMPs during the trial with an evaluation of the compliance.

These drugs are considered to be non-investigational medicinal products (NIMPs) in this Trial. Drops usage is always noted in Moorfields patient notes (each research patient has their own) by the person instilling the drops, and the type of drops and time of day is noted. Giving patients drops in Moorfields requires full training.

7.5 Accountability of IMP(s)

IMP shipping arrangement instructions for site will be described in the Summary of Drug Arrangements.

Usual procedures for monitoring of temperature and transport conditions of the IMP will apply and will be documented on the IMP shipping form. Upon receipt of the IMP, the site pharmacy will confirm receipt of the IMPs by posting/faxing back the accompanying shipping form to the supplier and copies retained at trial sites file. In cases where the IMP was damaged or not stored correctly this will warrant an urgent notification to the manufacturer, ModePharma, and a replacement will be arranged. ModePharma will be responsible for dispatching replacement IMPs to sites. Site pharmacy will be responsible for logging receipt of the IMPs on the site accountability log within the site pharmacy file. Site pharmacy will be responsible for storing the IMP in line with storage requirements as set out in this protocol. Site pharmacy will monitor temperature of IMP storage and report to the sponsor any temperature excursions that have occurred. Details of reporting temperature excursion are in the Summary of drug arrangements and in the SOP for IMP Management. Full IMP accountability will be conducted during the trial. All IMP dispensed by pharmacy will be logged on the site accountability log within the site pharmacy file.

Once the IMP is dispensed, the IMP will be administered to participants initially 40 mg per day, escalating after one month to 80 mg per day. Participants will be advised on how to take their medication at their study visit and thereafter at home. For this purpose, all participants will be given a drug diary which will document their drug compliance. This information will also be provided in the patient information leaflet. Patients will be instructed to bring the bottles, drug diary, and unused IMP back at the next visit so that the research staff can conduct a pill count. The administration of the IMP will be documented in the source data and CRF.

All used/unused IMPs will be returned to site pharmacy, to be then updated in the drug accountability log in the pharmacy site file. Drug destruction will be conducted, once authorised by the sponsor and in accordance with local practice, and this will be documented in the drug destruction log in the hospital pharmacy file.

Detailed instructions are contained in the summary of drug arrangements

7.6 Concomitant medication

All medications are permitted, apart from those outlined below. Concomitant medications will be recorded in the participant's medical records/CRF/eCRF.

The following medications have known interactions with Simvastatin and increases the risk of Myopathy and are therefore, contra-indicated:

- **Potent inhibitors of cytochrome P450 3A4** (e.g. Itraconazole, Ketoconazole, Posaconazole, Erythromycin, Clarithromycin, Telithromycin, HIV protease inhibitors (e.g. nelfinavir), Nefazodone, Ciclosporin, Danazol, Gemfibrozil
- **Fibrates**
- **Cyclosporin**
- **Fluconazole**
- **Danazol**
- **Gemfibrozil**
- **Amiodarone**
- **Calcium Channel Blockers**(e.g. Verapamil, Diltiazem and Amlodipine)
- **Niacin**
- **Grapefruit Juice**

The following medication have known interactions with Simvastatin and caution and careful monitoring is required:

- **Colchicine**
- **Fusidic acid** (Temporary suspension of simvastatin treatment may be considered. If it proves necessary, patients on fusidic acid and simvastatin should be closely monitored).
- **Moderate inhibitors of CYP3A4**
- **Rifampicin** (patients on long term therapy may experience loss of efficacy)
- **Lomitapide** (patients with homozygous familial hypercholesterolemia and treated with Lomitapide, the dose of simvastatin must not exceed 40mg)

7.7 Post-trial IMP arrangements

The IMP will not be provided to trial participants post-trial participation in any circumstance.

8. Selection of Participants

8.1 Eligibility of trial participants

All potential participants must meet all the inclusion and exclusion criteria as set out in sections 8.1.1 and 8.1.2. No eligibility waivers or deviations will be permitted.

8.1.1 Trial participant inclusion criteria

The following inclusion criteria must be met (answer yes) when assessing patient's eligibility onto the trial.

1. Patients must have a confirmed diagnosis of multiple sclerosis according to revised Mc Donald criteria and have entered the secondary progressive stage or a diagnosis of Primary Progressive MS.(Polman et al., 2011, Lublin, 2014)
   Steady progression rather than relapse must be the major cause of increasing disability in the preceding 2 years. Progression can be evident from either an increase of at least one point on the EDSS or clinical documentation of increasing disability.

2. EDSS 4.0 – 6.5 (inclusive).

3. Male and Females aged 18 with no upper age limit

4. Females of childbearing potential and males with partners who are of childbearing age must be willing to use an effective method of contraception (Double barrier method of birth control or True abstinence) from the time consent is signed until 6 weeks after treatment discontinuation and inform the trial team if pregnancy occurs. For the purpose of clarity, True abstinence is when this is in line with the preferred and usual lifestyle of the subject. Periodic abstinence (e.g., calendar, ovulation, symptothermal, post-ovulation methods), declaration of abstinence, withdrawal, spermicides only or lactational amenorrhoea method for the duration of a trial, are not acceptable methods of contraception.

5. Females of childbearing potential have a negative pregnancy test within 7 days prior to being registered/randomised. Participants are considered not of child bearing potential if they are surgically sterile (i.e. they have undergone a hysterectomy, bilateral tubal ligation, or bilateral oophorectomy) or they are postmenopausal.

6. Willing and able to comply with the trial protocol (e.g. can tolerate MRI and fulfils the requirements for MRI, e.g. not fitted with pacemakers or permanent hearing aids) ability to understand and complete questionnaires.

7. Willing and able to provide written informed consent.

8. Willing to ingest gelatine (placebo will contain this). Participants must therefore be informed sensitive to personal beliefs e.g. faith, diet.

8.1.2 Trial participant exclusion criteria

Patients presenting with any of the following exclusion criteria (i.e. answers yes) at screening will not be eligible to proceed with the trial:

1. Unable to give informed consent.

2. Those that have experienced a relapse or have been treated with steroids (both i.v. and oral) for multiple sclerosis relapse within 3 months of the screening visit. These patients may undergo a further screening visit once the 3 month window has expired and may be included if no steroid treatment has been administered in the intervening period. Patients on steroids for another medical condition may enter as long as the steroid prescription is not for multiple sclerosis (relapse/ progression).

3. Patient is already taking or is anticipated to be taking a statin or lomitapide for cholesterol control.

4. Any medications that unfavourably interact with statins as per Spc recommendations e.g.: fibrates, nicotinic acid, cyclosporin, azole anti-fungal preparations, macrolideantibiotics, protease inhibitors, nefazodone, verapamil, amiodarone, large amounts of grapefruit juice or alcohol abuse within 6 months.

5. The use of immunosuppressants (e.g. azathioprine, methotrexate, cyclosporin) or disease modifying treatments (avonex, rebif, betaferon, glatiramer, dimethyl fumerate, fingolimod) within the previous 6 months.

6. The use of mitoxantrone if treated within the last 12 months.

7. Patient has received treatment with alemtuzumab.

8. Use of other experimental disease modifying treatment (including research in an investigational medicinal product) within 6 months of baseline visit.

9. Active Hepatic disease or known severe renal failure (creatinine clearance <30ml/min).

10. Screening levels of alanine aminotransferase (ALT), aspartate aminotransferase (AST) or creatine kinase (CK) are three times the upper limit of normal patients.

11. If the patient reports any ophthalmic conditions such as glaucoma, ocular trauma or degenerative eye disease. . Cataracts are acceptable as long as they have not been advised to have surgery. No restrictions on post surgical care, unless the patient reports sight restricting capsule opacity.

12. Patient unable to tolerate or unsuitable to have baseline MRI scan (e.g. metal implants, heart pacemaker) or MRI scan not of adequate quality for analysis (e.g. too much movement artefact).

13. Females who are pregnant, planning pregnancy or breastfeeding.

14. Allergies to IMP active substance or to any excipients of IMP and placebo or other conditions that contraindicate use of galactose (eg. Hereditary galactose intolerance, Lactase deficiency, glucose-galactose malabsorption)

8.2 Recruitment

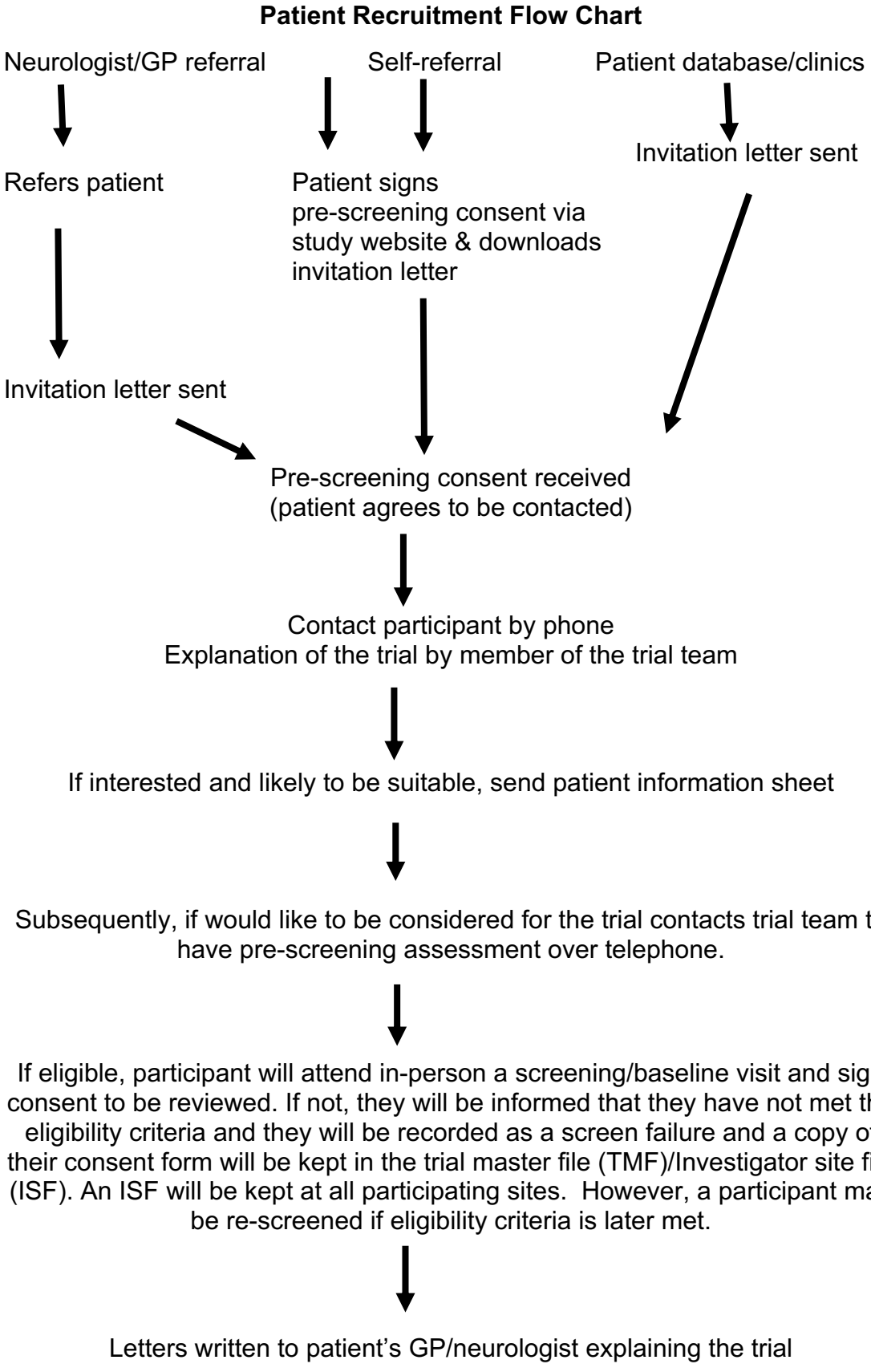
Participant recruitment at the site will only commence when the trial has

1. Been initiated by the Sponsor and
2. Issued with the 'Open to Recruitment' letter.

There are several routes of referral which are shown in the flowchart in section 8.2.1: Neurologist/GP referral from routine NHS clinics, self-referral and referral from known interested subjects. Patients who are happy to be contacted i.e. pre-screen consented, or have been acknowledged as happy to be contacted in a referral letter, will have a patient information sheet (PIS) mailed to them following an explanation of the trial by a member of the study team. A request to organise a telephone pre-screening visit to explain the trial and ensure the patient is likely to fulfil the criteria to enter the trial will also be arranged as per flowchart 8.2.1. Subsequently if the patient is interested in joining the trial and they appear to meet all entry criteria, a combined screening/baseline visit will be arranged. If the patient is eligible and wishes to enter the trial, they sign appropriate consent both to enter the trial, for contact to be made with their GP/consultant, and for medical information to be released about their condition. Letters are to be written both to the patient's GP and neurologist explaining the trial.

All procedures on human subjects will be performed following approval from the MHRA, REC and Health Research Authority (HRA) to allow trial activity at Moorfields Eye Hospital and The National Hospital for Neurology and Neurosurgery. Procedures will be performed as per protocol and Good Clinical Practice (GCP) guidelines.

8.2.1 Patient Recruitment Flow Chart



8.2.2 Retention

Every effort will be made to retain patients in-trial. Drug compliance and commitment to study visits will be monitored by the research team through the use of drug diaries completed by the trial participants in addition to a pill count at the relevant visits. The short duration of the study (four months on treatment) should increase the probability of a high patient retention versus a longer duration study. For those participants who are unable to tolerate the Simvastatin dose at 40 mg or 80 mg see section 10.2.

8.3 Informed consent procedure

It is the responsibility of the Investigator, or a person delegated by the Investigator to obtain written informed consent from each participant prior to participation in the trial, following adequate explanation of the aims, methods, anticipated benefits and potential hazards of the trial.

The person taking consent will be GCP trained, suitably qualified and experienced, and will have been delegated this duty by the CI/ PI on the Staff Signature and Delegation of Tasks.

"Adequate time" must be given for consideration by the participant before taking part. Consent will be sought at least 24 hours after being given the study documentation. It must be recorded in the medical notes when the participant information sheet (PIS) has been given to the participant.

The Investigator or designee will explain that participants are under no obligation to enter the trial and that they can withdraw at any time during the trial, without having to give a reason.

No clinical trial procedures will be conducted prior to the participant giving consent by signing the Consent form. Consent will not denote enrolment into trial.

A copy of the signed informed consent form will be given to the participant. The original signed form will be retained in the trial file at site and a copy placed in the medical notes.

The PIS and consent form will be reviewed and updated if necessary throughout the trial (e.g. where new safety information becomes available) and participants will be re-consented as appropriate.

9. Trial procedures

All procedures will be carried out as specified in this section and the schedule of assessments (appendix 1).

9.1 Visit 0 Pre-Screening Assessments within 8 weeks prior to baseline visit (telephone)

The pre-screening visit will occur within 8 weeks prior to the baseline visit.

At this visit, the trial will be explained to participant and eligibility for the trial will be assessed using the pre-screening questionnaire.

If the patient is eligible as per pre-screen entry criteria, they will be asked to return for baseline (Visit 1) assessments.

9.2 Visit 1 Screening/Baseline combined assessment (Day 0)

At this visit (which may be conducted over two days), the following will be assessed:

- Informed consent
- Medical History & Contraindications
- Physical examination & Medical review**
- Vital signs inc. pulse, blood pressure, temperature
- Concomitant medications
- EDSS disability assessment
- MSFC inc. 25FTW, 9HPT
- SDMT
- FAB
- Questionnaires (MSIS-29v2, MSWsv2, EQ5D5L)
- Safety Bloods (see section 11.1 for list of laboratory tests)
- Bloods for Immunology and biomarkers
- Urine pregnancy test for females of child bearing potential
- MRI inc. ASL / Questionnaire
- Modified Vascular Function Retinal Imaging Questionnaire
- Visual assessment (likely to take place on day 2 of this visit)
- Retinal Imaging (Advanced retinal imaging, OCT – likely to take place on day 2 of this visit)
- Full eligibility assessment

- Randomisation (see section 10)
- Drug dispensation at 40mg dose (see section 10.1) * .
- Drug diary issued
- Emergency telephone contact given

Participants will be advised on the administration of the medication and will be given a study specific patient card which will have study title, IMP details, patient ID and contact details of the out of hours contact in cases of emergency (see section 9.3.6). A drug diary will also be issued for participants to document compliance to IMP. Participants will be reminded to bring the drug diary to the next visit.

This visit will take place across two sites. Visit 1 assessments will take place over two days, one for each site with the option to complete all assessments on one day if feasible. Randomisation and drug dispensation will take place on day 1 of visit 1.

* Study medication must only be dispensed after randomisation i.e. once all day 1 of visit 1 assessments (with the exception of visual assessment and advanced retinal imaging) have been completed and the relevant safety reports have been obtained. All eligibility criteria has to be fulfilled and no exclusion criteria must be identified. As the study medication is best taken in the evening and due to the volume of assessments required, it will be advisable for the patient to take study medication on the evening of day 2 of visit 1 (if visit 1 takes place over two days). For the purpose of safety, the study participant will be advised to contact the study team if a complication as a result of taking the study medication arises. Possible adverse events and side effects will be included in the PIS.

** Medical review will encompass any medical or MS-related symptoms that have arisen.

9.3 Follow-up assessments

9.3.1 Visit 2 (Week 4+1 week)

- Recording of AEs and concomitant medications
- Physical Examination & Medical Review**
- Vital signs inc. pulse, blood pressure, temperature
- Safety bloods (see section 11.1 for list of laboratory tests)
- Bloods for Immunology and biomarkers
- Drug compliance (pill count and drug diary review)
- Uptitration of drug at 80mg dose.
- MRI appointment for next visit booked/date confirmed with patient

- Retinal imaging appointment for next visit booked/date confirmed with patient
- Patient reminded to bring diary card, trial medication bottles with unused trial medication back for the next visit.

** Medical review will encompass any medical or MS-related symptoms that have arisen.

If a patient is unable to attend the clinic at week 4 or within the visit window, a TC will be arranged to check for AEs and acceptability to uptitrate and an appointment nearest to the timeframe will be scheduled.

9.3.2 End of Study treatment visit (Week 16 +1 week)

At this visit, any remaining study medication will be returned to site pharmacy.

- Recording of AEs and concomitant medications
- Physical Examination & Medical Review**
- Vital signs inc. pulse, blood pressure, temperature
- EDSS disability assessment
- MSFC inc. 25FTW, 9HPT
- SDMT
- Questionnaires (MSIS-29v2, MSWsv2, EQ5D5L)
- Safety Bloods (see section 11.1 for list of laboratory tests)
- Bloods for Immunology and biomarkers
- Urine pregnancy test for females of child bearing potential
- MRI inc. ASL questionnaire follow-up
- Retinal Imaging Vascular Function Questionnaire
- Retinal Imaging (Advanced retinal imaging, OCT)
- Drug compliance (pill count and drug diary review)
- MRI appointment booked/date confirmed with patient
- Retinal imaging booked/date confirmed with patient

As at screening/baseline (visit 1), the assessment will take place across two sites. All assessments will take place over two days, one for each site with the option to complete all assessments on one day if feasible.

** Medical review will encompass any medical or MS-related symptoms that have arisen.

If a patient is unable to attend the clinic within the visit window, a TC will be arranged to check for AEs and an appointment nearest to the timeframe will be scheduled.

9.3.3 End of Study Follow-up (Week 20+2 weeks)

The following assessments will be covered:

- Recording of AEs and concomitant medications
- Physical Examination & Medical Review**
- Vital signs inc. pulse, blood pressure, temperature
- EDSS disability assessment
- MSFC inc. 25FTW, 9HPT
- SDMT
- FAB
- Questionnaires (MSIS-29v2, MSWsv2, EQ5D5L)
- Safety Bloods(see section 11.1 for list of laboratory tests)
- Bloods for Immunology and biomarkers
- Urine pregnancy test for females of child bearing potential
- MRI inc. ASL questionnaire follow-up
- Retinal Imaging Vascular Function Questionnaire
- Retinal Imaging(Advanced retinal imaging, OCT)

  As at screening/ baseline (visit 1) and end of study treatment visit, the assessment will take place across two sites. All assessments will take place over two days, one for each site with the option to complete all assessments on one day if feasible.

** Medical review will encompass any medical or MS-related symptoms that have arisen.

9.3.4 Unscheduled visits (Between V1-EOS Follow-up)

Participants will be instructed to contact the local study team between scheduled visits should they suspect a relapse or any adverse events that are deemed serious or require further examination. An unscheduled visit (either for or not for a relapse) can occur at the local study team's discretion and the following will be assessed and recorded:

- Recording of AEs and concomitant medications
- Physical Examination & Medical Review**
- Vital signs inc. pulse, blood pressure, temperature
- EDSS disability assessment
- Safety Bloods(see section 11.1 for list of laboratory tests)

** Medical review will encompass any medical or MS-related symptoms that have arisen.

9.3.5 Telephone Follow-up (As required)

Participants may be contacted by a member of the trial team if there are safety concerns or updates to the trial. As stated in appendix 1, the participant as standard will be asked if they have any side effects (as listed in section 4), concomitant medications and adverse events will also be checked. Medical review and drug compliance will be dependent on the circumstances of the participant and the timepoint in the study.

9.3.6 Procedure for emergency telephone contact

An emergency phone will be kept by a medically qualified member of the study team on rotation. They will then advise the patient as per seriousness of the medical emergency as to how they should proceed e.g. A&E admission.

10. Randomisation Procedures

Randomisation will take place at Visit 1. Participants are considered to be enrolled into the trial following consent and the completion of all entry-criteria assessments (carried out on day 1 of visit 1). It may not be possible to complete all visit 1 assessments in one day so visit 1 may occur over 2 days. Randomisation will take place on day 1 of visit 1. The entry-criteria assessments at visit 1 will be prioritised for the purpose of randomisation on day 1 of visit 1, with the advanced retinal imaging and visual assessments (not required to confirm eligibility for the study) carried out on day 2 of visit 1 after randomisation (when visit is across 2 days). The patient will be instructed not to take the study medication until all study assessments are completed on day 2 of visit 1. If visit 1 is completed over 1 day, the patient can take study medication on the evening when all visit assessments are complete.

Screening/baseline visit and eligibility criteria form and randomisation will be performed via an on line system hosted by a specialist company (www.sealedenevelope.com) who will hold the randomisation list (to conceal actual treatment allocation to the research team) and provide 24/7 randomisation services. Detailed instruction on logging in and randomising participants on this system is in the randomisation SOP. After randomisation, the site research team will be given a unique trial randomisation number via email from sealedenvelope.com. Randomisation details of patients will be entered on a trial subject enrolment log and the participant will be given a study specific patient card which will have study title, IMP details, patient ID and contact details of the out of hours contact in cases of emergency. Section 21.3 describes how assignment to treatment groups will be done and the statistical methods used to generate randomisation.

10.1 Treatment Schedule

The starting dose at baseline will be 40mg of Simvastatin or placebo (one tablet) to be taken orally in the evening. This will be up-titrated at Visit 2 (week 4) to 80mg (two tablets) if all safety parameters have been met at visit 2.

Participants will be allocated one bottle each containing 220 tablets for the duration of the study. There will therefore be one drug dispensation at baseline and the patient will be reminded to up titrate after one month at Visit 2.

10.2 Dose Modifications

If the participant is able to tolerate the 40 mg dose, after 4 weeks they will be uptitrated to 80 mg. If the participant is unable to tolerate the 40 mg dose at 4 weeks or at any point during the study, the medication will be withdrawn (e.g. any significant side effect as listed in section 4). If the participant is able to tolerate the 40 mg but not the 80 mg dose, then the participant will continue on this dose until the end of the study. They will then be re-approached at week 12 to uptitrate to 80mg if tolerated. If this is not tolerated, they will remain on 40 mg until the end of study.

Participants who were unable to tolerate the 40 mg dose at 4 weeks, and were withdrawn at this stage, will be re-approached to re-start the drug at 40 mg at week 12. Those participants who were unable to tolerate 40 mg beyond 4 weeks will have their study medication withdrawn and not re-approached at week 12.

This assessment will be made by the treating physician. The final decision will be made by the CI. The uptitration is to ensure that the end of study MRI is conducted on treatment.

See section 14.2 for treatment stopping rules.

11 Laboratory Assessments and Procedures

11.1 Local laboratories

The following tests will be carried out at Central Laboratories (Institute of Ophthalmology).

Blood samples from these patients will be taken at baseline and at weeks 4, 16 and 20 to investigate the effect of statins on vascular leakage and free radical damage. Biomarkers will be determined as follows: (i) For RNA/DNA oxidative damage serum levels of 8-hydroxyguanosine (8-OHG)/8-hydroxydeoxyguanosine (8-OHdG); (ii) Protein oxidative damage will be determined by assaying plasma proteins for nitrotyrosine and carbonyl content; and (iii) Detection of lipid oxidative damage by assaying for the advanced lipid peroxidation end products 4-hydroxynonenal (4-HNE

or HNE), malondialdehyde (MDA), 8-iso-prostaglandin F2α and thiobarbituric acid reactive substances (TBARS) (Miller et al., 2012).

All assays will be conducted using standard commercial kits (Cell Biolabs). To determine dysfunction of the blood-brain barrier (BBB) circulating levels of S100B and ubiquitin C-terminal hydrolase 1 (UCHL1) will be measured. Detection will be through the use of commercially available ELISA kits. In addition circulating cholesterol levels will be determined.

Details on handling, processing, storage and shipment of these samples are in the laboratory SOP.

The following safety blood tests will be carried out at Local Laboratories (Queens Square):

BLOOD:

Analyte	Units
SODIUM	mmol/L
POTASSIUM	mmol/L
CHLORIDE	mmol/L
UREA	mmol/L
CREATININE	umol/L
BILIRUBIN	Umol/L
ALKALINE PHOSPHATASE	IU/L
ALANINE TRANSFERASE	IU/L
CK	IU/L
TOTAL PROTEIN	g/L
ALBUMIN	g/L
GLOBULIN	g/L
TRIGLYCERIDES	mmol/L
CHOLESTEROL	mmol/L
HDL CHOLESTEROL	mmol/L
LDL CHOLESTEROL	mmol/L
ESTIMATED GFR	mL/min/1.73sqm
THYROID STIMULATING HORMONE	mIU/L
HAEMOGLOBIN	g/L
HCT	%
RED CELL COUNT	x10^12/L
MCV	fL
MCHC	g/L
RDW	

Analyte	Units
PLATELET COUNT	x10^9/L
MPV	fL
WHITE CELL COUNT	x10^9/L
NEUTROPHILIS	x10^9/L
LYMPHOCYTES	x10^9/L
MONOCYTES	x10^9/L
EOSINOPHILIS	x10^9/L
BASOPHILIS	x10^9/L

URINE:

Urine analysis: Pregnancy test (dipstick)

12. Clinical Procedures and Data Collection

Clinical examination will include:

Clinician observed expanded disability status score (EDSS) is a method of quantifying disability in MS and records changes in disability over time. The EDSS scale ranges from 0 (no disability) to 10 (death due to MS) in 0.5 unit increments that represent higher levels of disability. Scoring is based on an examination by a neurologist and encompasses pyramidal, cerebellar, brainstem, sensory, bowel/bladder function in addition to visual, cerebral and other functions.

MSFC inc. 9HPT, 25TFW, PASAT comprises quantitative functional measures of three key clinical aspects of MS: leg function/ambulation (25TFW), arm/hand function (9HPT), and cognitive function/working memory (PASAT). However, PASAT will not be performed in this study as the SDMT is able to measure this component.

Frontal Assessment Battery (FAB) is a concise cognitive test in neurodegenerative disease with frontal involvement.

Symbol Digit Modalities Test (SDMT) is measure of cognitive impairment. The subject is asked to match single digits to symbols using a key as a guide that pairs the numbers to the symbols. They are presented with a page headed by a key that pairs the single digits 1–9 with nine symbols and they then write or orally report their responses in a scoring form. It can be administered in oral and written form and is timed and guided by a trained examiner ie. suitably qualified member of the research team.

Patient reported multiple sclerosis impact scale version 2 (MSIS-29v2) is a self-administered questionnaire that asks to what degree the impact of MS has on a person’s day-to-day life during the past two weeks.

Patient reported Multiple Sclerosis Walking Score version 2 (MSWSv2) is a self-administered questionnaire that measures walking performance.

Concomitant medication: all over-the counter or prescription medication, vitamins, and/or herbal supplements will be recorded.

MRI is a non-invasive test that produces detailed images of the brain utilising magnetic field and radio waves, without radiation.
In this study we will use ASL, a sophisticated MRI technique that measures brain cerebral blood flow, which is a process of delivering blood and nutrients to the capillary beds of the brain and the time taken by blood to reach the capillary bed.
We will also measure brain tissue loss and quantify lesion load.

All will be measured over time to determine any changes.

MRI ASL questionnaire: Brain perfusion is affected by numerous factors related to demographics, physiology, lifestyle, diet and medication use which in turn can affect the MRI analysis. This questionnaire will measure the impact of these factors on MRI.

Retinal Imaging Vascular Function Questionnaire: This is an abbreviated version of the ASL questionnaire to be provided on the day of retinal imaging. This questionnaire accounts for caffeine, tobacco, alcohol and sleep effect.
Advanced retinal imaging including OCT and AOSLO. The light sensitive layer of the back of the eye, the retina, can be affected in MS and we can image this layer in a number of non-invasive ways. OCT is a method of imaging the retina using light. Similar to ultrasound, an OCT device shines light into the eye and detects the light which is returned, allowing us to “see” the retinal layers of the back of the eye in cross section. The same technique can be used to see the blood vessels of the retina and form a map of their locations, known as OCT Angiography. The quality of our images using these techniques is impeded by small optical changes which occur in everyone’s eyes. These small changes can be adjusted for using an “adaptive optics” imaging device, which allows us to look at the smallest blood vessels and cells in the retina in real time. We can also use standard colour photography techniques to take photos of the retinal vessels at different light wavelengths, which allows us to visualise oxygen levels within these blood vessels.

12.1 Assessment of IMP/NIMP compliance

Noncompliance to the Protocol study procedures will be documented by the investigator and reported to the Sponsor as agreed. Persistent noncompliance may lead the patient to be withdrawn from the study. If a participant is 80% non-compliant as measured by the drug diary, then they will be withdrawn from treatment.

13. Monitoring

13.1 Study Monitoring

The sponsor will determine the appropriate level and nature of monitoring required for the trial. Risk will be assessed on an ongoing basis and adjustments made accordingly. The degree of monitoring will be proportionate to the objective, purpose, phase, design, size, complexity, blinding, endpoints and risks associated with the trial. A trial specific oversight and monitoring plan will be established for studies. The trial will be monitored in accordance with the agreed plan.

13.2 Recording of subject compliance information

A drug diary will be kept by the participant and completed on a daily basis for the duration of the study.

14. Discontinuation/withdrawal of participants

14.1 Protocol Treatment Discontinuation

In consenting to participate in the trial, participants are consenting to trial treatment, assessments, follow-up and data collection.

14.2 Discontinuation of Trial Treatment for clinical reasons

A participant may be withdrawn from trial treatment whenever continued participation is no longer in the participant's best interests, but the reasons for doing so must be recorded. Reasons for discontinuing treatment may include:

1 disease progression whilst on therapy

2 unacceptable toxicity (e.g. toxicity as listed in section 4 e.g. LFT >3x ULN)

3 intercurrent illness which prevents further treatment

4 patients withdrawing consent to further trial treatment (see section 14.3)

5 Any alterations in the participant's condition which justifies the discontinuation of treatment in the site investigator's opinion

6 Persistent non-compliance to protocol requirements

7 Patient unable to tolerate 40 mg Simvastatin

The decision to withdraw a participant from treatment must be recorded in the CRF and medical notes, and the sponsor when required should be notified in writing.

In these cases participants remain within the trial for the purposes of follow-up for safety and or data analysis according to the treatment option to which they have been allocated.

14.3 Participant withdrawal from trial treatment

In consenting to the trial, participants are consenting to trial treatments, trial follow-up and data collection. If a participant expresses their wish to withdraw from trial treatment, sites should explain the importance of remaining on trial follow-up and seek permission to allow use of routine follow-up data to be used for trial purposes. The importance of safety follow-up is explained in the participant in the Participant Information Sheet.

As participation in the trial is entirely voluntary, the participant may choose to discontinue trial treatment at any time without penalty or loss of benefits to which they would otherwise be entitled. Although not obliged to give a reason for discontinuing their trial treatment, a reasonable effort should be made to establish this reason, whilst remaining fully respectful of the participant's rights. If the participant gives a reason for their withdrawal, this should be recorded in the CRF and medical notes.

Participants who discontinue protocol treatment, for any of the above reasons, should remain in the trial for the purpose of follow-up and analysis.

If a participant is lost to follow-up at a site every effort should be made to contact the participant's GP to obtain information on the participant's status

14.4 Withdrawal of Consent to Data Collection

If a participant explicitly states they do not wish to contribute further data to the trial their decision must be respected and recorded in the CRF and medical notes.

14.5 Replacements

Participants who stop trial follow-up early will not be replaced.

14.6 Stopping rules

The trial may be stopped before completion for the following reasons:

On the recommendation of the Independent Data Monitoring Committee (IDMC)

On the recommendation of the sponsor and CI

If a participant is unable to tolerate Simvastatin at 40mg or 80mg dosage (see section 10.2).

14.7 Definition of End of Trial

- The expected duration of the trial is 2 years from recruitment of the first participant.
- The end of trial is defined as the date when sample analysis for Immune Parameters and Biomarkers has been completed.

15. Recording and reporting of adverse events and reactions

Collection, recording and reporting of adverse events (including serious and non-serious events and reactions) to the sponsor will be completed according to the sponsor's SOP (INV/S05).

15.1 Definitions

Table 1: Adverse Event Definitions

Adverse Event (AE)	Any untoward medical occurrence in a patient or clinical trial participant administered a medicinal product and which does not necessarily have a causal relationship with this treatment. Therefore an AE can be any unfavourable or unintended change in the structure (signs), function (symptoms) or chemistry (laboratory data) in a participant to who an IMP or procedural intervention has been administered, including occurrences which are not necessarily caused by or related to that product.
Adverse Reaction (AR)	Any untoward and unintended response in a participant to an investigational medicinal product which is related to any dose administered to that participant. This includes medication errors, uses outside of protocol (including misuse and abuse of product
Serious Adverse Event (SAE), Serious Adverse Reaction (SAR) or Unexpected Serious Adverse Reaction	Any adverse event, adverse reaction or unexpected adverse reaction, respectively, that: • results in death, • is life-threatening*, • requires hospitalisation or prolongation of existing hospitalisation**,

	• results in persistent or significant disability or incapacity, or • consists of a congenital anomaly or birth defect *A life- threatening event, this refers to an event in which the participant was at risk of death at the time of the event; it does not refer to an event which hypothetically might have caused death if it were more severe. ** Hospitalisation is defined as an in-patient admission, regardless of length of stay. Hospitalisation for pre-existing conditions, including elective procedures do not constitute an SAE."
*A life- threatening event, this refers to an event in which the participant was at risk of death at the time of the event; it does not refer to an event which hypothetically might have caused death if it were more severe. ** Hospitalisation is defined as an in-patient admission, regardless of length of stay. Hospitalisation for pre-existing conditions, including elective procedures do not constitute an SAE.	
Unexpected Adverse Reaction (UAR)	An adverse reaction the nature and severity of which is not consistent with the information about the medicinal product in question set out: (a) in the case of a product with a marketing authorization, in the summary of product characteristics for that product, (b) in the case of any other investigational medicinal product, in the investigator's brochure relating to the trial in question.
Suspected Unexpected Serious Adverse Reaction (SUSAR)	• An unexpected adverse reaction which is also categorised as serious.
Important Medical Event	These events may jeopardise the participant or may require an intervention to prevent one of the above characteristics/consequences. Such events should also be considered 'serious'.

15.2 Recording adverse events

All adverse events following IMP administration will be recorded in the medical records in the first instance. As simvastatin is a licensed product with a well-established safety profile, AEs that are non–serious or MS related (see section 15.5 for MS expected adverse events) will be recorded in the source data (Medical records and Participant diary cards) only.

All adverse events will be recorded with clinical symptoms and accompanied with a simple, brief description of the event, including dates as appropriate.

Clinically significant abnormalities in the results of objective tests (e.g. laboratory variables) will also be recorded as adverse events in the medical notes and if are assessed as serious they will also be recorded on the SAE log and in the CRF. If these events are not expected as part of disease or IMP, these will be recorded as unexpected.

All adverse events will be recorded until 6 weeks after the participant's final clinical visit (EOS).

15.3 Assessment of Adverse Events

Each adverse event will be assessed for severity, causality, seriousness and expectedness as described below.

15.3.1 Severity

Severity or grading of AEs

Grade	Degree of Severity
1	Mild, with mild or no symptoms; no interventions required
2	Moderate; minimal intervention indicated; some limitation of activities
3	Severe but not life threatening; hospitalisation required; limitation of patient's ability to care for him/herself
4	Life threatening; urgent intervention required
5	Death related to adverse event

15.3.2 Causality

The assessment of relationship of adverse events to the administration of IMP is a clinical decision based on all available information at the time of the completion of the case report form.

The following categories will be used to define the causality of the adverse event:

Category	Definition
Definitely:	There is clear evidence to suggest a causal relationship, and other possible contributing factors can be ruled out.
Probably:	There is evidence to suggest a causal relationship, and the influence of other factors is unlikely
Possibly	There is some evidence to suggest a causal relationship (e.g. the event occurred within a reasonable time after administration of the trial medication). However, the influence of other factors may have contributed to the event (e.g. the participant's clinical condition, other concomitant events).
Unlikely	There is little evidence to suggest there is a causal relationship (e.g. the event did not occur within a reasonable time after administration of the trial medication). There is another reasonable explanation for the event (e.g. the participant's clinical condition, other concomitant treatments).
Not related	There is no evidence of any causal relationship.
Not Assessable	Unable to assess on information available.

15.3.3 Expectedness

Category	Definition
Expected	An adverse event which is consistent with the information about the IMP listed in the Investigator Brochure (or SPC if Licensed IMP) **or clearly defined in this protocol.**
Unexpected	An adverse event which is not consistent with the information about the IMP listed in the SPC * **or clearly defined in this protocol.**

* this includes listed events that are more frequently reported or more severe than previously reported

The reference document to be used to assess expectedness against the IMP is the SPC for Simvastatin 40mg film coated tablets (Sandoz Limited)

The following events listed below describe expected procedural related AEs:

- MRI is generally well tolerated. There can occasionally be some discomfort and/or claustrophobia.

- Discomfort from glare with optical imaging.

15.3.4 Seriousness

All events are assessed for seriousness as defined for an SAE in section 15.1.

15.4 Procedures for recording and reporting Serious Adverse Events

All serious adverse events (SAEs/SARs/SUSARs) will be recorded in the medical records and the CRF, and the sponsor's SAE log. The SAE log of SAEs will be reported to the sponsor at least once or twice per year in liaison with JRO Pharmacovigilance Manager.

All SAEs will be recorded from the time of the first enrolled participant's drug release (at Visit 2) until 6 weeks post-treatment (defined as six weeks beyond end of treatment).

All SAEs (except those specified in section 15.5 as not requiring reporting to the Sponsor), must be recorded on a serious adverse event (SAE) form. The CI/PI or designated individual will complete the sponsor's SAE form and email the form to the Sponsor at SAE@ucl.ac.uk within 24 hours of his / her becoming aware of the event. The Chief or Principal Investigator will respond to any SAE queries raised by the sponsor as soon as possible.

Completed SAE forms must be sent within 24 hours of becoming aware of the event to the Sponsor
Email forms to SAE@ucl.ac.uk

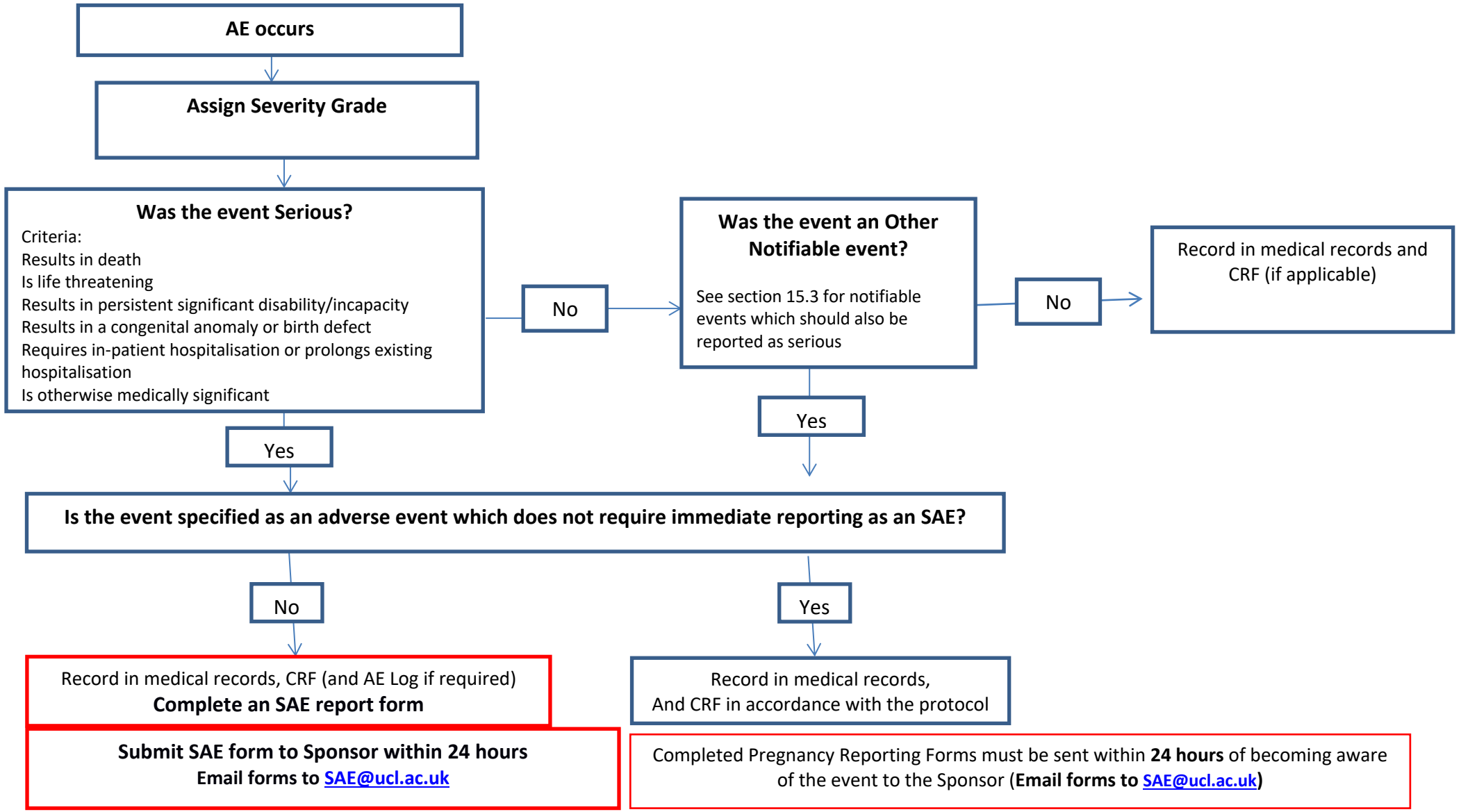
Reporting to the sponsor will be completed as per the sponsor's SOP and using the UCL SAE form (INV/S05) as amended for the trial.

SAE's will be reported to the sponsor until the end of the trial. SAR and SUSAR will need to be reported to the Sponsor irrespective of how long after IMP administration the reaction has occurred.

Participants must be followed up until clinical recovery is complete and laboratory results have returned to normal or baseline values, or until the event has stabilised. Follow-up should continue after completion of protocol treatment and/or trial follow-up if necessary.

Follow-up SAE forms (clearly marked as follow-up) should be completed and emailed to the JRO as further information becomes available.

15.4.1 Flow Chart for SAE reporting



15.5 Serious Adverse Events which do not require immediate reporting

SPMS and PPMS are progressive neurological conditions and as such deterioration in neurological symptoms is expected. Symptoms of MS disease progression will be RECORDED in the participants' medical notes and in the CRF. However, SAE forms will not be completed and sent to the sponsor. The following SAEs are deemed as symptoms of MS disease progression and do not require immediate reporting:

- natural changes in motor, sensory, balance, sphincter (including urinary tract infections), visual, cognitive and fatigue levels

Symptoms of disease progression will be graded as follows:

Grade 1 relapse: relapse not treated with corticosteroids

Grade 2 relapse: relapse treated with corticosteroids, but not requiring hospitalisation

Grade 3 relapse: relapse treated with corticosteroids and requiring in-patient hospitalisation; or relapse not treated with corticosteroids but requiring in-patient hospitalisation

If the participant feels they are experiencing a relapse, they should contact their local MS team (nurse/consultant) or General Practitioner as per routine practice, so that appropriate management can occur. They should also inform the study team at their next scheduled visit, so that the relapse can be documented. At the Investigator's/nurse's discretion the patient can attend for an unscheduled visit, see section 9.3.4.

If the frequency or severity of these symptoms is not consistent with the SPC or disease the event must be reported to the sponsor as an SAE in the normal way

15.6 Notification of Deaths

All deaths will be reported to the sponsor. This report will be immediate.

15.7 Reporting SUSARs

The sponsor will notify the main REC and MHRA of all SUSARs. SUSARs that are fatal or life-threatening must be notified to the MHRA and REC within 7 days after the sponsor has learned of them. Other SUSARs must be reported to the REC and MHRA within 15 days after the sponsor has learned of them.

15.8 Unblinding

As this is a double-blind trial, the option to unblind treatment is essential. This will only occur for a participant when it is felt necessary to do so on clinical grounds. Only authorised users, eg. An unblinded pharmacist, will be issued with an unblinding account via 'Sealed Envelope'. Other access will be at the discretion of the chief investigator.

In the event of an emergency, the unblinding service will be available 24 hours a day, 7 days a week and will be appropriately backed up.

15.8.1 Emergency Unblinding

The trial code will only be broken for valid medical or safety reasons e.g. in the case of a severe adverse event where it is necessary for the investigator or treating health care professional to know which treatment the participant is receiving before the participant can be treated. Subject always to clinical need, where possible, members of the research team should remain blinded.

The code breaks for the trial are held at www.sealedenevelope.com
In the event that unblinding is required a formal request will be made by the Investigator/treating health care professional to an individual authorised and delegated to perform code break.

If the person requiring the unblinded information is a member of the Investigating team then a request to the authorised individual to unblind will be made and the treatment allocation information obtained.

If the person requiring the unblinded information is not the CI/PI then that healthcare professional will contact the Investigating team to request the code break. Unblinding will take place if in the opinion of a treating physician a patient's health is compromised. The authorised individual will break the code and immediately inform the treating healthcare professional of the participant's treatment allocation. The treating physician has the ultimate decision and right to unblind the patient.

On receipt of the treatment allocation details the CI/PI or treating health care professional will treat the participant's medical emergency as appropriate.

The CI/PI will document the breaking of the code and the reasons for doing so on the CRF and unblinding log and will file this, in the site file and medical notes. It will also be documented at the end of the trial in any final trial report and/or statistical report.

The CI/Investigating team will notify the JRO in writing as soon as possible following the code break detailing the necessity of the code break.

The written information will be disseminated to the Trial Management Group.

For detail instructions on unblinding, please refer to 'Unblinding SOP' for further details.

15.8.2 Unblinding for the submission of SUSAR reports

The following procedure will be used to unblind for the submission of a SUSAR report to the regulatory agencies.

1. A representative of the Sponsor will be authorised to access the code break system [setup through specialist 'Sealed Envelope'] for the purposes of unbinding for the submission of a SUSAR.
2. The Sponsor will follow the SOP on unblinding.

3. On receipt of the treatment allocation, the Sponsor will provide the unblinded information on the e-SUSAR website form.
4. Unblinded information in the SUSAR reports will not be forwarded to the trial team and kept in the JRO sponsor file.
5. SUSAR reports will be disseminated to Investigators at site(s) but will remain blinded.
6. The unblinded information will not be forwarded to the trial team and will be kept in the JRO sponsor file.

Sealed Envelope provides a comprehensive randomisation system via secure SSL connections and the randomisation application conforms to the requirements of FDA 21 CFR part 11, Electronic Records; Electronic Signatures and ICH GCP. User accounts are by invitation only and are created and managed by a designated administrator. In addition, no one can delete records from the randomisation database, so all randomisations have to be accounted for and audit log files detailing all activity on the randomisation system are available to the trial manager.

16. Development Safety Update Reports

The sponsor will provide the main REC and the MHRA with Development Safety Update Reports (DSUR) which will be written in conjunction with the trial team and the Sponsor's office. The report will be submitted within 60 days of the Developmental International Birth Date (DIBD) of the trial each year until the trial is declared ended.

17. Pregnancy

If a female participant or the female partner of a male participant becomes pregnant at any point during the trial, a completed trial specific Pregnancy Reporting Form will be emailed to the Sponsor at SAE@ucl.ac.uk within 24 hours of his / her becoming aware of the event in line with the Sponsors SOP (JRO/INV/S05). The Chief or Principal Investigator will respond to any queries raised by the sponsor as soon as possible.

The Sponsor must be kept informed of any new developments involving the pregnancy through the completion of a follow-up Pregnancy Reporting Form. Any pregnancy that occurs in a female trial subject during a clinical trial should be followed to termination or to term.

Consent to report information regarding the pregnancy and follow up of a child born must be obtained from the pregnant participant or pregnant partner of a participant. A trial-specific pregnancy monitoring information sheet and informed consent form for trial participants and partners of trial participants must be used for this purpose.

With consent additional information regarding the pregnancy will be collected and reported to the Sponsor, the Sponsor will advise on the length of follow up of the pregnancy/ child on a case by case basis.

18. Overdose

The research team will record details of reported overdoses on the deviation log and inform UCL as soon as possible after being made aware of the information. Sources of information can include patient-reported, pill counts, diary cards and drug charts.

In the event that an SAE is associated with the overdose, the SAE reporting procedure should be followed (section 15.3). Details of the overdose will documented in the SAE form.

An overdose is defined as taking double the normal medication/day for 1 day or more. If an overdose has taken place, the patient will suspend medication for at least 48 hours, and resume the previous dose as soon as possible afterwards, at the discretion of the PI. The patient will continue in trial.

To date, a few cases of overdosage have been reported; the maximum dose taken was 3.6 g. All patients recovered without sequelae. There is no specific treatment in the event of overdose. In this case, symptomatic and supportive measures should be adopted. Source:
https://www.medicines.org.uk/emc/product/4555/smpc#OVERDOSE

19 Reporting Urgent Safety Measures and other safety events

If any urgent safety measures are taken the CI/ PI shall immediately and in any event no later than 3 days from the date the measures are taken, give written notice to the MHRA, the relevant REC and Sponsor of the measures taken and the circumstances giving rise to those measures.

19.1 Notification of Serious Breaches to GCP and/or the protocol (SPON/S15)

A “serious breach” is a breach which is likely to effect to a significant degree –

(a) the safety or physical or mental integrity of the participants of the trial; or

(b) the scientific value of the trial.

The sponsor of a clinical trial shall notify the licensing authority in writing of any serious breach of –

(a) the conditions and principles of GCP in connection with that trial; or (b) the protocol relating to that trial, as amended from time to time, within 7 days of becoming aware of that breach.

The sponsor will be notified immediately of any case where the above definition applies during the trial conduct phase. The sponsor’s SOP on the ‘Notification of violations, urgent safety measures and serious breaches’ will be followed.

20. Data management and quality assurance

20.1 Confidentiality

All data will be handled in accordance with the UK Data Protection Act 1998.

The Case Report Forms (CRFs) and drug diaries will not bear the participant's name or other personal identifiable data. The participant's initials, date of birth and trial identification number, will be used for identification and this will be clearly explained to the patient in the Patient information sheet. Patient consent for this will be sought.

20.2 Data collection tools and source document identification

Data will be collected from sites on Trial specific paper case report forms (CRFs) will be provided for source documentation and an electronic excel database will act as the electronic CRF.

Source data are contained in source documents and must be accurately transcribed on to the CRF. Examples of source documents are medical records which include laboratory and other clinical reports etc.

A source document list will be implemented prior to the start of the trial to identify:

- which data is to be recorded directly onto the CRF;
- which data is recorded firstly into source documents, such as medical notes, and then transcribed into the CRF; and
- which data is not to be recorded in the CRF but only recorded in source documents, e.g., participant questionnaires and diary cards.

It is the responsibility of the investigator to ensure the accuracy of all data entered in the CRFs. The delegation log will identify all those personnel with responsibilities for data collection and handling, including those who have access to the trial database.

All CRFs will be paper-based and used as source documentation. Additional clinical information will be documented in the patient's hospital notes.

The paper CRFs will be stored at Queen Square Multiple Sclerosis Centre, Floor 1 of UCL Institute of Neurology. This is a secure area only accessible by designated employees via an entry card system with additional security present at street access.

All efforts will be made to provide complete data (eg. telephoning patients with missing data or attempts to obtain clarification on data at follow-up visits).

20.3 Completing Case Report Forms

All CRFs must be completed and signed by staff that are listed on the site staff delegation log and authorised by the CI to perform this duty. The CI is responsible for the accuracy of all data reported in the CRF. A PDF file will be periodically obtained and filed from the excel database that act as eCRF to record any changes to the data.

20.4 Data handling and analysis

A trial specific data management SOP will be in place for the trial. This will contain more details of the database software, the process of database design, data entry, data quality checks, data queries, data security, database lock and any data transfer if applicable

This will be in accordance with the UK Data Protection Act 2018 as well as UCL Information Security Policy and Trust Information Governance Policy. There will be a documented record of data transfer and measures in place for the recovery of original information after transfer.

21. Statistical Considerations

21.1 Primary outcomes

A sophisticated magnetic resonance imaging (MRI) technique, called arterial spin labelling (ASL), will be employed to evaluate the effect of high dose statin on brain haemodynamics. Specifically, patients on statin or placebo will be subjected to multiple delay time ASL to quantify arterial hemodynamic parameter bolus arrival time (BAT) and cerebral blood flow (CBF) in normal-appearing white matter (NAWM) and deep gray matter as previously described (Paling et al., 2014). ASL is an MRI method that allows non-invasive measurement of CBF using inversion of arterial water spins as a tracer. In a recent study (Paling et al., 2014) the Golay team has demonstrated alteration in cerebral arterial hemodynamics in MS, in particular an increase in cerebral blood flow (CBF) in NAWM (14.4±4.4 versus 10.1±2.1 mL/100 g per min, $P<0.001$), and a decrease in CBF in the deep gray matter (40.3±12.0 versus 46.0±5.7 mL/100 g/min, $P<0.005$) in patients with MS compared with controls. As such, we expect ASL to be able to detect subtle changes in CBF between baseline, 16 and 20 weeks between placebo and simvastatin treated patients in the current study, including potential waning of the effects of the drug over time.

21.2 Secondary outcomes

21.2.1 MRI parameters

Total and regional grey matter volumes, including thalamic volumes, will be calculated, and changes in volumes over time using longitudinal VBM will be investigated.

21.2.2 Retinal imaging parameters

21.2.2.1 Vascular imaging

As microvascular perfusion cannot be measured directly in most of the brain we will use the retina, as this is an accessible extension of the brain that lies outside the skull and thus lends itself to non-invasive imaging. Applicants Dr Adam Dubis and Professor John Greenwood (UCL Institute of Ophthalmology and Moorfields Eye Hospital) will lead this aspect of the study. We will use a purpose built microscope that enables us to focus on, and image in real time, retinal photoreceptors, retinal capillary microvessels and measure capillary flow dynamics at rest and under retinal stimulation (Chui et al, 2012; Dubra and Sulai, 2011; Sulai et al. 2014, Scoles et al, 2014, Zhong et al, 2008).

Until recently the non-invasive visualisation of the smallest capillaries, blood cells and measurements of microvascular retinal blood flow in the CNS has not been possible. This is now achievable through coupling adaptive optics (AO) technology to current scanning light ophthalmoscopy (SLO) imaging capabilities. This results in an imaging system that overcomes the optical imperfections of the eye, providing near diffraction limited (2μm lateral resolution) viewing of the living human retina. These new confocal and non-confocal (split detection) imaging techniques now allow visualisation of the smallest capillaries and individual blood cells, including erythrocytes, moving through the vascular lumen.

This ground-breaking development allows for more accurate calculations of retinal perfusion and blood flow levels at the capillary bed and this will be used to gain unprecedented insight into microvascular perfusion of the living human eye in healthy, diseased and treated patients. In conjunction with the imaging described above, we will determine relative retinal vessel oxygen saturation and vessel width with the Oxymap T1 installed on a conventional Topcon fundus camera, and obtain non-invasive wide-field maps of both retinal (superficial and deep) and choroidal vascular plexuses using the optical coherence tomography angiography (OCTA).

21.2.2.2 Neuronal imaging

In addition to using the AOSLO to measure the vascular parameters described above, it will also be employed to obtain high-resolution retinal neuronal structural data including the retinal nerve fibre layer (RNFL), and rod and cone photoreceptor mosaics. We will also use spectral-domain OCT (SDOCT) to evaluate retinal lamination, total retinal thickness and inner retinal thickness (including RNFL thickness).

This advanced retinal imaging approach will allow us to evaluate changes in both retinal microvasculature and neuronal integrity, determine any relationships, and compare this to other brain perfusion or structural measures. All measurements will require correction for retinal magnification, so axial length and corneal curvatures measures will be taken with Zeiss IOLmaster.

21.2.3 Lab Measurements

21.2.3.1 Immune parameters

In our previous study we determined multiple immune parameters in patients following 6, 12, and 24 months of treatment and contrary to expectations found no change in those patients on 80mg/kg simvastatin. One reason for this may be that immune modulation by statins is temporary due to the induction of compensatory mechanisms. To test this, phenotypic markers will be investigated in whole blood specimens collected from placebo and statin treated patients at baseline and 1 month. This will investigate CD4+T cells intracellular cytokine expression (IFN-γ and IL-17) as markers of Th1 and

Th17 T cell populations, respectively on unstimulated T cells and cells stimulated with phorbol 12-myristate 13-acetate (PMA) and ionomycin. The co-expression of CD4+ and intracellular expression of FoxP3 and IL-10 will be examined as markers of regulatory T cells.

This component of the work will be led by Dr Virginia Calder (UCL Institute of Ophthalmology).

21.2.3.2 Biomarkers

Blood samples from these patients will be taken at baseline and at 16 weeks to investigate the effect of statins on vascular leakage and free radical damage. For determining the impact of statins on oxidative damage we will measure the following biomarkers: (i) For RNA/DNA oxidative damage we will determine serum levels of 8-hydroxyguanosine (8-OHG)/8 hydroxydeoxyguanosine (8-OHdG); (ii) Protein oxidative damage will be determined by assaying plasma proteins for nitrotyrosine and carbonyl content; and (iii) Detection of lipid oxidative damage by assaying for the advanced lipid peroxidation end products 4-hydroxynonenal (4-HNE or HNE), malondialdehyde (MDA), 8-isoprostaglandin F2α and thiobarbituric acid reactive substances (TBARS) (Miller et al., 2012).

All assays will be conducted using standard commercial kits (Cell Biolabs). To establish whether there is dysfunction of the blood-brain barrier (BBB) and if so whether statins improve barrier function, we will measure circulating levels of S100B and ubiquitin C-terminal hydrolase 1 (UCHL1). These biomarkers have been reported to increase in the serum following disruption of the BBB (Marchi et al., 2003; Blyth et al., 2011) and will be detected by commercially available ELISA kits. In addition we will measure changes in circulating cholesterol.

This part of the study will be overseen by Professor John Greenwood of the UCL (Institute of Ophthalmology).

21.2.4 Other assessments

21.2.4.1 MRI parameters

In addition to ASL, we propose to explore the changes in the behaviour over time of conventional and advanced imaging measures, which may be influenced by the effects of simvastatin.

We will combine the well-established imaging measures that reflect both neurodegeneration, such as brain grey matter atrophy, and neuro-inflammation, such as the number of new or enlarging T2 lesions, with novel measures (i.e., NODDI-derived measures and myelin maps), that have potential to detect more specific neuro-axonal abnormalities and metabolic changes, and any effects of simvastatin.

These novel markers may provide complementary information to that given by the retinal microvascular study, ASL and clinical measures (see statistical paragraph below for a comment on the role of these measures).

(1) Diffusion weighted imaging (DWI) is an MR imaging technique based upon the measurement of the random Brownian motion of water within a voxel of tissue. This technique has been used to analyse the microstructure of neuronal tissue in particular myelin and axonal integrity. Multi-shell DWI acquisition allows the use of several multi-fibres and multi-shell modelling approaches, such as Diffusion Kurtosis Imaging (DKI) and Neurite Orientation Dispersion and Density imaging (NODDI), which have been successfully used to study patients with MS. It has been demonstrated that NODDI has higher sensitivity and specificity than standard Diffusion Tensor Imaging (DTI).

(2) Macromolecular tissue volume (MTV) is a method of myelin mapping to determine the role of myelin loss or changes in progressive MS. With the macromolecular volume being made up of 50% myelin, we are able to use an in-house analysis pipeline to calculate the MTV - a surrogate marker of brain myelin volume. This metric, alongside diffusion weighted imaging will provide micro-structural detail into the cross-sectional and longitudinal changes occurring in the brain parenchyma of people with progressive MS.

(3) Grey matter atrophy, which is significantly associated with long-term disability in SPMS (Fisniku et al., 2008) and correlates with physical disability better than white matter atrophy (Roosendaal et al.,2011). Our previous simvastatin trial demonstrated a reduction of 43% in the annualized rate of whole brain atrophy associated with the drug (Chataway et al., 2014), but the rate of grey matter atrophy was not assessed. The recent Lamotrigine trial in patients with SPMS demonstrated that the grey matter atrophy was greater than white matter atrophy (-1.18% per year vs. 0.12% per year), and was the only atrophy measure that correlated with clinical changes; in addition, no pseudo-atrophy was seen in the grey matter (Kapoor et al., 2010). Total and regional grey matter volumes, including thalamic volumes, will be calculated, and changes in

volumes over time using longitudinal VBM will be investigated.

Atrophy measures will be performed at baseline 16 and 20 weeks to assess the rate of atrophy; the extra time point added after the end of the study (20 weeks) when patients are off treatment will allow us to take into account a possible reduced volume in patients on treatment which results from pseudo-atrophy, rather than lack of neuroprotective effects of simvastatin. With regard to the atrophy calculation, T2 and T1 weighted conventional scans will be also acquired to perform the lesion-filling technique that reduces the impact of white matter lesions on grey matter volume (Chard et al., 2010).

(4) Number of new or enlarging T2 lesions, as surrogate markers for the inflammatory process, and number of new hypo-intense lesions seen on T1 weighted spin-echo, as a marker of tissue destruction.

This part of the study will be led by Professor Olga Ciccarelli, NMR Unit, UCL Institute of Neurology.

21.2.4.2 Clinical measures

(1) Clinician observed expanded disability status score (EDSS)

(2) Clinician observed 25 foot timed walk and 9HPT as part of the MSFC assessment.

(3) Patient reported multiple sclerosis impact scale version 2 (MSIS-29v2)

(4) Patient reported Multiple Sclerosis Walking Score version 2 (MSWSv2).

(5) Frontal Assessment Battery (FAB) and Single Digit Modality Test (SDMT).

21.2.4.3 Health Economic outcomes

A standard health economic measure will be applied, the EQ5D5L questionnaire.

21.2.4.4 Retinal Imaging Metrics

(1) Vascular imaging: adaptive optics and scanning light ophthalmoscopy (AOSLO) of retinal capillary microvessels (Dubra and Sulai, 2011; Sulai et al. 2014). This enables us to calculate retinal perfusion and measure blood flow dynamics at the capillary level. We will measure vein and arteriole wall thicknesses and erythrocyte occupancy in the capillaries. We will also look at how flow changes between resting and retinal stimulation (Zhong et al, 2008). Briefly, this will be accomplished by flashing a dim light and looking

at how blood cell movements change and vessel walls expand. Metrics will be occupancy before and after stimulation and vessel width before and after flashing.

(2) Relative retinal vessel oxygen saturation and vessel width: using the Oxymap T1 installed on a conventional Topcon fundus camera we will be able to measure relative venous and artery blood pO2 levels near the optic nerve (central 3 disk diameters).

(3) Non-invasive wide-field maps of both retinal (superficial and deep) and choroidal vascular plexuses: using optical coherence tomography angiography (OCTA) vessel density and organisation (fractal dimension) will be assessed.

(4) Spectral-domain OCT (SDOCT): to evaluate retinal lamination, total retinal thickness, inner retinal thickness (including RNFL thickness), outer retinal thickness and the inner and outer segment lengths.

22. Sample size and recruitment

22.1 Sample size calculation

The power calculation (N=20 subjects per arm) is based on the ability to detect a 30% change in perfusion induced by statins at 0.8 power and 5% significance level. An expected mean grey matter CBF of 40 mL/100g per min and a standard deviation per subject of 12 mL/100g per min were chosen leading to N=17 per group. Accounting for drop-outs and problems in imaging patients (e.g. motion artefacts (20%) gives N=20 subjects per group. A hypothetical increase in CBF by 30% was estimated based on a previous paper comparing the effects of normal doses of statins on healthy volunteers (Xu et al., 2008). Any potential regression to the mean, which was not accounted for above will lead to a lower number of subjects per arm being necessary.

22.2 Planned recruitment rate

Patients will be recruited over one year. Based upon a projected recruitment figure of 3-4 patients per month, the target recruitment number (n=40) is expected to be achievable. This is supported by the large size of the MS patient population in the London area and the multi-site nature of the referral system working out of two MS specialist centres (Imperial College Healthcare NHS Trust & UCLH). In addition, there is no licensed treatment currently available for the SPMS population.

22.3 Randomisation methods

This study will have a participant randomised design with equal allocation between treatment arms. Randomisation with a minimization algorithm will be used, using up to a maximum of four binary variables:

- gender

- binary age (≤55/>55 years old)
- binary disability (EDSS ≤ 5.0/>5.0)
- binary progressive clinical phenotype (SPMS/PPMS)

The cut-offs have been decided based on the literature: an age ≤ 55 years old was part of the inclusion criteria for the ORATORIO trial (ref: Montalban et al., NEJM 2016); in the same trial an EDSS score of 5.0 or lower was considered as 'less disabled', for which shorter disease durations were assumed/required to enter the trial (ref: Montalban et al., NEJM 2016). The study is exploratory and the number of subjects/arm is estimated based on established measures of within and between subject standard deviations using ASL, based on a large test-retest study (Petersen et al., 2010).

Randomisation will be performed by the PI or delegated member of the clinical investigating team at local sites using the web-based randomisation service, Sealed Envelope. A random sequence for study arm allocation will be computer generated by Sealed Envelope providing a unique trial identification code for each recruited participant.

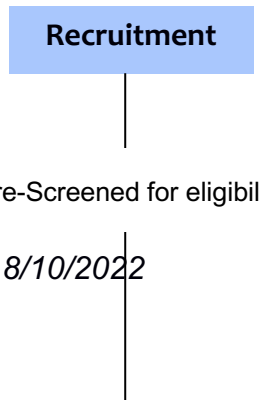
Eligibility and consent will be verified before each patient is randomised. Study arm allocation into two treatment arms (1:1) will take into consideration these minimisation factors:

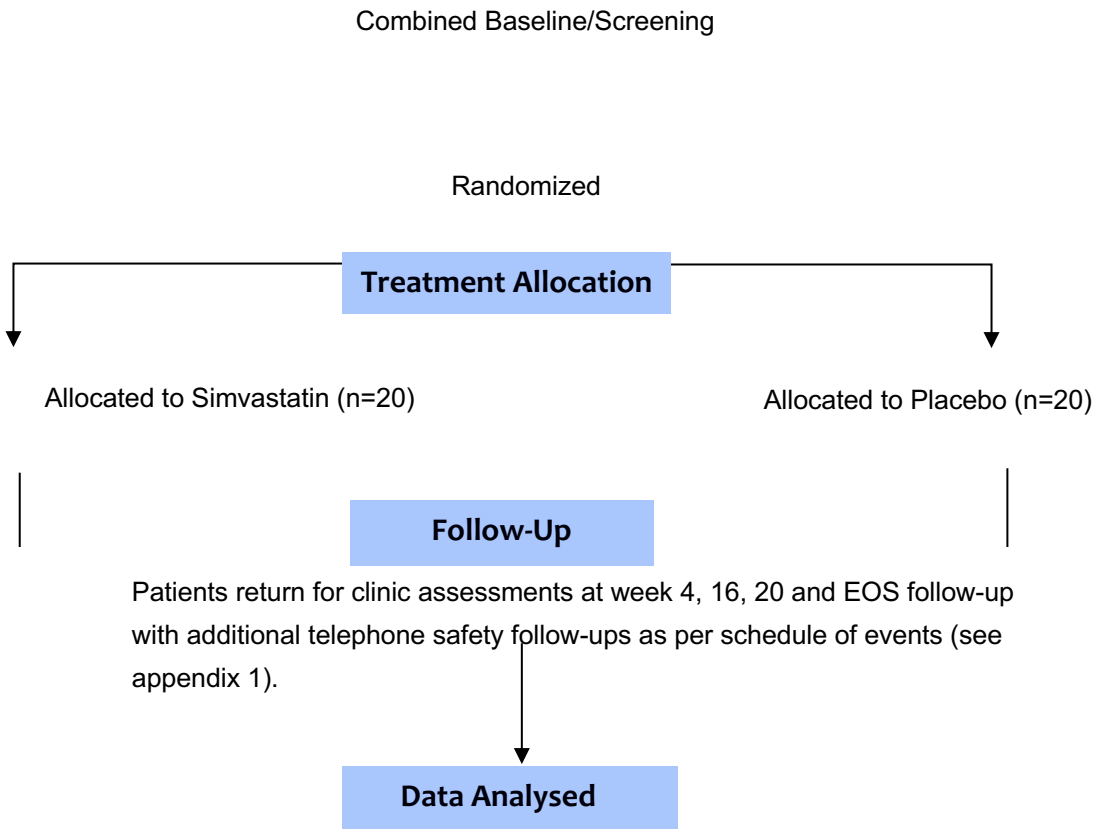
Randomisation with minimisation will ensure comparability of the two study arms, and prevent selection bias.

Sealed Envelope will generate unique identifiers for every active/placebo drug kit. The drug kit identification codes will be provided to Sealed Envelope and the Qualified Person (QP) at drug manufacturing site (Mode Pharma) who will ensure that trial drug and placebo packs are labelled appropriately, and that the trial team and participants remain blind to treatment allocation. At baseline, the investigator will enter the patient's unique trial identification code into the SealedEnvelope.com website which will then provide the drug identification code of the active/placebo drug kit to be dispensed. Sufficient number of simvastatin/placebo drug kits will be provided to ensure availability of adequately labelled kits for Pharmacy dispensing.

23. Statistical analysis plan

23.1 Summary of baseline data and flow of participants





23.2 Statistical Analysis Plan

The stats analysis plan will be produced well in advance of seeing the data. It will specify both the primary analysis (in detail) and the secondary analyses (in less detail), including details of the analysis methods and any pre-specified covariates for adjustment such as the minimisation variables. It will also provide details of adverse events analyses and per-protocol analysis using adherence information. The analysis plan will describe contingency analysis should the assumptions of the primary methods not be satisfied by the data. A CONSORT flow diagram will be produced.

23.3 Primary outcome analysis

The primary outcome ASL measured CBF will be compared between patients on simvastatin or placebo using multiple linear regressions at 16 weeks as the dependent variable, and age, gender or CBT at baseline and treatment group entered as covariates. Whenever the variable 'treatment group' is significant (at 5% significance level), it will be assumed that there is a treatment effect. The same models will be used to investigate the effect of simvastatin on the other imaging outcome measures.

Checks for model assumptions:

For all regression-type approaches, we will assess the normality of the residuals (of each one of the fitted models) through q-q plots. Residual homoscedasticity will be assessed through two-way scatter plots of the residuals over fitted values. Once we build the model with all possible predictors as explanatory variables, the assumption of the linear relationship between the dependent variable and each one of the predictors individually, given the presence of the other predictors, will be assessed through investigating different functional forms of the predictor and their impact on the R^2 of the model. The independence of observations will be always assumed.

Violations of model assumptions:

If the main assumption violated is that of homoscedasticity (i.e. there is residual heteroscedasticity), robust estimations of the standard errors (SE) of the regression parameters will be made, using the sandwich estimator of the SE. Whenever the residual distributions show a clear deviation from normality, bootstrap-based approaches will be used, with at least 1000 replication samples: bias-corrected and accelerated bootstrap-based 95% Confidence Intervals (95% CI) will be computed for each estimated parameter.

23.4 Secondary outcome and other exploratory analyses

Metrics for quantifying blood flow from retinal imaging are in development, and have not previously been applied in MS patients. Retinal vessel walls will be assessed in a similar fashion to that outlined by Chui et al (2013). Arterial wall thickness will be assessed as a function of lumen thickness. In the first instance normative data will be obtained from age matched controls prior to imaging patients with MS. Subsequently appropriate multigroup statistical tests will be applied. Capillary network density will be assessed using similar methods to those described by Tam et al., (2010). Calculating blood velocity will be done building up spatio-temporal analysis outlined by Tam et al., (2011).

Exploratory analyses will be performed to assess the associations between ASL changes (dependent variable) and all secondary outcome measures (explanatory variables). An interaction term such as ‘secondary outcome measure change’ X ‘treatment group’ will be included in the model as an explanatory variable. Whenever it becomes significant it will indicate that simvastatin influences the association between primary and secondary outcome measures. Although the sample size of this study was based on the ASL, we estimated that the number of patients that we would need to detect a reduction in Glutamate of 1.824 that represents a 20% treatment effect (Azevedo et al., 2014), is equally 17 per arm (80% power). Similarly, an increase in neurite density of 0.128 that represents a 20% treatment effect (Magnollay et al., 2013) would require 13 per arm (80% power). Additionally, even if the number of patients per arm will not be sufficient to see a significant treatment effect of this size, this study will provide information on the temporal behaviour of these MRI parameters that can be used to power future neuroprotective trials.

Model assumptions will be also checked as described above (23.3), and any violations of the model assumptions will be dealt with in a similar way.

23.5 Sensitivity and other planned analyses

The Trial Statistician will be responsible for all statistical aspects of the trial from design through to analysis and dissemination.

An analysis of the missingness patterns in the data will be performed. Baseline clinical, demographical and neuroimaging characteristics of those patients with missing visits will be compared with those of patients without missing values, to investigate the assumption of missing at random (MAR). If there is no evidence against MAR, multiple imputation methods will be performed, and any serious discrepancy between the complete case results and the imputation results will be reported. Worst and best case sensitivity analyses will also be performed.

In general, given that we will use randomisation with minimisation, we do not expect major imbalances at baseline. However, should there be any, we will consider adjusting the models for the imbalanced variable.

23.6 Interim analysis

Due to the short-term nature of the study and small sample size, an interim analysis will not be required.

23.7 Other Statistical Considerations

Any deviation(s) from the original statistical plan will be described and justified in the protocol and/or in the final report, as appropriate.

24. Record keeping and archiving

At the end of the trial, all essential documentation will be archived securely by the CI and trial sites for a minimum of 5 years from the declaration of end of trial. Any destruction of these essential documents will require sponsor authorisation/approval.

Essential documents are those which enable both the conduct of the trial and the quality of the data produced to be evaluated and show whether the site complied with the principles of Good Clinical Practice and all applicable regulatory requirements.

The sponsor will notify sites when trial documentation can be archived following submission of the End of Study report. All archived documents must continue to be available for inspection by appropriate authorities upon request.

25. Oversight Committees

25.1 Trial Management Group (TMG)

A Trial Management Group (TMG) will be set up to assist with developing the design, co-ordination and strategic management of the trial. The membership, frequency of meetings, activity (including trial conduct and data review) and authority will be covered in the TMG terms of reference.

The study will be overseen by two principal investigators (Prof John Greenwood and Prof Richard Nicholas) in close partnership with the other co-applicant (Prof Jeremy Chataway). Prof Richard Nicholas has experience of managing multi-centre studies and coordinating the appropriate approvals to deliver a successful result. Professor John Greenwood has managed many successful grants (both project and programme) a number of which have been multisite and multidisciplinary. As this is a multidisciplinary study effective collaboration between the different components is essential. For this reason a Trial Management Group (TMG), will be established and will meet every month with an initial meeting 1 month from trial commencement due to the short nature of the trial. The TMG will also comprise members of the research group.

The PIs and the clinical research fellows will report the progress of the project and key issues related to it to the TMG, who will advise. The aim of this group is to ensure that the interests and needs of patients, the public, and clinicians are taken into account and that the project is efficiently run. This TMG will help to ensure that the milestones are met, and that the dissemination of findings maximises the impact of the project.

We will set up a website with updates on the trials for both the lay and scientific community and for the patients participating in the research study. Interaction through Q&A and email will be encouraged. A link will be included in the UCL Institute of Neurology, Institute of Ophthalmology and Imperial websites. We will provide patients with a lay summary of our study at the end of the study and when major results are published. This will be done through email, by post, and by updating the study-specific website.

26. Direct Access to Source Data/Documents

The investigator(s)/ institution(s) will permit trial-related monitoring, audits, REC review, and regulatory inspection(s), providing direct access to source data/documents. Trial participants are informed of this during the informed consent discussion. Participants will consent to provide access to their medical notes.

27. Ethics and regulatory requirements

The sponsor will ensure that the trial protocol, participant information sheet, consent form, GP letter and submitted supporting documents have been approved by the appropriate regulatory body (MHRA in UK) and an appropriate research ethics committee, prior to any participant recruitment. The protocol, all other supporting documents including and

agreed amendments, will be documented and submitted for ethical and regulatory approval as required. Amendments will not be implemented prior to receipt of the required approval(s).

Before the site may be opened to recruit participants, the Chief Investigator/Principal Investigator or designee must receive HRA approval and capacity and capability confirmed in writing from their Trust Research & Development (R&D). It is the responsibility of the CI/ PI or designee at each site to ensure that all subsequent amendments gain the necessary approvals, including HRA approvals (where required) at the site. This does not affect the individual clinician's responsibility to take immediate action if thought necessary to protect the health and interest of individual participants.

An annual progress report (APR) will be submitted to the REC within 30 days of the anniversary date on which the favourable opinion was given, and annually until the trial is declared ended. The chief investigator will prepare the APR.

Within 90 days after the end of the trial, the CI/Sponsor will ensure that the main REC and the MHRA are notified that the trial has finished. If the trial is terminated prematurely, those reports will be made within 15 days after the end of the trial.

The CI will supply the Sponsor with a report of the clinical trial which complies with the format as defined by the EMA. This will then be uploaded to EudraCT for availability to the MHRA and a copy of the report will be submitted to the main REC, within 1 year after the end of the trial.

28. Monitoring requirement for the trial

The sponsor will determine the appropriate level and nature of monitoring required for the trial. Risk will be assessed on an ongoing basis and adjustments made accordingly.

The degree of monitoring will be proportionate to the objective, purpose, phase, design, size, complexity, blinding, endpoints and risks associated with the trial.

A trial specific oversight and monitoring plan will be established for studies. The trial will be monitored in accordance with the agreed plan.

Also see section 13.1

29. Finance

Simvastatin in progressive MS is fully funded by an MS Society grant number 44.
Additional funding has been secured from the Multiple Sclerosis Trials Collaboration (MSTC) – a registered charity (1113598).

Prof Richard Nicholas is a trustee of MSTC.

29.1 Insurance

University College London holds insurance against claims from participants for injury caused by their participation in the 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. University College London 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 University College London 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 Sponsor's Insurers, via the Sponsor's office.

Hospitals selected to participate in this clinical trial shall provide clinical negligence insurance cover for harm caused by their employees and a copy of the relevant insurance policy or summary shall be provided to University College London, upon request.

30. Publication policy

30.1 Trial Results

The results of the trial will be disseminated regardless of the direction of effect.

30.2 Authorship

The success of the study is dependent upon the collaboration of all participants. For this reason, credit for the main results will be given to all those who have collaborated in the study, through authorship and by contribution.

Uniform requirements for authorship for manuscripts submitted to medical journals will guide authorship decisions. These state that authorship credit should be based only on substantial contribution to:

- Conception and design, or acquisition of data, or analysis and interpretation of data.
- Drafting the article or revising it critically for important intellectual content.
- Final approval of the version to be published.
- And that all these conditions must be met (www.icmje.org).

In light of this, the Chief Investigator and Research Team (as documented in this protocol) will be named as authors in any publication, and an appropriate first author agreed through discussion amongst the TMG members.

The Simvastatin in progressive MS team should be acknowledged in all publications, as should UCL as sponsor and MS Society and MSTC as funders.

Other key individuals will be included as authors or contributors as appropriate and at the discretion of the TMG. We will include collaborators who will be listed as

contributors for the main study publication, and for PIs we will endeavour to name them as co-authors on the primary publication subject to this being acceptable inclusion criteria by the target journal. Any disputes relating to authorship will be resolved by the CI in consultation with the TMG.

30.3 Reproducible Research

All proposed publications and presentations must be discussed with the sponsor, co-CIs and funders (MS Society, MSTC) prior to their release and will be in line with UCLs publication policy.

The clinical study report will be used for publication and presentation at scientific meetings.

Summaries of results will also be made available to Investigators for dissemination within their clinics (where appropriate and according to their discretion).

31. References

Antonopoulos, A.S., Margaritis, M., Shirodaria, C. and Antoniades, C. (2012). Translating the effects of statins: From redox regulation to suppression of vascular wall inflammation Thromb. Haemost. 108:840–848.

Azevedo, C.J., Kornak, J., Chu, P., Sampat, M., Okuda, D.T., Cree, B.A., Nelson, S.J., Hauser, S.L. and Pelletier, D. (2014). In vivo evidence of glutamate toxicity in multiple sclerosis. Ann. Neurol.76:269-278. doi: 10.1002/ana.24202. [Epub 2014 Jul 9].

Bennett, J., de Seze, J., Lana-Peixoto, M., Palace, J., Waldman, A., Schippling, S., Tenembaum, S., Banwell, B., Greenberg, B., Levy, M., Fujihara, K., Chan, K., Kim, H., Asgari, N., Sato, D., Saiz, A. Wuerfel, J., Zimmermann, H., Green, A., Villoslada, P. and Paul, F; with the GJCF-ICC&BR. (2015). Neuromyelitis optica and multiple sclerosis: Seeing differences through optical coherence tomography. Mult. Scler. Feb 6. pii: 1352458514567216. [Epub ahead of print].

Blyth, B.J., Farahvar, A., He, H., Nayak, A., Yang, C., Shaw, G. and Bazarian, J.J. (2011). Elevated serum ubiquitin carboxy-terminal hydrolase L1 Is associated with abnormal blood–brain barrier function after traumatic brain injury. J. Neurotrauma 28:2453–2462.

Chard, D.T., Jackson, J.S., Miller, D.H. and Wheeler-Kingshott, C.A. (2010). Reducing the impact of white matter lesions on automated measures of brain gray and white matter volumes. J. Magn. Reson. Imaging 32:223-228.

Chataway, J., Schuerer, N., Alsanousi, A., Chan, D., MacManus, D., Hunter, K., Anderson, V., Bangham, C.R., Clegg, S., Nielsen, C., Fox, N.C., Wilkie, D., Nicholas, J.M., Calder, V.L., Greenwood, J., Frost, C. and Nicholas, R. (2014). 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 383:2213-2221.

Chui, T.Y., VanNasdale, D. A, & Burns, S. A. (2012). The use of forward scatter to improve retinal vascular imaging with an adaptive optics scanning laser ophthalmoscope, Biomed. Opt. Express 3, 2537-2549.

Chui, T.Y., Gast, T.J. and Burns, S.A. (2013). Imaging of vascular wall fine structure in the human retina using adaptive optics scanning laser ophthalmoscopy. Invest. Ophthalmol. Vis. Sci. 54:7115-7124.

De Keyser, J., Steen, C., Mostert, J.P. and Koch, M.W. (2008). Hypoperfusion of the cerebral white matter in multiple sclerosis: possible mechanisms and pathophysiological significance. J. Cereb. Blood Flow Metab. 28:1645–1651.

D'Haeseleer, M., Beelen, R., Fierens, Y., Cambron, M., Vanbinst, A-M., Verborgh, C., Demey, J. and De Keyser, J. (2013). Cerebral hypoperfusion in multiple sclerosis is reversible and mediated by endothelin-1. Proc Natl Acad Sci USA 110:5654-5658.

Dubra, A. and Sulai, Y. (2011). Reflective afocal broadband adaptive optics scanning ophthalmoscope. Biomed. Opt. Express 2:1757-1768.

Endres, M., Laufs, U., Huang, Z., Nakamura, T., Huang, P., Moskowitz, M.A. and Liao, J.K. (1998). Stroke protection by 3-hydroxy-3-methylglutaryl (HMG)-CoA reductase inhibitors mediated by endothelial nitric oxide synthase. Proc. Natl. Acad. Sci. USA 95:8880–8885.

Fisniku, L.K., Chard, D.T., Jackson, J.S., Anderson, V.M., Altmann, D.R., Miszkiel, K.A., Thompson, A.J. and Miller, D.H. (2008). Gray matter atrophy is related to long-term disability in multiple sclerosis. Ann. Neurol. 64:247-254.

Fox, R.J., Thompson, A., Baker, D., Baneke, P., Brown, D., Browne, P., Chandraratna, D., Ciccarelli, O., Coetzee, T., Comi, G., Feinstein, A., Kapoor, R., Lee, K., Salvetti, M., Sharrock, K., Toosy, A., Zaratin, P. and Zuidwijk, K. (2012). Setting a research agenda for progressive multiple sclerosis: the International Collaborative on Progressive MS. Mult. Scler. 18:1534-1540.

Gegg, M., Harry, R., Hankey, D., Zambarakji, H., Pryce, G., Baker, D., Adamson, P., Calder, V. and Greenwood, J. (2005). Suppression of autoimmune retinal disease by lovastatin does not require TH2 cytokine induction. J. Immunol. 174:2327-2335.

Giannopoulos, S., Katsanos, A.H., Tsivgoulis, G. and Marshall, R.S. (2012). Statins and cerebral hemodynamics. J. Cereb. Blood Flow Metab. 32:1973–1976.

Grecescu, M. (2014). Optical Coherence Tomography versus Visual Evoked Potentials in detecting subclinical visual impairment in multiple sclerosis. J. Med. Life 7:538-541.

Greenwood, J., Walters, C.E., Pryce, G., Kanuga, N., Beraud, E., Baker, D., and Adamson, P. (2003). Lovastatin inhibits brain endothelial Rho-dependent lymphocyte migration and attenuates experimental autoimmune encephalomyelitis. FASEB J. 17: 905-907.

Greenwood, J., Steinman, L. and Zamvil, S.S. (2006). Statin therapy and autoimmune disease: from protein prenylation to immunomodulation. Nat. Rev. Immunol. 6: 358-370.

Greenwood, J. and Mason, J.C. (2007). Statins and the vascular endothelial inflammatory response. Trends Immunol. 28: 88-98.

Greenwood, J., Heasman, S.J., Alvarez, J.I., Prat, A., Lyck, R. and Engelhardt, B. (2011). Leukocyteendothelial cell crosstalk at the blood-brain barrier: A prerequisite for successful immune cell entry to the brain. Neuropath. Appl. Neurobiol. 37:24-39.

Haendeler, J., Hoffmann, J., Zeiher, A.M. and Dimmeler, S. (2004). Antioxidant effects of statins via Snitrosylation and activation of thioredoxin in endothelial cells. A novel vasculoprotective function of statins. Circulation 110:856-861.

Huang-Link, Y.M., Al-Hawasi, A. and Lindehammar, H. (2014). Acute optic neuritis: retinal ganglion cell loss precedes retinal nerve fiber thinning. Neurol. Sci. Oct 14. [Epub ahead of print]

Kapoor, R., Furby, J., Hayton, T., Smith, K.J., Altmann, D.R., Brenner, R., Chataway, J., Hughes, R.A. and Miller, D.H. (2010). Lamotrigine for neuroprotection in secondary progressive multiple sclerosis: a randomised, double-blind, placebo-controlled, parallel-group trial. Lancet Neurol. 9:681-688.

Kutzelnigg, A., Lucchinetti, C.F., Stadelmann, C., Bruck, W., Rauschka, H., Bergmann, M.,Schmidbauer, M., Parisi, J.E. and Lassmann, H. (2005). Cortical demyelination and diffuse white matter injury in multiple sclerosis. Brain 128:2705-2712.

Laufs, U., La Fata, V., Plutzky, J. and Liao, J.K. (1998). Upregulation of endothelial nitric oxide synthase by HMG CoA reductase inhibitors. Circulation 97:1129–1135.

Liao, J.K. (2002). Beyond lipid lowering: the role of statins in vascular protection. Int. J. Cardiol. 86:5-18.

Lublin, F., Miller, D., Freedman, M., Creem B., Wolinsky, J., Weiner, H., Lubetzki, C., Hartung, H-P., Montalban, X., Uitdehaag, B., Merschhemke, M., Li, B., Putzki, N., Liu, F., Haring, D., Kappos, L. (2016). Oral fingolimod in primary progressive multiple sclerosis (INFORMS): a phase 3, randomised, double-blind, placebo-controlled trial. Lancet 387:1075–1084.

Lublin FD. New multiple sclerosis phenotypic classification. Eur Neurol. 2014;72 Suppl 1:1-5

Mackenzie, I.S., Morant, S.V., Bloomfield, G.A., MacDonald, T.M. and O'Riordan, J. (2014). Incidence and prevalence of multiple sclerosis in the UK 1990-2010: a descriptive study in the General Practice Research Database. J. Neurol. Neurosurg. Psychiatry 85:76-84.

Magliozzi, R., Howell, O., Vora, A., Serafini, B., Nicholas, R., Puopolo, M., Reynolds, R. and Aloisi, F. (2007). Meningeal B-cell follicles in secondary progressive multiple sclerosis associate with early onset of disease and severe cortical pathology. Brain 130:1089-1104.

Magnollay, L., Grussu, F., Wheeler-Kingshott, C., Sethi, V., Zhang, H., Chard, D., Miller, D.H. and Ciccarelli, O. (2013). Application of orientation dispersion and density imaging (NODDI) to RRMS. ECTRIMS P445s.

Mahad, D.H., Trapp, B.D. and Lassmann, H. (2015). Pathological mechanisms in progressive multiple sclerosis. Lancet Neurol. 14:183-193.

Marchi, N., Rasmussen, P., Kapural, M., Fazio, V., Kight, K., Mayberg, M.R., Kanner, A., Ayumar, B., Albensi, B., Cavaglia, M. and Janigro, D. (2003). Peripheral markers of brain damage and blood-brain barrier dysfunction. Restor. Neurol. Neurosci. 21:109–121.

Mason, J.C. (2003). Statins and their role in vascular protection. Clin. Sci. (Lond). .105:251-266.

Miller, E., Mrowicka, M., Saluk-Juszczak, J. and Ireneusz, M. (2011). The level of isoprostanes as a non-invasive marker for in vivo lipid peroxidation in secondary progressive multiple sclerosis. Neurochem Res 36:1012–1016.

Mraiche, F., Cena, J., Das, D. and Vollrath, B. (2005). Effects of statins on vascular function of endothelin-1. Br. J. Pharmacol. 144:715-726.

Neuhaus, O. and Hartung, H.P. (2007). Evaluation of atorvastatin and simvastatin for treatment of multiple sclerosis. Expert Rev. Neurother. .7:547-56.

Olesen, J., Gustavsson, A., Svensson, M., Wittchen, H.U. and Jönsson, B. (2012). CDBE2010 study group; European Brain Council. The economic cost of brain disorders in Europe. Eur. J. Neurol. 19:155–162.

Pahan, K., Sheikh, F.G., Namboodiri, A.M. and Singh, I. (1997). Lovastatin and phenylacetate inhibit the induction of nitric oxide synthase and cytokines in rat primary astrocytes, microglia, and macrophages. J. Clin. Invest. 100:2671-2679.

Paling, D., Thade Petersen, E., Tozer, D.J., Altmann, D.R., Wheeler-Kingshott, C.A., Kapoor, R., Miller, D.H. and Golay, X. (2014). Cerebral arterial bolus arrival time is prolonged in multiple sclerosis and associated with disability. J. Cereb. Blood Flow Metab. 34:34-42.

Paraskevas, K.I. (2008). Statin treatment for rheumatoid arthritis: a promising novel indication. Clin. Rheumatol. 27:281-287.

Petersen, E.T., Mouridsen, K. and Golay, X. all named co-authors of the QUASAR test-retest study. (2010). The QUASAR reproducibility study, Part II: Results from a multi-center Arterial Spin Labeling test-retest study. Neuroimage 49:104-113.

Polman CH, Reingold SC, Banwell B, et al. Diagnostic criteria for multiple sclerosis: 2010 revisions to the McDonald criteria. Ann Neurol. 2011 Feb;69(2):292-302

Roosendaal, S.D., Bendfeldt, K., Vrenken, H., Polman, C.H., Borgwardt, S., Radue, E.W., Kappos, L., Pelletier, D., Hauser, S.L., Matthews, P.M., Barkhof, F. and Geurts, J.J. (2011). Grey matter volume in a large cohort of MS patients: relation to MRI parameters and disability. Mult. Scler. 17:1098-1106.

Schmeer, C., Kretz, A. and Isenmann, S. (2006). Statin-mediated protective effects in the central nervous system: general mechanisms and putative role of stress proteins. Restor. Neurol. Neurosci. 24:79–95.

Scoles, D., Sulai, Y. N., Langlo, C. S., Fishman, G. A., Curcio, C. A., Carroll, J., & Dubra, A. (2014). In Vivo Imaging of Human Cone Photoreceptor Inner Segments. Investigative Ophthalmology & Visual Science, *55*(7), 4244–4251.

Sulai, Y.N., Scoles, D., Harvey, Z. and Dubra, A. (2014). Visualization of retinal vascular structure and perfusion with a nonconfocal adaptive optics scanning light ophthalmoscope. J. Opt. Soc. Am. A. Opt. Image Sci. Vis. 31:569-579.

Tam, J., Martin, J.A. and Roorda, A. (2010). Noninvasive visualization and analysis of parafoveal capillaries in humans. Invest. Ophthalmol. Vis. Sci. 51:1691-1698.

Tam J, Tiruveedhula P, Roorda A. (2011). Characterization of single-file flow through human retinal parafoveal capillaries using an adaptive optics scanning laser ophthalmoscope. Biomed. Opt. Express 2:781-793.

van der Most, P.J., Dolga, A.M., Nijholt, I.M., Luiten, P.G.M. and Eisel, U.L.M. (2009). Statins: mechanisms of neuroprotection. Prog. Neurobiol. 88:64–75.

Vollmer, T., Key, L., Durkalski, V., Tyor, W., Corboy, J., Markovic-Plese, S., Preiningerova, J., Rizzo, M., Singh I. (2004). Oral simvastatin treatment in relapsing-remitting multiple sclerosis. Lancet 363:1607-1608.

Walters, C.E., Pryce, G., Hankey, D.J.R., Sebti, S.M., Hamilton, A.D., Baker, D., Greenwood, J. and Adamson, P. (2002). Inhibition of rho GTPases with protein prenyl transferase inhibitors prevents leukocyte recruitment to the CNS and attenuates clinical signs of disease in an animal model of multiple sclerosis. J. Immunol. 168:4087-4094.

Weber, M.S., Youssef, S., Dunn, S.E., Prod'homme, T., Neuhaus, O., Stuve, O., Greenwood, J., Steinman, L. and Zamvil, S.S. (2006). Statins in the treatment of central nervous system autoimmune disease. J. Neuroimmunol.178:140-148.

Xu, G., Fitzgerald, M.E., Wen, Z., Fain, S.B., Alsop, D.C., Carroll, T., Ries, M.L., Rowley, H.A., Sager, M.A., Asthana, S., Johnson, S.C. and Carlsson, C.M. (2008). Atorvastatin therapy is associated with greater and faster cerebral hemodynamic response. Brain Imaging Behav. 2:94.

Young, R.P. and Hopkins, R.J. (2013). Update on the potential role of statins in chronic obstructive pulmonary disease and its co-morbidities. Expert Rev. Respir Med. 7:533-544.

Yuan, C., Zhou, L., Cheng, J., Zhang, J., Teng, Y., Huang, M., Adcock, I.M., Barnes, P.J. and Yao, X. (2012). Statins as potential therapeutic drug for asthma? Respir. Res. 13:108.

Zhang, H., Schneider, T., Wheeler-Kingshott, C.A. and Alexander, D.C. (2012). NODDI: practical in vivo neurite orientation dispersion and density imaging of the human brain. Neuroimage 61:1000-1016.

Zhong, Z. Petrig, B.L., Qi, X & Burns, S.A. (2008). In vivo measurement of erythrocyte velocity and retinal blood flow using adaptive optics scanning laser ophthalmoscopy," Opt. Express 16, 12746-12756.

Appendix 1 - schedule of assessments

Visits	**Visit 0 Pre-screening**	**Visit 1* (Combined Screening/ Baseline)**	**Visit 2**	**Visit 3* (End of Study Treatment Visit)**	**Visit 4* (End of Study Follow-up)**	**Unscheduled (inc. relapse if indicated)**	**Telephone / e-mail Follow Up**
Visit Windows (1 week is equivalent to 7 days e.g. 4 weeks (1 month) is equivalent to 28 days)	**within 8 weeks**	**Day 0**	**Week 4 (+1 week)**	**Week 16 (+1 week)**	**Week 20 (+2 weeks)**	**Between V1 to EOS Follow-up**	**As required**
Pre-screening questionnaire	X						
Inclusion/Exclusion criteria review	X	X					X
Informed consent		X					
Medical history		X					
Con-meds		X	X	X	X	X	X
Medical review[1]		X	X	X	X	X	X
Recording of AEs			X	X	X	X	X
Physical examination		X	X	X	X	X	
Vital Signs		X	X	X	X	X	
Disability Assessment (EDSS)		X		X	X	X	
MSFC (9HPT, 25TFW)		X		X	X		
SDMT		X		X	X		
FAB		X			X		
MSIS-29v2		X		X	X		
MSWSv2		X		X	X		
EQ5D5L		X		X	X		

Visits	**Visit 0 Pre-screening**	**Visit 1* (Combined Screening/ Baseline)**	**Visit 2**	**Visit 3* (End of Study Treatment Visit)**	**Visit 4* (End of Study Follow-up)**	**Unscheduled (inc. relapse if indicated)**	**Telephone / e-mail Follow Up**
Visit Windows (1 week is equivalent to 7 days e.g. 4 weeks (1 month) is equivalent to 28 days)	**within 8 weeks**	**Day 0**	**Week 4 (+1 week)**	**Week 16 (+1 week)**	**Week 20 (+2 weeks)**	**Between V1 to EOS Follow-up**	**As required**
Safety bloods (see section 11.1 for list of laboratory tests)		X	X	X	X	X	
Urine pregnancy test[4]		X		X	X		
Immunology and biomarkers		X	X	X	X		
MRI		X		X	X		
ASL questionnaire		X					
ASL questionnaire follow-up				X	X		
Visual assessment		X					
Retinal Imaging Vascular Assessment Questionnaire		X		X	X		
Advanced retinal imaging inc. OCT*		X		X	X		
Randomisation		X					
Drug dispensed[3]		X (40mg)					
Drug uptitration[3]			X (80 mg)				
Drug Diary issued		X					
Confirmation to dose[2]		X					
Drug accountability (diary)[5]			X	X			
Drug compliance[5]			X	X			X
Telephone contact							X

***** *This visit will take place across two sites. The assessments may be split across two days. Day 1 assessments will take place at the UCL Institute of Neurology & National hospital for neurology and neurosurgery and day 2 assessments (visual assessment and Advanced Retinal Imaging) will take place at Moorfields Eye Hospital. Patients will be dispensed the drug on Day 1 of visit 1 but will be instructed not to take the drug until the evening of Day 2 of visit 1 (if over 2 days) after all ophthalmic assessments are completed. See Section 10 for full details.*

[1] *This will encompass any medical or MS-related symptoms that have arisen between Visit 1 and subsequent visits.*

[2] *Study medication must only be dispensed after randomisation once all day 1 of visit 1 assessments have been completed and the relevant safety reports have been obtained. Patients will be dispensed the drug on Day 1 of visit 1 but will be instructed not to take the drug until the evening of Day 2 (if over 2 days) of visit 1 after all ophthalmic assessments are completed. See Section 10 for full details.*

[3] *Participants will be allocated 220 tablets each for the duration of the study. There will therefore be one drug release at baseline and the patient will be reminded to uptitrate after one month at Visit 2. The patient will take 40mg x 2 tablets for the dose of 80mg for a period of 12 weeks. The neurologist will issue the drugs, diary and record compliance at the relevant visits.*
For the purpose of safety, the study participant will be contacted by telephone and adverse events assessed by the neurologist. If there are no issues identified, the participant will be advised to take the study medication and encouraged to contact a member of the research team if problems subsequently arise.

[4] *For female subjects only*

[5] *This will include a drug diary review and pills count.*