A phase 3 randomised, double blind, clinical trial investigating the effectiveness of repurposed simvastatin compared to placebo, in secondary progressive multiple sclerosis, in slowing the progression of disability

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1 Administrative information

This document was constructed using the Comprehensive Clinical Trials Unit (CCTU) at UCL Protocol template Version 5. It describes the MS-STAT2 trial, sponsored by UCL and co-ordinated by CCTU.

It provides information about procedures for entering participants into the trial, and provides sufficient detail to enable: an understanding of the background, rationale, objectives, trial population, intervention, methods, statistical analyses, ethical considerations, dissemination plans and administration of the trial; replication of key aspects of trial methods and conduct; and appraisal of the trial's scientific and ethical rigour from the time of ethics approval through to dissemination of the results. The protocol should not be used as an aide-memoire or guide for the treatment of other patients. Every care has been taken in drafting this protocol, but corrections or amendments may be necessary. These will be circulated to registered investigators in the trial. Sites entering participants for the first time should confirm they have the correct version through a member of the trial team at CCTU.

CCTU supports the commitment that its trials adhere to the SPIRIT guidelines. As such, the protocol template is based on an adaptation of the Medical Research Council CTU protocol template (2012) and the Standard Protocol Items: Recommendations for Interventional Trials (SPIRIT) 2012 Statement for protocols of clinical trials[1] . The SPIRIT Statement Explanation and Elaboration document[2] can be referred to, or a member of CCTU Protocol Review Committee can be contacted for further detail about specific items.

1.1 Compliance

The trial will be conducted in compliance with the approved protocol, the Declaration of Helsinki (2008), the principles of Good Clinical Practice (GCP) as laid down by the Commission Directive 2005/28/EC with implementation in national legislation in the UK by Statutory Instrument 2004/1031 and subsequent amendments, the Human Tissue (Quality and Safety for Human Application) Regulations 2007, the UK Data Protection Act, and the National Health Service (NHS) UK Policy Framework for Health and Social Care. International sites will comply with the principles of GCP as laid down by ICH topic E6 (Note for Guidance on GCP), Commission Directive 2005/28/EC, the European Directive 2001/20/EC (where applicable), the EU Tissue and Cells Directives 2004/23/EC, 2006/17/EC and 2006/86/EC, and other national and local applicable regulations. Agreements that include detailed roles and responsibilities will be in place between participating sites and CCTU.

Participating sites will inform CCTU as soon as they are aware of a possible serious breach of compliance, so that CCTU can fulfil its requirement to report the breach if necessary within the timelines specified in the UK Clinical Trials Regulations (currently 7 days). For the purposes of this regulation a 'serious breach' is one that is likely to affect to a significant degree:

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

1.2 Sponsor

UCL is the trial sponsor and has delegated responsibility for the overall management of the MS-STAT2 trial to CCTU. Queries relating to UCL sponsorship of this trial should be addressed to the CCTU Director or via the Trial Team.

1.3 Structured trial summary

Primary Registry and Trial Identifying Number	ClinicalTrials.gov: NCT03387670
Date of Registration in Primary Registry	29 Dec 2017
Secondary Identifying Numbers	ISRCTN : ISRCTN82598726 EudraCT #: 2017-003328-56 UCL R & D ID # (Sponsor): 17/0158 CTU Trial Adoption Group #: CTU/2014/107 IRAS #: 232288
Source of Monetary or Material Support	National Institute of Health Research-Health Technology Assessment – [NIHR-HTA] HTA Project # : 15/57/143
Sponsor	University College London with sponsor responsibilities delegated to CCTU.
Contact for Public Queries	ctu.enquiries@ucl.ac.uk
Contact for Scientific Queries	Dr Jeremy Chataway UCL Institute of Neurology **Address**: Queen Square Multiple Sclerosis Centre Russell Square House, 1ST Floor, Room 107 London WC1B 5EH **Email** : J.chataway@ucl.ac.uk **Telephone**: 02031087414
Public Title	MS-STAT2 - Multiple Sclerosis – Simvastatin Trial 2
Scientific Title	MS-STAT2 - A phase 3 randomised, double blind, clinical trial investigating the effectiveness of repurposed simvastatin compared to placebo, in secondary progressive multiple sclerosis, in slowing the progression of disability.
Countries of Recruitment	• England • Scotland • Wales

	• Northern Ireland • Eire
Health Condition(s) or Problem(s) Studied	Secondary Progressive Multiple Sclerosis
Intervention(s)	**<u>Simvastatin (Active Treatment)</u>** - **Low dose (Initial)**: 40mg simvastatin (1x 40mg tablet taken once daily at night) from baseline (M0/Week 0) for 1 month. *Dose escalation at visit 3 (M1/Week 4)* - **High dose**: 80mg simvastatin (2x 40mg tablets taken once daily at night) for 35 months; or until end of clinic follow up **<u>Placebo</u>** - **Low dose (Initial)**: 1x tablet taken once daily at night from baseline (M0/Week 0) for 1 month. *Dose escalation at visit 3 (M1/Week 4)* - **High dose**: 2x tablets taken once daily at night for 35 months; or until end of clinic follow up

Key Inclusion and Exclusion Criteria	**Inclusion Criteria** 1. Patients with a confirmed diagnosis of multiple sclerosis (MS)[3-5] that have entered the secondary progressive stage at randomisation.[6] 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 Expanded Disability Status Scale (EDSS), or clinical documentation of increasing disability 2. EDSS 4.0 - 6.5 (inclusive) 3. Aged 25 to 65 years old 4. Male or Female 5. Patients must be able and willing to comply with the terms of this protocol. 6. Written informed consent provided **Exclusion Criteria** 1. Relapse within **3 months** of baseline visit 2. Patients that have been treated with steroids (intravenous and/or oral) due to MS relapse/progression within 3 months of baseline 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 (***Note****: Patients on steroids for another medical condition may be included in the trial provided the steroid prescription is not for MS relapse/progression)* 3. Significant organ co-morbidity e.g. cardiac failure, renal failure, malignancy

	4. Screening levels of alanine aminotransferase (ALT) / aspartate aminotransferase (AST) or creatinine kinase (CK) ≥ 3x upper limit of normal (ULN) 5. Current use of a statin; or any use within the last 6 months 6. Medications that interact unfavourably with simvastatin as outlined in the current summary of product characteristics (SmPC); including but not limited to CYP3A4 inhibitors (e.g. itraconazole, ketoconazole, posaconazole, voriconazole, fluconazole, HIV protease inhibitors (e.g. nelfinavir), boceprevir, erythromycin, clarithromycin, telithromycin, telaprevir, nefazodone, fibrates (including fenofibrates), nicotinic acid (or products containing niacin), azole anti-fungal preparations, macrolide antibiotics, protease inhibitors, verapamil, amiodarone, amlodipine, gemfibrozil, ciclosporin, danazol , diltiazem, rifampicin , fusidic acid, grapefruit juice or alcohol abuse 7. Primary progressive MS 8. Diabetes Mellitus Type 1 9. Uncontrolled hypothyroidism 10. Female participants that are pregnant or breast feeding. Women of child bearing potential (WOCBP) who are unwilling or unable to use an acceptable method to avoid pregnancy for the entire study period, and up to 4 weeks after the last dose of study drug 11. Use of immunosuppressants (e.g. azathioprine, methotrexate, ciclosporine) or disease modifying treatments (avonex, rebif, betaferon, glatiramer) within the previous 6 months.

	12. Use of mitoxantrone, natalizumab, alemtuzumab, daclizumab or other monoclonal antibody treatment, if treated within the last 12 months 13. Use of fingolimod, fumarate, teriflunomide within the last 12 months 14. Use of other experimental disease modifying treatment within the last 6 months 15. Commencement of Fampridine ≤ 6 months from day of randomisation 16. Concurrent participation in another clinical trial of an investigational medicinal product or medical device 17. Patients with rare hereditary problems of galactose intolerance, the lapp lactase deficiency or glucose-galactose malabsorption
Study Type	A multicentre, interventional phase 3 trial including randomisation, double blinding, placebo control, and parallel group evaluation of simvastatin as a treatment for slowing the progression of disability in patients with secondary progressive multiple sclerosis.
Anticipated Date of First Enrolment	November 2017
Target Sample Size	1180
Primary Outcome(s)	Outcome - Time to initial disability progression between the simvastatin and placebo arm. The initial disability progression event is finalised as positive if disability is sustained and confirmed ≥6* months later. Metric - Expanded Disability Status Scale (EDSS) Time point – EDSS will be measured on a 6 monthly basis from baseline until last available EDSS score recorded at last attended clinic appointment /via telephone.

	Progression of disability is defined as an increase of at least 1 point if EDSS baseline score is <6, or an increase of 0.5 point if baseline EDSS score is ≥6. **Participants presenting with an initial disability progression (based on EDSS scores) at visit 10 clinic follow up with less than 6 months to the end of trial may have the event finalised as positive 3-6 months later.*
Key Secondary Outcomes	1. To examine the clinical effect of neuroprotection based on clinician and patient reported outcome measures; 2. To estimate the incremental cost and cost-effectiveness of simvastatin versus standard care for the trial period and for the lifetime horizon; <u>Clinician reported outcomes</u> ▪ A modified Multiple Sclerosis Functional Composite (MSFC) outcome measure comprised of three components. The Symbol Digit Modalities Test (SDMT) will replace the Paced Auditory Serial Addition Test (PASAT), one of the three components in the standard MSFC. - 25 foot walk (T25FW) - 9 Hole peg test (9HPT) - Symbol digit modalities test (SDMT) ▪ Sloan Low Contrast Visual Acuity (SLCVA) ▪ Relapse assessment – number and severity ▪ Frontal Assessment Battery (FAB) ▪ Modified Rankin Scale (mRS) ▪ Brief International Cognitive Assessment For Multiple Sclerosis (BICAMS), a composite cognitive assessment tool comprising of the three components namely; - Symbol Digit Modalities Test (SDMT)

	- California Verbal Learning Test- II (CVLT- II) - Brief Visuospatial Memory Test- Revised (BVMT-R) <u>Patient reported measures</u> ▪ MS Impact Scale-29 v2 (MSIS-29v2) ▪ MS Walking Scale-12 v2 (MSWS-12v2) ▪ ABILHAND-23 ▪ EQ-5D 5L ▪ SF-36 v2 ▪ Modified Fatigue Impact Scale – 21 (MFIS-21) ▪ Chalder Fatigue Questionnaire (CFQ)

1.4 Roles and responsibilities

These membership lists are correct at the time of writing; please see terms of reference documentation in the TMF for current lists.

1.4.1 Protocol contributors

Name	Affiliation	Role
Dr Jeremy Chataway	University College London	Chief Investigator
Professor Chris Frost	London School of Hygiene and Tropical Medicine (LSHTM)	Statistician/Co-applicant
Dr Jennifer Nicholas	London School of Hygiene and Tropical Medicine (LSHTM)	Trial Statistician/Co-applicant
Dr Nicholas Richard	Imperial College Healthcare NHS Trust	Co-applicant
Professor Sue Pavitt	University of Leeds	Co-applicant
Professor Siddharthan Chandran	University of Edinburgh	Co-applicant
Dr Helen Ford	Leeds Teaching Hospitals NHS Trust (LTHT)	Co-applicant
Professor Gavin Giovannoni	Queen Mary University of London (QMUL)	Co-applicant
Professor Olga Ciccarelli	University College London	Co-applicant
Marie Braisher	University College London	Co-applicant
Professor Alan Thompson	University College London	Co-applicant
Professor John Greenwood	University College London	Co-applicant
Director	University College London (Comprehensive Clinical Trials Unit)	Director CCTU/ Co-applicant
Dr Martha Bajwa Joseph	University College London (Comprehensive Clinical Trials Unit) – UCL CCTU	Trial Manager
Torsten Chandler	University College London (Comprehensive Clinical Trials Unit) - UCL CCTU	Health Economist

1.4.2 Role of trial sponsor and funders

Name	Affiliation	Role
Nicholas Freemantle	UCL CCTU	Overall supervision of UCL CCTU sponsorship Ultimate authority for writing the report and decision to submit for publication will lie with the chief investigator.
NIHR-HTA	-	Funder

1.4.3 Trial Team

Name	Affiliation	Role and responsibilities
Dr Jeremy Chataway	UCL	Chief Investigator - Overall responsibility for the trial
Marie Braisher	UCL	Research Manager
Dr Marta Campos	UCL CCTU	Clinical Project Manager
Dr Martha Bajwa Joseph	UCL CCTU	Trial Manager
Nina Kneffel	UCL CCTU	Data Manager
Dr Jennifer Nicholas	LSHTM	Trial Statistician

1.4.4 Trial Management Group

Name	Affiliation	Role and responsibilities
Dr Jeremy Chataway	UCL	Chief Investigator /Chair
Professor Chris Frost	LSHTM	Senior Statistician
Dr Jennifer Nicholas	LSHTM	Trial Statistician
Dr Nevin John	UCL	Research Fellow
Dr Helen Ford	LTHT	Principal investigator/Recruitment Hub Lead
Professor Sue Pavitt	University of Leeds	Co-applicant
Marie Braisher	UCL	Research Manager
Dr Martha Bajwa Joseph	UCL CCTU	Trial Manager
Dr Marta Campos	UCL CCTU	Project Manager

Nina Kneffel	UCL CCTU	Data Manager
Torsten Chandler	UCL CCTU	Health Economist
Stuart Nixon	UK Multiple Sclerosis Society (UK-MSS)	Lay representative

1.4.5 Trial Steering Committee

Name	Affiliation	Role and responsibilities
Dr Brendan McLean	Royal Cornwall Hospitals NHS Trust	Independent Chair
Dr Jeremy Chataway	UCL	Chief investigator
Professor Thomas Jaki	Lancaster University	Independent Statistician
Dr Victoria Williams	Guy's and St Thomas's NHS	Independent Neurologist
Trishna Vohra	Not Applicable	Independent lay representative
Professor Chris Frost	LSHTM	(Observer) Lead Statistician
Dr Jennifer Nicholas	LSHTM	(Observer) Trial Statistician

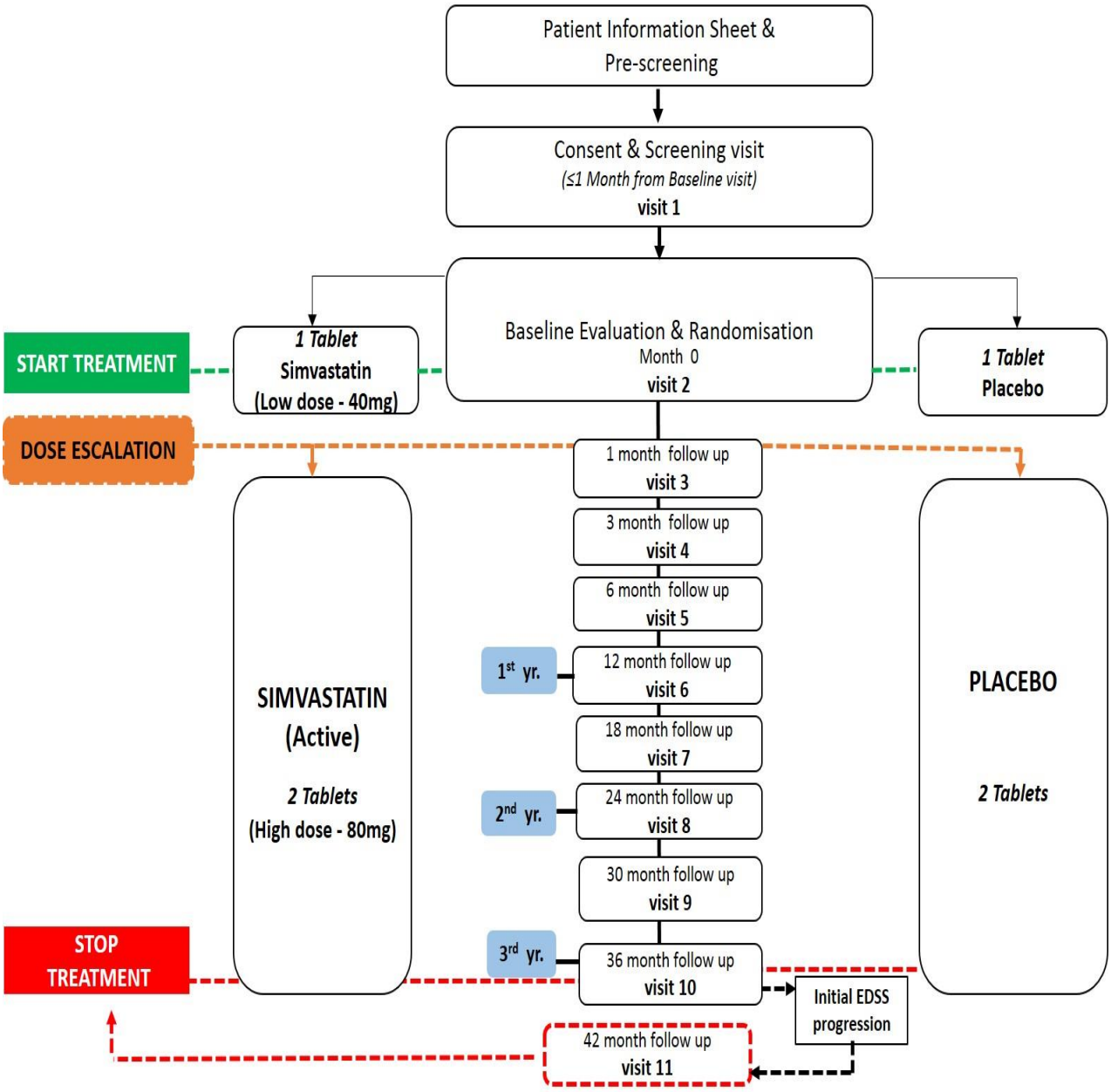
1.4.6 Independent Data Monitoring and Ethics Committee

Name	Affiliation	Role and responsibilities
Professor Graeme McLennan	University of Aberdeen	Chair (Professor of Statistics/Triallist)
Professor Emeritus Michael Hutchinson	University College Dublin	Independent Member (Clinical Research Professor / Neurologist)
Dr Heather Wilson	Royal Free Hospital	Independent Member (Neurologist)
Professor Chris Frost	LSHTM	(Observer) Lead Statistician
Dr Jennifer Nicholas	LSHTM	(Observer) Trial Statistician

1.4.6 Recruitment Management Group

Name	Affiliation	Role and responsibilities
Dr Jeremy Chataway	UCL	Chief Investigator
Dr Helen Ford	LTHT	Principal Investigator
Marie Braisher	UCL	Research Manager
Dr Marta Campos	CCTU	Project Manager
Dr Martha Bajwa Joseph	CCTU	Trial Manager
Stuart Nixon	UK Multiple Sclerosis Society (UK-MSS)	Lay representative

2 Trial Diagram



3 Abbreviations

AE	Adverse Event
AR	Adverse Reaction
ALT	Alanine Aminotransferase
AST	Aspartate Aminotransferase
BVMT-R	Brief visuospatial memory test- Revised
BICAMS	Brief International Cognitive Assessment For Multiple Sclerosis
CA	Competent Authority
CCTU	Comprehensive Clinical Trials Unit
CI	Chief Investigator
CK	Creatinine Kinase
CRF	Case Report Form
CFQ	Chalder Fatigue Questionnaire
CSRI	Client Services Receipt Inventory
CTA	Clinical Trial Authorisation
CVLT-II	California Verbal Learning Test- second edition
DM	Diabetes Mellitus
DMT	Disease modifying treatment
DSUR	Development Safety Update Report
EC	Ethics Committee
EDSS	Expanded Disability Status Scale
EQ-5D-5L	EuroQol 5 Dimension 5 Levels
EU	European Union
FDA	(US) Food and Drug Administration
FWA	Federal Wide Assurance
GCP	Good Clinical Practice
9HPT	9-Hole Peg Test
HMG-CoA	3-Hydroxy-3-methylglutaryl-coenzyme A
HTA	Health Technology Assessment
HRA	Health Research Authority
ICH	International Conference on Harmonisation
IMP	Investigational Medicinal Product
ITT	Intention to Treat
LFT	Liver Function Test
MHRA	Medicines and Healthcare products Regulatory Agency
MRI	Magnetic Resonance Imaging
MS	Multiple Sclerosis
MS-CTN	Multiple Sclerosis Clinical Trials Network
MSFC	Multiple Sclerosis Functional Composite
MSS	Multiple Sclerosis Society
MS-SMART	Multiple Sclerosis Secondary Progressive

	Multiple Arm Randomisation Trial
MS-STAT	Multiple Sclerosis Simvastatin [Phase 2 trial]
MS-STAT2	Multiple Sclerosis Simvastatin 2 [Phase 3 trial]
MSWS-v2	Multiple Sclerosis Walking Scale – version2
MFIS-21	Modified Fatigue Impact Scale – 21 Item (MFIS-21)
PI	Principal Investigator
PIS	Participant Information Sheet
PPE	Patient Public Engagement
PPI	Patient Public Involvement
PwMS	People with Multiple Sclerosis
PwSPMS	People with Secondary Progressive Multiple Sclerosis
PROM	Patient reported outcome measure
QA	Quality Assurance
QALYs	Quality-adjusted life-years
QC	Quality Control
QMMP	Quality Management and Monitoring Plan

RCT	Randomised Controlled Trial
REC	Research Ethics Committee
RRMS	Relapsing Remitting Multiple Sclerosis
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
SAR	Serious Adverse Reaction
SDMT	Single Digit Modality Test
SF-36 v2	36-item Short Form Health Survey (version 2)
SLCVA	Sloan Low Contrast Visual Acuity
SmPC	Summary of Product Characteristics
SPMS	Secondary Progressive Multiple Sclerosis
SSA	Site Specific Approval
SUSAR	Suspected Unexpected Serious Adverse Reaction
T25FW	Timed 25 Foot Walk
TMF	Trial Master File
TMG	Trial Management Group
TMT	Trial Management Team
ToR	Terms of Reference
TSC	Trial Steering Committee
UCL	University College London

4 Glossary

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 product. AEs are excluding MS related relapses.

Case Record Form a paper or electronic document designed to record all events within the study protocol required on each trial subject.

Hyperlipidaemia: This is a group of inherited or acquired conditions in which an abnormally elevated level of serum triglyceride or serum cholesterol is seen (typically in the range of 2-3 times the upper limit of normal). This is distinguishable from elevated levels of cholesterol resulting from high dietary fat intake.

Macular – is the small central area of the retina surrounding the fovea. It is responsible for central vision.

Optical Coherence Tomography – is a non-invasive high resolution imaging modality for obtaining cross-sectional images and 3 dimensional images of the retina in vivo. It is analogous to ultrasound but instead of using acoustic echoes it uses light reflections to acquire images.

Optic Disc – is the ocular end of the optic nerve head. It denotes the exit of retinal nerve fibres from the eye and the entrance of blood vessels to the eye.

Papillo-macular bundle - collection of retinal ganglion cells that carry the information from the macula (the central retina) to the optic nerve and on to the brain. If damaged, central visual field defects occur.

Primary Progressive Multiple Sclerosis (PPMS) - Diagnosis with PPMS requires 1 year of disease progression in addition to 2 of the following 3 findings: positive brain MRI (9 T2 lesions or 4 or more T2 lesions with positive visual evoked potential); positive spinal cord MRI (2 focal T2 lesions); or positive cerebrospinal fluid (CSF).

Progression of disability - defined as an increase from baseline of at least 1 point if baseline EDSS is less than 6 or at least 0.5 point if baseline EDSS is 6 or more.

Relapse: A relapse will be defined as new or worsening neurological symptom(s) in the absence of fever, lasting for more than 24 hours, and have been preceded by a period of clinical stability of at least 30 days, with no other explanation than MS.

Retina – is a light sensitive nerve tissue in the eye that converts light into electrical impulses that are sent along the optic nerve to the brain.

Retinal ganglion cell layer – It lies next to the RNFL in the retina. It is formed by the retinal nerve ganglion cell bodies. It lies between the RNFL and the inner plexiform layer.

Retinal nerve fibre layer (RNFL) – Innermost retinal layer. It is formed by axons of retinal ganglion cells traversing the retina to leave the eye at the optic disc. It is highly back scattering on OCT.

Retinal nerve fibre layer thickness – the distance between the vitreoretinal interface and the anterior boundary of the retinal pigment epithelium and choriocapillaris. An automated segmentation algorithm based on reflectivity changes between adjacent retinal layers calculates the RNFL thickness. These two boundaries are the sharpest edges in each OCT A scan because of the high contrast in optical reflectivity between the relatively non-reflective vitreous and the reflective neuro-sensory retina and between the minimally reflective photoreceptor outer segments and the highly reflective retinal pigment epithelium/choriocapillaris.

Women of Child-Bearing Potential (WOCBP): WOCBP (excluding women who are post-menopausal or permanently sterilised) must be using an acceptable method of contraception to avoid pregnancy throughout the study and for 4 weeks after the last dose of study drug in such a manner that the risk of pregnancy is minimized.

5 Introduction

5.1 Background and Rationale

Multiple sclerosis (MS) is the commonest acquired disabling neurological disease affecting young adults in temperate latitudes. It is a progressive disorder of the brain and spinal cord, the exact cause of which is unknown at present. It is thought to result from a combination of genetic and environmental factors, affecting approximately 120,000 people in the UK and 2.5M globally.[7]

Most patients with MS experience two stages of disease: early MS (relapsing-remitting MS, RRMS) due to bouts of inflammation-mediated demyelination and neuroaxonal damage that is partially reversible, and late MS (secondary progressive MS, SPMS), which affects the majority (up to 70%) of patients usually after 10-15 years from diagnosis. SPMS results from progressive neuroaxonal degeneration that causes accumulating and irreversible disability, characterised by a range of severe problems affecting walking, balance, manual function, vision, cognition, pain control, bladder and bowel function.

The pathological process driving the accrual of disability in SPMS is not known at present, but could include continuous compartmentalised inflammation, mitochondrial dysfunction, and iron deposition.

Unlike RRMS, where there are up to a dozen effective disease modifying treatments (DMTs), there is no proven DMT for SPMS – it is therefore a major unmet health need for the NHS. SPMS has significant financial costs for the NHS, patients and their caregivers. In the UK, MS has been estimated to cost the NHS and society £3.3-4.2 billion/year,[8] with the costs increasing as the disability progresses.

CLINICAL TRIAL FAILURE IN SPMS

Although immunomodulatory anti-inflammatory DMTs are increasingly effective in reducing relapse frequency in RRMS, they have been unsuccessful in slowing disease progression in SPMS. This is the overwhelming conclusion from an analysis of 18 phase 3 trials (n=8500), of which 70% of the population had SPMS, all performed in the last 25 years.[9] The review concluded that there is no current disease modifying treatment (DMT) for SPMS. Modalities such as classical immunosuppression (e.g. cyclophophamide and azathioprine), betainterferon, gammaglobulin and oral cannabinoid have all failed. Trial failure has been recently reinforced again by the failure of Natalizumab (a standard DMT used in RRMS) to reach its primary

endpoint in the phase 3 ASCEND trial [NCT01416181] and the cancellation of the planned INSPIRE trial [NCT02430532] with Dimethylfumarate (DMF)/Tecfidera.

Ultimately, this provides strong evidence that RRMS and SPMS have differential pathological substrates. RRMS reflects focal, largely white matter, immunologically driven inflammation, whilst SPMS is dominated by widespread neurodegeneration. Consequently the absence of effect of anti-inflammatory drugs on the neurodegenerative (SPMS) phase of MS is not unexpected. A number of other important reasons for trial failure, apart from low biological knowledge have also been elaborated: inadequate phase 2 work, underpowered phase 3 trials with short trial duration and the difficulties with a poly-outcome measure in a complex and dynamic disease. Despite this identified unmet clinical need for effective neuroprotection, which has been prioritised by patient and professional groups there are comparatively few clinical trials that aim to modify the SPMS disease course. Of the 411 open trials for MS currently listed on ClinicalTrials.gov (http://clinicaltrials.gov/ accessed in 2016) *only* 21 (5.1%) were for SPMS, and of these, many are symptomatic studies.

WHAT ARE STATINS?

Simvastatin is a member of the statin family which are lipid-lowering oral drugs that inhibit 3-hydroxy-3-methylglutaryl-coenzyme A (HMG-CoA) reductase, the main regulatory enzyme of cholesterol biosynthesis. In addition to their lipid-lowering effects, statins have numerous anti-inflammatory and immunomodulatory properties.[10-12]

Statins are used in the treatment of primary hyperlipidaemia, and for secondary prevention of myocardial and cerebral ischaemia. The latest meta-analysis from the Cholesterol Treatment Trialists' (CTT) Collaboration using individual patient data from 174,000 participants in 27 randomised trials, found that for each 1mmol/L reduction in Low-density lipoprotein (LDL) there was about a fifth reduction in major vascular events; these were independent of sex, and benefit was seen in both primary and secondary prevention settings. Clinical benefits noted in these disorders are due to both direct cholesterol lowering, and to cholesterol-independent effects.

STATINS AND MULTIPLE SCLEROSIS

MS-STAT Trial

MS-STAT, a phase 2 trial of 140 People with Secondary Progressive Multiple Sclerosis (PwSPMS) randomised to receive repurposed high-dose simvastatin (80mg) or placebo for 2 years. The result from this trial was reported by our group in 2014.[13] MS-STAT trial results showed that use of high dose simvastatin (80mg /day) was safe, well tolerated, and reduced the progression of annualised brain atrophy by 43% over 2 years. This was a large and highly significant effect. Simvastatin had modest, but significant effects on two of the secondary clinical outcomes. To minimise the possibility that unknown changes in imaging volumes could take place (such as pseudo-atrophy), both the initial and final magnetic resonance (MR) imaging were done off-medication. This technique supports the contention that the noted reduction was due to a real effect on ongoing disease-related progression (disease-modifying or neuroprotective), rather than to an indirect and short-term effect of drug presence (e.g. on hydration). Furthermore, differences between the two groups were consistently seen over 0–12 months, 12–25 months, and 0–25 months. Moreover, the rate of atrophy in the placebo group was very similar to the 0·64% per year reported in a study of more than 130 patients with untreated SPMS.[14]

The primary outcome measure was the annualised rate of whole brain atrophy measured from serial volumetric MRI (an established biological marker of disability in this context). In the intention-to-treat analysis the mean atrophy rate was lower in the simvastatin group at 0.288% (SD 0.521) per year than in the placebo group at 0.584% (0.498) per year. The adjusted difference in atrophy rate between the groups was −0.254% per year (95% CI −0.422 to −0.087; p=0.003), which is a 43% reduction in annualised rate of atrophy. More than three quarters of patients in the simvastatin group had a lower atrophy rate than the mean rate in the placebo group. The results from the per protocol analysis were very similar to those found for the intention-to-treat analysis. The mean atrophy rate was lower in the simvastatin group (0.298% [SD 0.562] per year) than in the placebo group (0.589% [0.528] per year), with adjusted difference of −0.279% per year (95% CI −0.488 to −0.071; p=0.009). There was a non-significant reduction (c30%) on T2 lesion accumulation, as seen in some trials in early MS.[15,16]

This effect on brain atrophy rate is positive, given that longitudinal studies have shown a relation between atrophy progression and disability.[17] Nonetheless, caution should be taken

regarding over-interpretation of brain imaging findings, because these might not necessarily translate into clinical benefit – hence the proposed MS-STAT2 trial.

A modest but significant effect in two of the secondary disability outcomes was noted, as assessed from a physician (EDSS) and patient reported (MSIS-29) viewpoint supporting a true effect on disease progression. However, because the study was phase 2, it was not designed to assess the proportions with confirmed EDSS progression. At 24 months a statistically significant difference was recorded in favour of simvastatin versus placebo for EDSS (difference −0.254; 95% CI −0.464 to −0.069; $p<0.01$) and total MSIS-29 (−4.78; 95% CI −9.39 to −0.02; $p<0.05$), in particular the MSIS-29 physical subscale (−3.73; −7.18 to −0.28; $p<0.05$), with a trend in the MSIS-29 psychological outcome that did not reach formal statistical significance (−1.09; −2.83 to 0.84; $p>0.10$). Over 24 months therefore, 54% progressed by ≥0.5 EDSS points in the placebo arm compared to 39% in the active arm. In the MSFC (standard) there was no significant difference between the simvastatin and placebo groups, though those on simvastatin had a slightly more favourable MSFC than placebo (0.289; 95% CI −0.333 to 0.961; $p>0.10$). Although, the EDSS is a clinically relevant score with well described limitations,[18] it remains the favoured outcome of regulators for trials,[19] and to discern an effect is encouraging.

Results for the per protocol analyses were similar to those for the intention to-treat analyses for all secondary outcomes. Post-hoc analysis has also confirmed the relationship between atrophy rate and final EDSS change in MS-STAT, such that PwSPMS with higher atrophy rates had on average greater progression of disability.[20] For each 1% per year higher rate of whole brain atrophy between baseline and 25 months there was a 0.26 greater increase in EDSS between baseline and 24 months (95% CI 0.08 to 0.48). Higher atrophy rate in the first 12 months was predictive of greater progression of disability, with an increase of 1% per year associated with 0.19 greater increase in EDSS over 24 months (95% CI 0.040 to 0.37).

This study was carried out in a typical SPMS cohort,[21,22] and supports a biologically plausible relation between MRI-derived whole-brain atrophy rate and disability measures in PwSPMS, as proposed by international expert groups on neuroprotection in MS.[19,23]

STATINS IN EARLY MS TRIALS

Eight Randomised Controlled Trials (RCTs) have been undertaken in *early* stage MS, using simvastatin and atorvastatin. The relapsing-remitting multiple sclerosis studies, as add-on to β-interferon, showed in totality, neither harm nor benefit on parameters such as relapse rate or MRI measures.[24-26] No emergent safety issues were identified. Below are some of the findings from various clinical trials using statins;

1. In clinically isolated syndrome (CIS) the STAyCIS study with atorvastatin, although not meeting the primary endpoint (a significant reduction in the proportions developing ≥3 new T2 lesions or ≥1 relapse over 12 months), did significantly reduce the proportion with new T2 lesions by 50%.[24]
2. A study of simvastatin in patients with optic neuritis followed-up for 6 months, showed a borderline benefit on contrast sensitivity and significant effects on several other visual secondary outcomes.[27] The failure to show a robust effect on the inflammatory component of early stage MS could be explained by insufficient power.
3. The largest study SIMCOMBIN (n=307) achieved 65% rather than 80% power for the primary endpoint.[15] Other contributory reasons for the trial results observed could be that statins might not possess the effective and sustained immunomodulatory properties seen in earlier experimental studies at the dosing schedules used in human trials. Indeed, in the MS-STAT trial, no notable effects of simvastatin was observed on the immune markers tested. The reasons for these might be drug tolerance (induction of long-term compensatory mechanisms acting before the 6 month assay time point), or that the in-vivo statin concentration was lower than that achieved in vitro.

5.1.1 Evidence supporting use of active treatment

In experimental allergic encephalomyelitis (EAE), the animal model of MS, statins attenuate the severity of disease progression by preventing or reversing chronic or relapsing paralysis. Statin-treated animals show a delayed and milder onset of first clinical signs and attenuation of relapses.[28-31]

In murine models, statins inhibit MHC class II-restricted antigen presentation, downregulate T-cell activation and proliferation and induce a shift from a pro-inflammatory Th1 to a Th2 phenotype.[10,31] Statins also block adhesion molecule expression and inhibit leucocyte migration through the blood-brain barrier.[28,32,33]

The MS-STAT investigators did not observe any changes to the immune system with regards to the parameters measured, thereby suggesting that other mechanisms are involved. There is increasing evidence that statins have cell protective properties[28,34-36] and improve cerebrovascular haemodynamics,[37] outcomes which are likely to benefit PwSPMS. This is consistent with growing evidence that patients with later stage MS exhibit vascular,[11,38] and brain parenchymal cell dysfunction.[35,36,39,40] However, the mechanisms underlying such protective properties of statins are complex. For instance, neuroprotection may be achieved through a reduction in free radical damage either by improving blood flow and reducing hypoxia-mediated reactive oxygen species (ROS) production, or through direct inhibition of cytotoxic pathways. Thus, statins inhibit inducible nitric oxide synthase (iNOS) activated microglia and astrocytes,[35,41] resulting in attenuated cytotoxic damage to neurons and oligodendrocytes. In addition, statins may exert a neuroprotective effect by preventing glutamate-mediated excitotoxicity.[42] Statins also have a beneficial effect on vascular function[11] and are increasingly seen as vasculoprotective.[11,43-46] As such, use of statins have been reported to improve vascular perfusion[37,47] and maintain/enhance blood vessel function[48] protecting the brain against long-term chronic hypoxic damage. This is especially relevant in light of growing evidence that dysfunctional/reduced blood flow in MS[49-52] 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 endothelial nitric oxide synthase (eNOS) activation[53] and inhibiting endothelin-1.[54]

Besides these cholesterol-independent effects of statins, it is also important to consider the possible involvement of cholesterol-dependent mechanisms in MS. Increasingly it is recognised that vascular comorbidity is associated with a substantial risk of disability in MS, [55,56] and as such the benefit observed in MS-STAT might also simply be due to the reduction in total cholesterol. Early evidence for the importance in vascular co-morbidity came from a study in 2010 where data from 9000 participants in the North American Research Committee on MS (NARCOMS) database was analysed.[57]

In summary, patients with vascular co-morbidities, before or during diagnosis, had a substantial effect on ambulatory disability, bringing forward the need for unilateral assistance by about 6 years. This has recently been further comprehensively reviewed in a large meta-analysis.[56] It

was found that the prevalence of hyperlipidaemia was 11% (5-16%) and hypertension 19% (14-23%) in the MS population, which increased with age. Of the seven studies that compared the prevalence of hyperlipidaemia in the MS population with a concurrent control, five reported it to be greater in the MS group. There was a smaller, but clear increase in other vascular co-morbidities such as coronary artery disease (2.5%), stroke (3%) and peripheral vascular disease (2%). It is apparent, therefore, that disability accumulation in MS may well be partially driven by the heightened vascular risk profile of people with MS, which will also be a function of age (and therefore secondary progression).

5.2 Objectives

5.2.1 Aim

To test the effectiveness of repurposed simvastatin (80mg) in a phase 3 double blind, randomised, placebo controlled trial (1:1) in patients with progressing SPMS, to determine if the rate of disability progression can be slowed over a 3 year period.

5.2.2 Objectives

5.2.2.1 Primary objective

The primary objective is to compare the effect of daily use Simvastatin (80mg) versus placebo on disability progression at 6 monthly intervals in PwSPMS based on change in EDSS scores compared to baseline.

Progression of disability will be defined as an increase of at least 1 point if EDSS baseline score <6, or an increase of 0.5 point if baseline EDSS score is ≥6. The initial disability progression event is finalised as positive if disability is sustained and confirmed ≥6 months later*.

The time to event analysis will be from randomisation until date of the initial disability progression (if subsequently confirmed).

The hypothesis is that repurposed Simvastatin (80mg) is a disease modifying treatment for patients with progressing SPMS.

**Participants presenting with an initial disability progression (based on EDSS scores) at visit 10 clinic follow up with less than 6 months to the end of trial may have the event finalised as positive 3-6 months later.*

5.2.2.2 Secondary objectives

1. To examine the clinical effects of neuroprotection as measured by clinician and patient reported outcome measures in both treatment groups. Time to disability progression will be evaluated for a secondary composite progression outcome measure.

   This composite outcome will be defined as one or more of: ≥20% increase in time taken to complete the 25 Foot Walk (T25FW); or ≥20% increase in time to complete 9 Hole Peg Test (9HPT); or increase in EDSS (0.5 point increase if baseline ≥6 /1.0 point increase if baseline <6). As with the primary outcome, the initial disability progression event will be finalised as positive if it is sustained and confirmed ≥6 months later*. The time to event analysis will be from randomisation until date of the initial disability progression (if subsequently confirmed).

   Mean values and changes in mean values from baseline will be presented for each of the secondary clinician and patient reported outcome measures. Evaluation of treatment effect will be based on differences in means between the treatment groups at visit 10.
   **Participants presenting with an initial disability progression (based on EDSS scores) at visit 10 clinic follow up with less than 6 months to the end of trial may have the event finalised as positive 3-6 months later.*

2. To estimate the incremental cost and cost-effectiveness of simvastatin versus standard care for the trial period and for the lifetime horizon.

Clinician Reported Outcomes

- A modified Multiple Sclerosis Functional Composite (MSFC) comprising - T25FW, 9HPT, SDMT
- Sloan Low Contrast Visual Acuity (SLCVA)
- Relapse assessment (number and severity)
- Frontal Assessment Battery (FAB)
- Modified Rankin Scale (mRS)
- Brief International Cognitive Assessment For Multiple Sclerosis (BICAMS) comprising – SDMT, CVLT-II, BVMT-R

Patient Reported Outcomes

- MS Impact Scale-29 version 2 (MSIS-29v2)
- MS Walking Scale-12 version 2 (MSWS-12v2)
- ABILHAND-23
- EQ-5D 5L
- Short Form-36 version 2 (SF-36v2)
- Modified Fatigue Index Scale - 21(MFIS-21)
- Chalder Fatigue Questionnaire (CFQ)

5.3 Trial Design

A multicentre, double blind parallel phase 3 trial. Patients will be randomly allocated 1:1 to receive either Simvastatin or Placebo;

- Simvastatin (Active)
- Low dose (Initial): 40mg (1x 40mg tablet taken once daily at night) *for 1 month* from Baseline (M0/week 0)

  Dose escalation at Visit 3 (M1/week 4)
- High dose: 80mg (2x 40mg tablet taken once daily at night) *for 35 months* [Visit 3 (M1/week 4) – Visit 10 (M36/ week 156)]; or end of clinic follow up

- Placebo
- Low dose (Initial) : 1x tablet taken once daily at night for *1 month* from Baseline (M0/week 0)

  Dose escalation at Visit 3 (M1/week 4)
- High dose : 2x tablet taken once daily at night *for 35 months* [from Visit 3 (M1/week 4) – Visit 10 (M36/ week 156)]; or end of clinic follow up

Detailed evaluation will take place at the time points outlined below;

- Visit 1 - Screening (-1M/-4 weeks)
- Visit 2 - Baseline/Randomisation (M0/week 0)
- Visit 3 - (M1/week 4)
- Visit 4 – **Telephone & Safety bloods (M3/week 12)**
- Visit 5 - (M6/week 26)
- Visit 6 - (M12/week 52)
- Visit 7 - (M18/week 78)
- Visit 8 - (M24/week 104)
- Visit 9 - (M30/week 130)
- Visit 10 - (M36/week 156)[#]

[#]*Participants with an initial disability progression based on EDSS scores recorded at visit* 10 *will have an additional appointment scheduled up to 6 months later. Participants will continue taking trial medication until their next clinic follow up appointment.*

Additional visit

- Visit 11 - (M42/week 182)

6 Methods

6.1 Site Selection

The trial sponsor has overall responsibility for site and investigator selection and has delegated this role to CCTU.

6.1.1 Study Setting

MS-STAT2 trial will be conducted across Neurology Outpatient departments/Clinical Research Facilities throughout the UK and Eire.

6.1.2 Site/Investigator Eligibility Criteria

Appropriate service support and research costs have been developed in partnership across participating sites to ensure that MS-STAT2 trial is appropriately resourced to successfully deliver the desired participants to time and budget. Once a site has been assessed as being suitable to participate in the trial, the trial team will provide them with a copy of the approved MS-STAT2 protocol and relevant Summary of Product Characteristics (SmPC) /Investigator Brochures.

To participate in the MS-STAT2 trial, investigators and trial sites must fulfil a set of criteria that have been agreed by the MS-STAT2 trial Sponsor and/or Trial Management Group (TMG) and that are defined below.

Eligibility criteria:

- A named clinician is willing and appropriate to take Principal Investigator responsibility
- Suitably trained staff are available to recruit participants, enter data and collect samples
- The site should have a pharmacy that is able to store and dispense the Investigational Medicinal Product (IMP) appropriately

6.1.2.1 Principal Investigator's (PI) Qualifications and Agreements

The investigator(s) must be willing to sign an Investigator Agreement to comply with the trial protocol (confirming their specific roles and responsibilities relating to the trial, and that their site is willing and able to comply with the requirements of the trial). This includes confirmation of appropriate qualifications, by provision of a CV, familiarity with the appropriate use of any investigational products, agreement to comply with the principles of GCP, to permit monitoring

and audit as necessary at the site, and to maintain documented evidence of all staff at the site who have been delegated significant trial related duties.

6.1.2.2 Resourcing at site

The investigator(s) should be able to demonstrate a potential for recruiting the required number of suitable subjects within the agreed recruitment period (i.e. the investigator(s) regularly treat(s) the target population). They should also have an adequate number of qualified staff and facilities available for the foreseen duration of the trial to enable them to conduct the trial properly and safely. Sites will be expected to complete a delegation of responsibilities log and provide staff contact details. The site should have sufficient data management resources to enable data entry and resolution of data queries when prompted by the trial team at the CCTU.

6.2 Site approval and activation

On receipt of the signed Clinical Trial Site Agreement, Investigator Agreement, approved delegation of responsibilities log and staff contact details, written confirmation will be sent to the site PI. The trial manager or delegate will notify the PI in writing of the plans for site activation. Sites will not be permitted to recruit any patients until a letter for activation has been issued. The Trial Manager or delegate will be responsible for issuing this after a green light to recruit process has been completed.

The site must conduct the trial in compliance with the protocol which was given favourable opinion by the Research Ethics Committee (REC) and as approved by the Sponsor, the regulatory authority and Health Research Authority (HRA). The PI or delegate must document and explain any deviation from the approved protocol, and communicate this to the trial team at CCTU.

A list of activated sites may be obtained from the Trial Manager.

6.3 Participants

6.3.1 Eligibility Criteria

Patients aged between 25 and 65 years with (progressing) SPMS who fulfil the revised McDonald criteria for MS,[58] in addition to ALL inclusion criteria and NONE of the exclusion criteria set out in the this protocol.

6.3.1.1 Participant selection

There will be **NO EXCEPTIONS** (waivers) to eligibility requirements at the time of randomisation. Questions about eligibility criteria should be addressed PRIOR to attempting to randomise the participant.

The eligibility criteria for this trial have been carefully considered and are the standards used to ensure that only medically appropriate participants are entered. Participants not meeting the criteria should not be entered into the trial for their safety and to ensure that the trial results can be appropriately used to make future treatment decisions for other people with similar diseases or conditions. It is therefore vital that exceptions are not made to these eligibility criteria.

Participants will be considered eligible for enrolment in this trial if they fulfil all the inclusion criteria and none of the exclusion criteria as defined below.

6.3.1.2 Participant Inclusion Criteria

1. Patients with a confirmed diagnosis of multiple sclerosis (MS) that have entered the secondary progressive stage at randomisation. 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 Expanded Disability Status Scale (EDSS), or clinical documentation of increasing disability;
2. EDSS 4.0 - 6.5 (inclusive);
3. Aged 25 to 65 years old;
4. Male or Female;
5. Patients must be able and willing to comply with the terms of this protocol;
6. Written informed consent provided.

6.3.1.3 Participant Exclusion Criteria

1. Relapse within **3 months** of baseline visit
2. Patients that have been treated with steroids (intravenous and/or oral) due to MS relapse/progression within 3 months of baseline 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 (***Note****: Patients on steroids for another medical condition may be included in the trial provided the steroid prescription is not for MS relapse/progression)*
3. Significant organ co-morbidity e.g. cardiac failure, renal failure, malignancy

4. Screening levels of alanine aminotransferase (ALT) / aspartate aminotransferase (AST) or creatinine kinase (CK) ≥ 3x upper limit of normal (ULN)

5. Current use of a statin; or any use within the last 6 months

6. Medications that interact unfavourably with simvastatin as outlined in the current summary of product characteristics (SmPC); including but not limited to CYP3A4 inhibitors (e.g. itraconazole, ketoconazole, posaconazole, voriconazole, fluconazole, HIV protease inhibitors (e.g. nelfinavir), boceprevir , erythromycin, clarithromycin, telithromycin, telaprevir, nefazodone, fibrates (including fenofibrates), nicotinic acid (or products containing niacin), azole anti-fungal preparations, macrolide antibiotics, protease inhibitors, verapamil, amiodarone, amlodipine, gemfibrozil, ciclosporin, danazol , diltiazem, rifampicin , fusidic acid, grapefruit juice or alcohol abuse
7. Primary progressive MS
8. Diabetes Mellitus Type 1
9. Uncontrolled hypothyroidism
10. Female participants that are pregnant or breast feeding. Women of child bearing potential (WOCBP) who are unwilling or unable to use an acceptable method to avoid pregnancy for the entire study period, and up to 4 weeks after the last dose of study drug.
11. Use of immunosuppressants (e.g. azathioprine, methotrexate, ciclosporine) or disease modifying treatments (avonex, rebif, betaferon, glatiramer) within the previous 6 months.
12. Use of mitoxantrone, natalizumab, alemtuzumab, daclizumab or other monoclonal antibody treatment, if treated within the last 12 months.
13. Use of fingolimod, fumarate, teriflunomide within the last 12 months.
14. Use of other experimental disease modifying treatment within the last 6 months
15. Commencement of fampridine ≤ 6 months from day of randomisation
16. Concurrent participation in another clinical trial of an investigational medicinal product or medical device
17. Patients with rare hereditary problems of galactose intolerance, the lapp lactase deficiency or glucose-galactose malabsorption

6.3.1.4 Eligibility Criteria for Individuals Performing the Interventions

All assessments will be performed by suitably qualified members of the clinical trial team trained in the use of all relevant MS scales used as part of the MS-STAT2 trial. PI delegated roles and responsibilities on this trial will be documented in the MS-STAT2 site delegation log. CVs and GCP certificates of all individuals working on the trial will be collected by the UCL CCTU MS-STAT2 trial team to document their qualifications and relevant experience. Protocol specific training will be provided to participating sites prior to site activation.

6.3.1.5 Co-enrolment Guidance

Patients that are currently taking or are anticipated to start taking statins are not eligible for enrolment to the MS-STAT2 trial.

6.3.1.6 Screening Procedures and Pre-randomisation Investigations

Written informed consent to enter and be randomised into the trial must be obtained from participants after explanation of the aims, methods, benefits and potential hazards of the trial and **BEFORE** any trial-specific procedures are performed, or any blood is taken for the trial. The only procedures that may be performed in advance of written informed consent being obtained are those that would be performed on all patients in the same situation as usual standard of care.

Once consented, the following assessments will be carried out to evaluate patient eligibility;

- An initial screening EDSS assessment will be carried out by a clinician or member of the clinical team
- Blood samples will be drawn to measure the following parameters; Creatinine and Electrolytes (CR & E), Full Blood Count (FBC), Liver Function Test (LFT), Creatinine Kinase (CK), Lipid profile, Thyroid function.
- Urine samples from all women of child bearing potential (WOCBP) will be tested to determine pregnancy status

If any of the screening blood tests results are classified clinically significant (CS), these can be repeated at the Baseline/ Randomisation visit (Visit 2 - M0/week 0). The repeat safety blood result(s) at baseline will be used to assess eligibility.

If a patient is ineligible at screening due to other factors aside from CS blood test result(s), they can be re-screened (where appropriate) after a minimum period of 1 month.

6.4 Interventions

6.4.1 Products

- ACTIVE TREATMENT - Simvastatin
- PLACEBO

6.4.1.2 Treatment Schedule (Simvastatin/Placebo)

Participants will follow the schedule outlined below for active treatment (Simvastatin)/Placebo (see Figure 1);

LOW DOSE (INITIAL):

- 40mg Simvastatin (1x 40mg tablet taken once daily at night) *for 1 month* from Baseline (M0/week 0)

OR

- 1x Placebo Simvastatin tablet taken once daily at night *for 1 month* from Baseline (M0/week 0)

Dose escalation at Visit 3 (M1/week 4)

HIGH DOSE:

- 80mg Simvastatin (2x 40mg tablet taken once daily at night) *for 35 months* [Visit 3 (M1/week 4) – Visit 10 (M36/ week 156)]; or end of clinic follow up

OR

- 2x Placebo Simvastatin tablets taken once daily at night) *for 35 months* [Visit 3 (M1/week 4) – Visit 10 (M36/ week 156)]; or end of clinic follow up

6.4.2 Dispensing

All study IMP will be dispensed by pharmacy departments within participating sites to coincide with participants' trial follow up visits.

- Visit 2 - Baseline/Randomisation (M0/week 0)
- Visit 3 - (M1/week 4)
- Visit 5 – (M6/week 26)
- Visit 6 – (M12/week 52)
- Visit 7 – (M18/week 78)

- Visit 8 – (M24/week 104)
- Visit 9 – (M30/week 130)

Additional dispensing*

- **Visit 10 (M36/Week 156) -** Participants with an initial disability progression based on EDSS scores recorded at Visit 10 – (M36/Week 156) will receive additional supply of study IMP to ensure adequate provision until their next scheduled visit (***additional visit* - Visit 11 - (M42/week 182**).

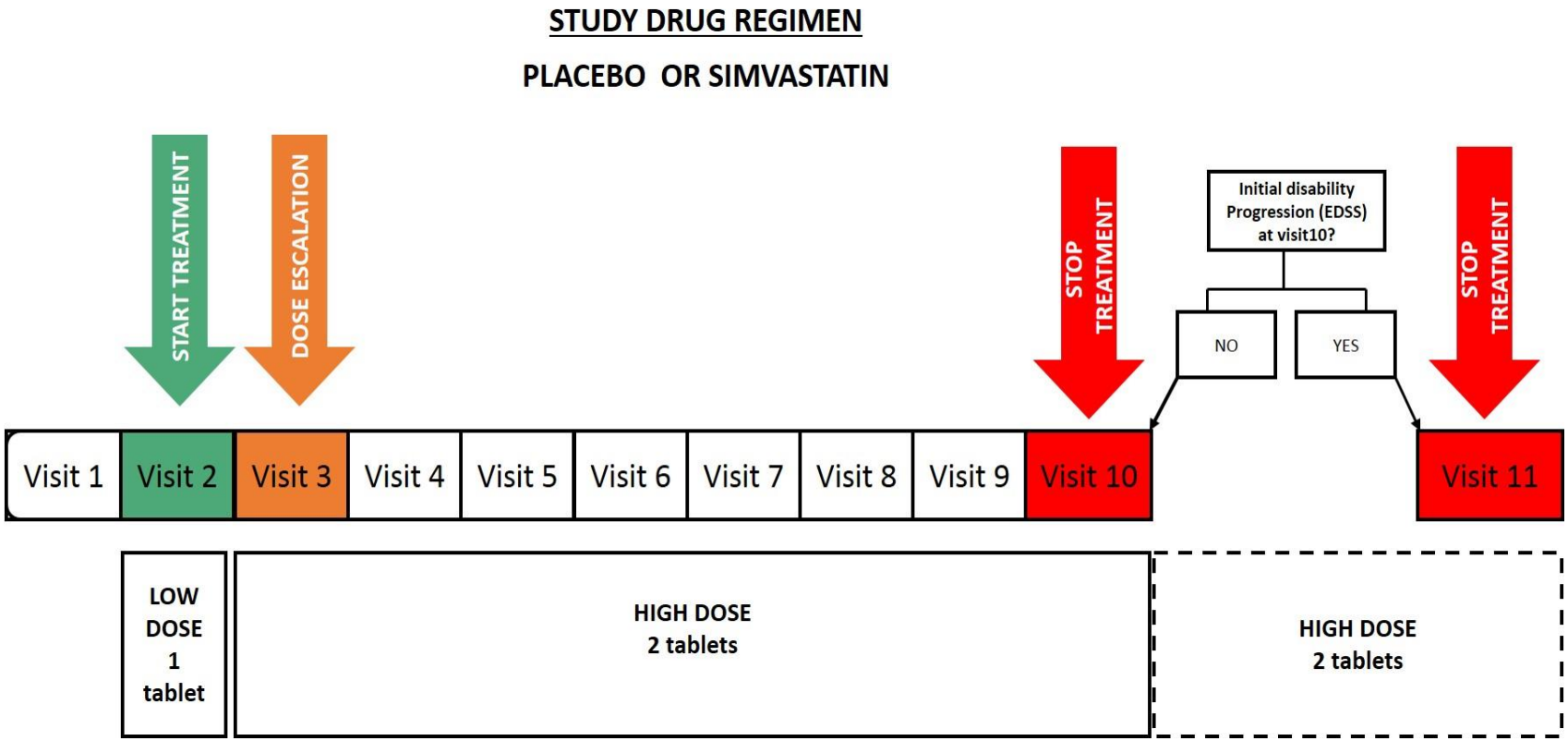


Figure 1: Dosing regimen for MS-STAT2. The schematic above depicts the dosing regimen for participants on Simvastatin/ Placebo from baseline until end of clinic follow up at visit 10 when participants are required to stop treatment and resume standard medical care. Participants with an initial disability progression based on EDSS scores recorded at Visit 10 – (M36/Week 156) will continue to take their assigned trial product (simvastatin/placebo) for an additional 6 months until the end of clinic follow up at visit 11 when they will stop treatment and resume standard medical care clinic.

6.4.3 Dose Modifications, Interruptions and Discontinuations – Simvastatin/Placebo

LABORATORY ABNORMALITIES

Hepatic Effects

Patients experiencing abdominal pain and additional symptoms consistent with diagnosis of hepatotoxicity which is supported by elevated alanine aminotransferase (ALT) or aspartate aminotransferase (AST) liver enzymes will undergo further investigation resulting in possible dose modification, or discontinuation of study IMP.

Patients with elevated ALT/AST defined as more than 3 times the upper limit of normal (≥3 x ULN) according to local practice will continue to take study medication unless a clinical decision is taken to stop. Patients will be invited to have a repeat blood test carried out within 2 weeks.

If abnormalities persist, dose reduction will be considered in patients on high dose of study IMP from 80mg/2 tablets down to 40mg/1 tablet. Patients currently on low dose of IMP (40mg /1 tablet) with persisting elevated ALT/AST (≥3x ULN) will have their trial medication stopped. If parameters return to baseline in patients on low dose study IMP (40mg/1 tablet) within 6 months of monitoring, patients may be placed back on the high dose study IMP (80mg/2 tablets).

It is recommended that patients presenting with elevated ALT/AST levels ≥5 x ULN should have their study IMP discontinued. These patients may remain in trial and continue all clinic follow up with no study IMP.

Myopathy/ Rhabdomyolysis

The risk of myopathy is increased by high levels of HMG-CoA reductase inhibitory activity in plasma. As with other HMG-CoA reductase inhibitors, the risk of myopathy/rhabdomyolysis is dose related. The risk of myopathy and rhabdomyolysis is significantly increased by concomitant use of simvastatin with potent inhibitors of CYP3A4 (such as itraconazole, ketoconazole, posaconazole, erythromycin, clarithromycin, telithromycin, HIV protease inhibitors (e.g. nelfinavir), nefazodone), as well as gemfibrozil, ciclosporin, and danazol. The risk of myopathy and rhabdomyolysis is also increased by concomitant use of amiodarone, amlodipine, verapamil, or diltiazem with doses of simvastatin. The risk of myopathy, including

rhabdomyolysis, may be increased by concomitant administration of fusidic acid with statins. Use of these drugs is contraindicated.

Consumption of grapefruit juice increases the risk of rhabdomyolysis and as such its use is contraindicated in those taking statins.

Investigators will review participants' concomitant medications at each clinic visit and address any changes that could potentially increase risk of myopathy/rhabdomyolysis.

Patients experiencing myalgia with elevated levels of creatinine kinase (CK, ≥3x ULN) will continue to take study medication unless a clinical decision is taken to stop. Patients will be invited to have a have a repeat blood test carried out within 2 weeks.

If abnormalities persist, dose reduction from 80mg/2 tablets down to 40mg/1 tablet will be considered in patients currently on high dose of study IMP (80mg/2 tablets). Patients currently on low dose of IMP (40mg/1 tablet) with persisting elevated CK levels (≥3x ULN) will have their trial medication stopped.

If parameters assessed return to baseline levels in patients on low dose study IMP (40mg/1 tablet) within 6 months of monitoring, patients may be placed back on the high dose study IMP (80mg/2 tablets).

It is recommended patients experiencing myalgia with elevated CK levels ≥5 times the ULN should have their study IMP discontinued. These patients may remain in trial and continue all clinic follow up with no study IMP.

Dose Modification as a result of Adverse Events:

Patients on low dose (40mg/1 tablet) study IMP reporting significant adverse events (with the exception of MS related relapses) prior to dose escalation may remain on the low dose (40mg/1 tablet) at the discretion of the site PI.

However, this does not prevent a subsequent increase in study IMP to 80mg/2 tablets once the adverse event/s reported are resolved and following clinical evaluation by the PI.

If a participant cannot tolerate the low dose (40mg/ 1 tablet) due to frequency of statin related common side effects experienced, (duration according to the Investigator's discretion), study IMP should be stopped. Patient will continue with all clinical follow up assessments. The

participant can be re-challenged at a later time point with low dose of study IMP at the discretion of the site PI.

Upon re-challenge, if the participant is unable to tolerate a low dose of study IMP (duration according to investigators discretion), they should be off medication for the remaining duration of the trial. The participant will remain in trial follow-up and complete all clinical assessments.

If a participant cannot tolerate the high dose (80mg/2 tablets) of study IMP, (duration according to the Investigator's discretion), the dose should be reduced to 40mg/1 tablet. The participant can be re-challenged at a later time point with high dose (80mg/2 tablets) study IMP.

If upon re-challenge with high dose (80mg/2 tablets) study IMP the participant is unable to tolerate study medication at this dose (duration according to local PI discretion), they should be placed back on low dose (40mg/1 tablet) study IMP.

Upon challenge on high dose (80mg/2 tablets) of study IMP on a second occasion, if participant cannot tolerate the dose again (duration according to the Investigator's discretion), investigator should consider reducing to a low dose (40mg/ 1 tablet) of study IMP for the remaining duration of the trial. A full record of medication administered must be logged.

6.4.4 Accountability

The trial pharmacist operating within pharmacy department at each participating site will be accountable for trial drug supplies.

6.4.5 Compliance and Adherence

Participants will be made aware of the importance of compliance with the trial protocol at baseline and subsequent follow up visits. Participants will be provided with a drug diary to record uptake of trial medication 30 days leading to their next scheduled clinic visit.

Compliance will also be assessed by direct questioning of participants at each follow up visit. Reasons for non-compliance will be sought and addressed where appropriate.

6.4.6 Concomitant Care

The following drugs have been found to interact unfavourably with simvastatin (please refer to the current SmPC for updated list of contraindicated drugs). Trial medication should be discontinued in the event that participants are advised to commence drug treatment containing any of the compounds/substances listed below;

- Itraconazole
- Ketoconazole
- Posaconazole
- Voriconazole
- Fluconazole
- HIV protease inhibitors (e.g. nelfinavir)
- Boceprevir
- Erythromycin
- Clarithromycin
- Telithromycin
- Telaprevir
- Nefazodone
- Fibrates (including fenofibrates)
- Nicotinic acid (or products containing niacin)
- Azole anti-fungal preparations
- Macrolide antibiotics
- Protease inhibitors
- Verapamil
- Amiodarone
- Amlodipine
- Gemfibrozil
- Ciclosporin
- Danazol
- Diltiazem
- Rifampicin
- Fusidic acid
- Grapefruit juice
- Alcohol abuse

6.4.7 Overdose of Trial Medication

Measures will be taken to minimise accidental overdose of trial medication by providing adequate education to trial participants. Accidental or deliberate overdose of trial medication will be treated accordingly. The re-introduction of trial medication dosing will be determined by the clinical investigator at the participating site. Any patient taking a deliberate overdose of trial medication will be withdrawn from the trial.

To date, a few cases of Simvastatin over dose have been reported; the maximum dose taken was 3.6g. 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.

6.4.8 Protocol Treatment Discontinuation

In consenting to the trial, participants are consenting to trial treatments, trial follow-up and data collection. However, an individual participant may stop treatment early or be stopped early for any of the following reasons:

- Unacceptable treatment toxicity or adverse event
- Inter-current illness that prevents further treatment
- Any change in the participant's condition that in the clinician's opinion justifies the discontinuation of treatment
- Withdrawal of consent by the participant

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.

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

6.5 Outcomes

6.5.1 Primary Outcomes

The time to initial disability progression between the simvastatin and placebo arm. The initial disability progression event is finalised as positive if disability is sustained and confirmed ≥6* months later.

Time to confirmed disability progression between simvastatin and placebo arm is based on change in EDSS scores compared to baseline. Progression of disability defined as an increase of at least 1 point if EDSS baseline score <6, or an increase of 0.5 point if baseline EDSS score is ≥6.

The classical measurement tool and industry standard for measuring the progression of disability is the Expanded Disability Status Scale (EDSS).[5] It is based largely on neurological examination (with some history). The EDSS quantifies disability in eight functional systems (FS- Pyramidal, Bowel and bladder, Cerebellar, Visual, Brainstem, Cerebral, Sensory and other) and allows neurologists to assign a functional system score (FSS) in each of these.

The EDSS scale ranges from 0 to 10, each 0.5 unit increment represents increasing levels of disability.

A recent systematic review of the psychometric properties of the EDSS encompassing 120 relevant full-text publications concluded that it was suitable and valid to detect patient-relevant endpoints in MS. The EDSS is widely used and supported by the Food and Drugs Administration (FDA) /European Medicines Agency (EMA) and pharmaceutical industries.

The initial screening EDSS assessment (Visit 1) will be conducted by a clinician, or member of the clinical team.

Subsequent EDSS assessments from randomisation (M0/Week 0) until the end of study will be conducted by the assessing clinician, or delegated member(s) of the clinical team.

The EDSS will be measured at multiple time points at 6 monthly intervals (refer to section 6.6 - participant timeline) in clinic or over the telephone.

The *initial* disability progression event is finalized as positive if it is confirmed ≥6 months later*. Participants with initial EDSS progression recorded at last scheduled clinic visit (visit 10 – M36/week 156) will have an additional appointment scheduled 6 months later (visit 11 – M42/week 180) to confirm disability progression.

**Participants presenting with an initial disability progression (based on EDSS scores) at visit 10 clinic follow up with less than 6 months to the end of trial may have the event finalised as positive 3-6 months later.*

6.5.2 Secondary Outcomes

1. Examine clinical effects of neuroprotection as measured by clinician and patient reported outcome measures in both treatment groups. Time to disability progression will be evaluated for a composite measure of disability progression: ≥20% increase in time taken to complete T25FW, or ≥20% increase in time to complete 9HPT, or increase in EDSS (0.5 point increase if baseline ≥6 /1.0 point increase if baseline <6). Each component of the composite outcome measure will also be examined using time to event analysis. Mean values and changes in mean values from baseline will be presented for each outcome measure. Evaluation of treatment effect will be based on differences in means between the treatment groups at visit 10.

2. To estimate the incremental cost and cost-effectiveness of simvastatin versus standard care for the trial period and for the lifetime horizon;

Clinician Reported Outcomes

- **A Modified Multiple Sclerosis Functional Composite (MSFC)** score comprised of 3 components (T25FW, 9HPT, SDMT). The Symbol digit modalities test (SDMT) will replace the Paced Auditory Serial Addition Test (PASAT), one of the three components in the Standard MSFC.

  - *25 foot walk (T25FW)*: The T25-FW is a quantitative mobility and leg function performance test based on a timed 25-foot walk. It is the first component of the MSFC to be administered at each visit. The patient is directed to one end of a clearly marked 25-foot course and is instructed to walk 25 feet as quickly as possible, but safely. The time is calculated from the initiation of the instruction to start and ends when the patient has reached the 25 feet mark. The task is immediately administered again by having the patient walk back the same distance. Patients may use an assistive device when carrying out this test.

- *9-Hole peg test (9-HPT)*: This is a simple, timed test of fine motor coordination. Reliability and validity have been assessed. Both the dominant and non-dominant hands must be tested. The patient should be seated at a table with the 9-HPT apparatus, a stopwatch started and the patient instructed to pick up the pegs, one at a time, as quickly as possible and put them into the peg holes. Once all nine pegs have been inserted, the patient should immediately remove the pegs, one at a time and replace them in the shallow container with the total time to complete the task being recorded. The procedure should be carried out twice with the dominant hand and twice with the non-dominant hand.

- *Symbol digit modalities test (SDMT)*: A brief measure of cognitive processing speed. It measures information processing speed for visually presented stimuli, but is self-paced, with at least equal reliability and sensitivity to the presence of worsening cognitive impairment. Participants are presented with a series of nine symbols, each paired with a single digit in a key at the top of an 8 ½ x 11 inch sheet. When prompted, participants are asked to voice the digit associated with each symbol as quickly as possible for 90 second. The single outcome measure is the number correct over the 90 second time span.

- **Sloan Low Contrast Visual Acuity (SLCVA)** - Sloan chart testing is a reliable, quantitative, and clinically practical measure of visual function that will be administered by trained assessors. The chart consists of rows of grey letters on a white background. Letters are displayed in decreasing order from the top of the chart to the bottom. Testing will be conducted at four different contrast levels (100%, 5%, 2.5% and 1.25%). The chart will be scored based on the number of letters correctly identified out of 70.

- **Frontal Assessment Battery *(*FAB*)*** – This is a brief battery of six neuropsychological tasks designed to assess frontal lobe function. The six *FAB* tasks assess conceptualisation (abstract reasoning), item flexibility (verbal fluency), motor programming (organisation, maintenance and execution of successive actions), sensitivity to interference (conflicting instructions), inhibitory control (inhibit inappropriate responses), and environmental autonomy. The test takes approximately 10 minutes to complete.

- **Brief International Cognitive Assessment For Multiple Sclerosis (BICAMS)** – This is a composite cognitive assessment tool comprising of the three components namely;

- *Symbol Digit Modalities Test (SDMT)* A brief measure of cognitive processing speed. It measures information processing speed for visually presented stimuli, but is self-paced, with at least equal reliability and sensitivity to the presence of worsening cognitive impairment. Participants are presented with a series of nine symbols, each paired with a single digit in a key at the top of an 8 ½ x 11 inch sheet. When prompted, participants are asked to voice the digit associated with each symbol as quickly as possible for 90 second. The single outcome measure is the number correct over the 90 second time span.

- *California Verbal Learning Test-II (CVLT-II)* – This is a neuropsychological test used to assess episodic verbal learning and memory. The examiner reads a list of 16 words. Patients are required to listen and recall as many of the items as possible. The reading list will be read out again and the recall recorded for both occasions. Participants are not required to recall items in any particular order.

    - *Brief visuospatial memory test- Revised (BVMT-R)* – This assessment tool is used to evaluate immediate visual learning and delayed visual memory as well as recognition. The examiner presents a visual display of six abstract designs to participants for three consecutive 10-second trials. After each trial, participants will be asked to draw as many designs as accurately as they can and in the correct location. They are again asked to reproduce the designs in the exact layout after a 25-minute delay filled with other distractor tasks. A forced-choice recognition trial is administered immediately following the delayed memory trial. Each design receives from 0-2 points representing accuracy and location. Total scores assigned range from 0-12.

- **Modified Rankin Scale (mRS)** – This is used to evaluate the degree of disability in daily activities of those with neurological disability. Score ranges from 0 (No symptoms) through to 6 (death). 0 (No symptoms), 1 (No significant disability), 2 (Slight disability), 3 (Moderate disability), 4 (Moderately severe disability), 5 (severe disability), 6 (death).

- **Relapse assessment –** SPMS is a progressive neurological condition and as such deterioration in neurological symptoms affecting the motor, sensory, balance, sphincter (including urinary tract infections), visual, cognitive and fatigue levels are expected. A relapse will be defined as new or worsening neurological symptom(s) in the absence of

fever, lasting for more than 24 hours, and have been preceded by a period of clinical stability of at least 30 days, with no other explanation than MS. Relapses will be excluded as AEs/SAEs/SARs and will not be reported as such. In addition, relapses will not be counted as AEs/SAEs/SARs, but will be collated separately. They will be graded as described in Table 1. The number of relapses and severity of each relapse will be compared between the treatment groups.

Grade of relapse	**Description of event**
Grade 1	Relapse not treated with corticosteroids
Grade 2	Relapse treated with corticosteroids, but not requiring hospitalisation
Grade 3	Relapse treated with corticosteroids and requiring in-patient hospitalisation; or relapse not treated with corticosteroids but requiring in-patient hospitalisation *Please note: SAE forms must be completed for participants reporting a grade 3 relapse and sent to the MS-STAT2 trial team at CCTU no more than 24 hours of the investigator becoming aware of the event.*

Table 1: Grading of MS related relapses

Patient Reported Outcomes

- **MS Impact Scale-29 version 2 (MSIS-29v2)** – A psychometrically validated patient-reported outcome measure increasingly used for measuring the impact of MS on people's lives. The 29-item scale assesses the impact of MS on people's health related quality of life in terms of their physical and psychological well-being over the **previous 2 weeks**. It has two subscales: a 20-item physical impact scale and a 9-item psychological impact scale, which can be combined into a total score. It is currently in its second version, which has four-point response categories for each item: "not at all," "a little," "moderately," and "extremely." Scores on the physical impact scale can range from 20 to 80 and on the psychological impact scale from 9 to 36, with lower scores indicating little impact of MS and higher scores indicating greater impact.

- **MS Walking Scale-12 version 2 (MSWS-12v2)** – This is a validated 12 item patient report measure on the impact of MS on the individual's walking ability over the **previous 2 weeks**. Response categories range from 1 ("not at all") to 5 ("extremely"). Patients are required to select one response per question. 3 out of the 12-items have 3 response categories, the remaining 9 items have five response categories. Each item will be summed to generate a total score and transformed to a scale with a range of 0 to 100 with high scores indicating greater impact on walking.

- **ABILHAND-23** - This is a measure of manual ability for adults with upper limb impairments. The 56-item scale measures an individual's ability to manage daily activities which require the use of the upper limbs. Items are summed to generate a total score and transformed to a scale with a range of 0 (poor manual ability) to 100 (good manual ability); Higher scores indicate less difficulty with everyday manual activities.

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

- **SF-36 v2** – A 36 item questionnaire grouped into 8 scales assessing : physical functioning (10 items) social functioning (2 items) role limitations due to physical problems (4 items),

role limitations due to emotional problems (3 items), mental health (5 items), energy/vitality (4 items), pain (2 items), and general health perception (5 items). An unscaled single item asks respondents about health change over the past year.

- **Modified Fatigue Impact Scale - 21 (MFIS-21)** – A 21 item questionnaire which measures the impact of fatigue on cognitive (10 items), physical (9 items) and psychosocial function (2 items) in patients with MS.

- **Chalder Fatigue Questionnaire (CFQ)** - 11-item questionnaire measuring the severity of physical and mental fatigue on two separate subscales. Seven items represent physical fatigue (items 1–7) and four represent mental fatigue (items 8–11)

6.6 Participant Timeline

Clinic visit number	VISIT 1	VISIT 2	VISIT 3	VISIT 4	VISIT 5	VISIT 6	VISIT 7	VISIT 8	VISIT 9	VISIT 10	VISIT 11[E]
Month (M)	**SCREENING (-1 month/ - 4 weeks)**	**M0 BASELINE**	**M1**	**M3 TELE PHONE**	**M6**	**M12**	**M18**	**M24**	**M30**	**M36**	**M42**
week number (window)		**Week 0**	**Week 4 (+/-1 week)**	**Week 12 (+/-1 week)**	**Week 26 (+/- 2 weeks)**	**Week 52 (+/- 2 weeks)**	**Week 78 (+/-2 weeks)**	**Week 104 (+/-2 weeks)**	**Week 130 (+/-2 weeks)**	**Week 156 (+/-2 weeks)**	**Week 182 (+/-2 weeks)**
Informed Consent	X										
Inclusion/exclusion criteria review	X	X									
Demography	X										
Review of medical and MS History	X										
Review EDSS – Treating clinician/delegate	X										
EDSS – Assessing clinician/delegate (Blinded)		X			X	X	X	X	X	X[E]	X
Physical examination	X		X		X	X	X	X	X	X	X
Vital signs	X		X		X	X	X	X	X		
Urine pregnancy test	X	X[A]									
Safety bloods (CR&E, FBC,LFT,CK)	X	X[B]	X	X[C]	X	X	X	X	X	X	X
Lipid profile	X					X		X		X	X
Thyroid function	X										
Compliance assessment			X	X	X	X	X	X	X	X	X
Relapse assessment (count & grade)	X	X	X	X	X	X	X	X	X	X	X
Adverse events		X	X	X	X	X	X	X	X	X	X
Concomitant Medication	X	X	X	X	X	X	X	X	X	X	X

Clinic visit number	VISIT 1	VISIT 2	VISIT 3	VISIT 4	VISIT 5	VISIT 6	VISIT 7	VISIT 8	VISIT 9	VISIT 10	VISIT 11[E]
Month (M)	**SCREENING (-1 month/ - 4 weeks)**	**M0 BASELINE**	**M1**	**M3 TELE PHONE**	**M6**	**M12**	**M18**	**M24**	**M30**	**M36**	**M42**
week number (window)		**Week 0**	**Week 4 (+/-1 week)**	**Week 12 (+/-1 week)**	**Week 26 (+/- 2 weeks)**	**Week 52 (+/- 2 weeks)**	**Week 78 (+/-2 weeks)**	**Week 104 (+/-2 weeks)**	**Week 130 (+/-2 weeks)**	**Week 156 (+/-2 weeks)**	**Week 182 (+/-2 weeks)**
Randomisation		X									
Dispense study IMP		X	X		X	X	X	X	X	X[D]	
Study IMP - Dose escalation			X								
MSFC: 9HTP, 25TFW, SDMT[F]		X			X	X	X	X	X	X	X
ABILHAND-23		X			X	X	X	X	X	X	X
SLCVA		X			X	X	X	X	X	X	X
MSIS-29v2		X			X	X	X	X	X	X	X
MSWS-12v2		X			X	X	X	X	X	X	X
EQ-5D 5L		X			X	X	X	X	X	X	X
SF-36 v2		X				X		X		X	
CSRI		X			X	X	X	X	X	X	X
BICAMS : SDMT[F], CVLT-II, BVMT-R		X			X	X	X	X	X	X	X
FAB		X			X	X	X	X	X	X	X
mRS		X			X	X	X	X	X	X	X
MFIS-21		X				X		X		X	
CFQ		X				X		X		X	

[A] If urine pregnancy test result from screening visit is within 7 days of baseline visit then there is no need to repeat the test, [B] Repeat safety blood tests if any parameter measured at screening visit is clinically significant (CS), [C] Patients to arrange safety bloods at their local GP surgery/bloods to be arranged by research team at study site, [D] Additional dispensing for participants with an initial disability progression (based on EDSS scores) at visit 10, [E] Additional visit scheduled 6 months later for participants with an initial disability progression at visit 10 (based on EDSS scores). Please note a small number of participants with less than 6 months to the end of trial may have appointment scheduled between 3-6 months after visit 10 follow up visit. [F] SDMT to be recorded once, records from which should make up the modified MSFC and BICAMS

Clinic visit number	VISIT 1	VISIT 2	VISIT 3	VISIT 4	VISIT 5	VISIT 6	VISIT 7	VISIT 8	VISIT 9	VISIT 10	VISIT 11[E]
Month (M)	**SCREENING (-1 month/ - 4 weeks)**	**M0 BASELINE**	**M1**	**M3 TELE PHONE**	**M6**	**M12**	**M18**	**M24**	**M30**	**M36**	**M42**
week number (window)		**Week 0**	**Week 4 (+/-1 week)**	**Week 12 (+/-1 week)**	**Week 26 (+/- 2 weeks)**	**Week 52 (+/- 2 weeks)**	**Week 78 (+/-2 weeks)**	**Week 104 (+/-2 weeks)**	**Week 130 (+/-2 weeks)**	**Week 156 (+/-2 weeks)**	**Week 182 (+/-2 weeks)**
SUB- STUDIES											
MRI		X				X		X		X	
Biomarker- bloods sLDH , sNFLand free serum haemoglobin		X	X		X	X	X	X	X	X	
OCT		X				X		X		X	

6.6.1 Early Stopping of Follow-up

If a participant chooses to discontinue their trial treatment, they should continue to be followed up as closely as possible to the follow-up schedule defined in the protocol, providing they are willing. They should be encouraged and facilitated not to leave the whole trial, even though they no longer take the trial treatment. If, however, the participant exercises the view that they no longer wish to be followed up either, this view must be respected and the participant withdrawn entirely from the trial. CCTU should be informed of the withdrawal in writing using the appropriate MS-STAT2 trial documentation. Data already collected will be kept and included in analyses according to the intention-to-treat principle for all participants who stop follow up early, unless participant withdraws consent for all data being held.

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

6.6.2 Participant Transfers

If a participant moves from the area making continued follow up at their consenting centre inappropriate, every effort should be made for them to be followed at another participating trial centre. Written consent should be taken at the new centre and then a copy of the participant's CRFs should be provided to the new centre. Responsibility for the participant remains with the original consenting centre until the new consent process is complete.

6.6.3 Loss to Follow-up

Every effort will be made to follow up participants. This may require tracing participants via their NHS number using NHS Spine which supports the IT infrastructure for health and social care in England once approvals for access has been granted.

Patients will be deemed "loss to follow up" if these avenues - using contact details provided, via next of kin ,through General Practitioner or NHS spine have been exhausted.

6.6.4 Trial Closure

The end of the trial will be defined as the date of the last patient's last clinic visit.

The REC and MHRA will be notified within 90 days of trial. A summary report of the research will be sent to the REC and MHRA within 12 months of the end of the trial.

A site may be deemed ''closed'' once all trial-related activities at that site are reconciled and/or complete, all outstanding data queries have been resolved and a letter confirming that close down is complete has been sent to the site PI from UCL CCTU.

6.7 Sample Size

The primary endpoint will be time to disability progression, assessed by EDSS as defined above. In order to have 90% power to demonstrate 30% relative reduction in disability progression, at the conventional 5% significance level, and after allowing for 20% drop out, 1180 patients are needed (590 patients per arm).

This sample size calculation assumes that in MS-STAT2 the placebo progression rate will be 40% by 36 months (visit 10), based on a review of all previous phase 3 trials in SPMS, [14] and the recent 3 year trials, which revealed 6 months confirmed progression rates of between 35-44%[22,59,60] . In the MS-STAT trial, high dose simvastatin reduced the rate of 1 month confirmed EDSS progression by 46% at 24 months (HR=0.52). However, given the lack of confirmation at 6 months and the shorter duration of that study, a more conservative 30% relative reduction was used in the power calculation for MS-STAT2. In MS-STAT, 6% of patients recruited were lost to follow-up by 2 years, with 9% of patients without 2 year data on EDSS. A larger drop-out rate is expected in MS-STAT2 given the longer duration of the trial and the multi-site design, with 20% dropout commonly seen in 3 year SPMS trials.

6.8 Recruitment and Retention

6.8.1 Recruitment

Patients will be identified via different routes; self- referral due to trial publicity on MS-STAT2 website, MS Society webpage, General Practitioner (GP) referral and clinic referral in participating neurology centres.

Depending on the route of identification several processes may then be used to follow up their suitability as a participant including:

- Patients may be briefed in clinic about the study directly by a member of the clinical team; and also to ensure that the patient is likely to fulfill the general criteria to enter the trial. Patients will be given a Patient Information Sheet (PIS).
- Patients may receive an initial telephone contact from a research nurse, to explain the trial and to ensure that the patient is likely to fulfill the general criteria to enter the trial. Patients will be sent a PIS.
- After a period of *at least* 24 hours after receiving the PIS, the patient will be contacted again and invited for a screening visit should they choose to take part in the trial.

Trial assessments will be conducted across Neurology outpatient departments/Clinical research facilities geographically spread throughout the UK and Eire (Figure 2).

The majority of participating sites taking part in the MS-STAT2 trial contributed in varying degrees to patient recruitment in previous trials led by the chief investigator (MS-STAT 1 and MS-SMART).

All participating centres have lead MS neurologists who are members of the Multiple Sclerosis Society – Clinical Trial Network (MSS-CTN) and are experienced MS triallists.

MS-STAT2 is a milestone driven trial which incorporates a STOP/GO progression (an internal feasibility phase) to provide confidence in achieving key deliverables for a study of this scale, and one with this level of investment. A formal STOP/GO will be performed 15 months after start of recruitment. It is anticipated that 53% of randomisations will be achieved at this juncture.

Ongoing monitoring of recruitment against set milestones will provide a crucial opportunity to review issues relating to number of sites open and randomisation targets at each recruiting centre. More importantly, it will provide the possibility of adopting strategies to maintain and increase patient recruitment across sites.

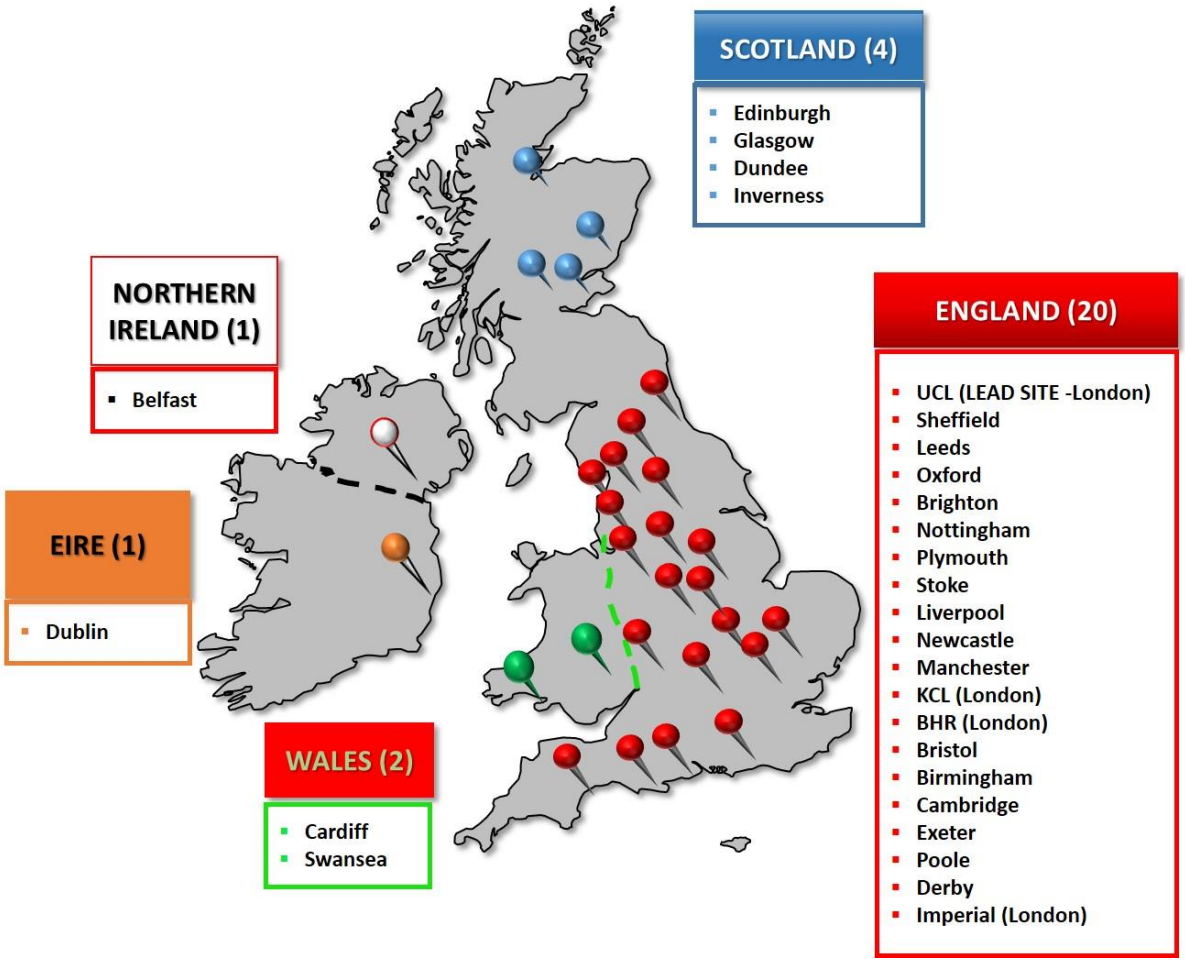


Figure 2: Schematic map of MS-STAT2 participating sites. The number of participating sites per country is provided in brackets.

6.8.2 Retention

The importance of attending scheduled follow up appointments until trial completion will be explained to all participants at the start of the trial to ensure that only those able to commit to the trial protocol are recruited.

MS-STAT2 has a strong patient and public involvement (PPI) strategy with significant contribution from UK MSS PPI representative and members of the UK MSS-PPI forum to maximise patient benefits. Useful feedback provided on factors that could have an impact on participation such as age, entry disability, trial schedule and disability fluctuation have been taken into consideration and embedded in the protocol to ensure that it is acceptable to the patient community and thereby promote retention to the trial.

The Forum and MS Society have agreed to work closely with the research team to maximise participant retention by co-developing a tailored communication plan including making use of the existing UK MSS programme of events; such as MS Life, Living with MS Events and the

Society publications, MS Matters and Teamspirit, to promote the study to people living with multiple sclerosis (PwMS), explaining importance of minimising drop-out and encouraging UK MS Register enrolment.

6.9 Assignment of Intervention

6.9.1 Allocation

6.9.1.1 Sequence generation

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:

- Sex (Male / Female)
- Age (< 45 years old / ≥ 45years)
- Baseline EDSS (4.0-5.5 / 6.0-6.5)
- Newly licensed Disease Modifying Drugs (DMD) for SPMS (≥2017) (Yes/No)
- Site

Randomisation with minimisation will ensure comparability of the two study arms, and prevent selection bias.[83]

The Trial Statistician 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 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 and subsequent clinic follow up visit, the investigator at each site 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 each site to ensure availability of adequately labelled kits for Pharmacy dispensing.

6.9.1.2 Allocation concealment mechanism

Sufficient number of labelled drug kits containing (simvastatin/placebo) will be dispensed following randomisation at visit 2 (M0/week 0), and at subsequent clinic follow up appointments where dispensing due to take place (Section 6.4.2 Dispensing).

The unique kit number(s) allocated to a participant at each clinic visit will be revealed to the investigator through Sealed Envelope.com (a password protected, secure web-based system) on entry of the participant's trial identification code and date of birth.

The investigator will provide details of the allocated kit number(s) assigned to each participant to enable dispensation of study IMP by the pharmacy department upon receipt of the prescription form and printed copy of allocated kit number(s). A full accountability trail will be maintained from receipt of study IMP in pharmacy, up to the point of dispensing and destruction of undispensed study IMP. The site pharmacist will remain blind to trial arm and study IMP (simvastatin/placebo) kit allocation.

6.9.1.3 Allocation Implementation

The responsibility for enrolling and prescribing study IMP to participant lies with the principal investigator (PI) at each recruiting site. Eligibility decisions will be made in line with the approved protocol. Other clinicians/delegate employed at the same clinical site as the PI may partake in patient enrolment and study IMP prescription provided appropriate training has been undertaken and approval is given by the site PI.

Person(s) delegated key tasks/roles must have full names recorded on the MS-STAT2 delegation log.

6.9.2 Blinding

Sealed Envelope will provide the participant trial identification codes at randomisation. The trial drug kit identification code list will be prepared by the Trial Statistician and provided separately to Sealed Envelope and to the QP who will ensure that labelling of trial drug packs occur in the correct manner with adequate safeguards in place, to ensure complete blinding of the IMP to all investigators, participants and the pharmacy staff on the study.

A secure web based service provided by Sealed Envelope is set up to enable the unblinding of individual patients, should the need arise. The trial drug kit labelling strategy employed ensures that the unblinding of an individual patient will not result in the unblinding of the entire trial arm.

6.9.3 Emergency Unblinding

All recruited participants will be given a card with contact details of the clinical trial team including emergency contact 24 hours a day, 7 days per week. In the event unblinding becomes necessary, emergency unblinding can occur at any time through the 24 hour web-based service offered by Sealed Envelope.com. It will occur for any participant experiencing a serious adverse event (SAE) for which the clinical management of the SAE will be facilitated by the unblinding of the participant's treatment allocation. The chief investigator (CI) will make this decision. It is anticipated that for the majority of instances, appropriate clinical management can proceed with the assumption that the patient has been treated with simvastatin without needing to unblind the participant.

Unblinding should usually only be performed in the case of a SUSAR. Unblinding will be carried out using the secure website access provided by Sealed Envelope and according to trial specific working practices.

6.10 Data Collection, Management and Analysis

6.10.1 Data Collection Methods

Each participant will be assigned a unique trial Participant Identification Number (PIN). Data will be collected at the time-points indicated in the Trial Schedule (Section 6.6 Participant Timeline).

All relevant patient data will be collected by delegated members of the clinical team across participating sites. All data will be handled in accordance with the Data Protection Act 1998.

Clinical trial team members across all participating sites will receive adequate training on MS-STAT2 protocol and MS assessment scales used as part of the trial. Certification on relevant MS assessment forms such as EDSS (certified by Neurostatus) may be required and documented accordingly.

Staff will receive training on data collection and use of the MS-STAT2 custom designed database. All queries raised by the MS-STAT2 trial team (CCTU) regarding data collection and/or data entry will be conducted in line with the CCTU and trial specific Data Management Standard Operating Procedure.

The preferred method of data collection is direct entry of data onto source documentation (e.g. patient notes) and then transcribed onto electronic case report forms (eCRFs) on the custom

designed database stored on servers based at UCL. The database is designed to capture all relevant clinical data and to allow formal statistical analysis.

Trial specific paper case report forms (pCRFs) will be designed by the MS-STAT2 trial team. The approved MS-STAT2 pCRFs will be provided to all participating centres. Data may be recorded on MS-STAT2 paper CRFs prior to entry onto the database (but this is not an essential step). The CRFs will not bear the patient's name, instead the patient's initials, date of birth and unique trial identification code number will be recorded, and used for identification.

The following data are from standardised tools that have been extensively validated in previous clinical trials. The printed questionnaires completed at each visit will be the source documents which will be filed with the CRF.

- Blood test results printout- anonymised, coded and dated
- Expanded Disability Status Scale (EDSS)
- MSFC - T25FW , 9HPT, SDMT
- Sloan Low Contrast Visual Acuity (SLCVA)
- MS Impact Scale-29 v2 (MSIS-29v2)
- MS Walking Scale-12 v2 (MSWS-12v2)
- ABILHAND-23
- BICAMS – SDMT, CVLT-II, BVMT-R
- FAB
- mRS
- EQ5D-5L
- SF-36v2
- Client services receipt inventory (CSRI)
- CFQ
- MFIS-21

6.10.2 Data Management

A custom designed database will be used to record and store all trial data collected. The database will only be made available to external regulators if requested, and specified users across participating sites. Delegated users will be assigned a username and password for access.

Each participant will be assigned a unique trial Participant Identification Number (PIN). Data will be entered under this identification number onto the MS-STAT2 custom designed database stored on the servers based at CCTU. The database will be password protected and only accessible to members of the MS-STAT2 trial team at CCTU, and external regulators if requested. The servers are protected by firewalls and are patched and maintained according to best practice. The physical location of the servers is protected by CCTV and security door access.

The database software provides a number of features to help maintain data quality, including; maintaining an audit trail, allowing custom validations on all data, allowing users to raise data query requests, and search facilities to identify validation failure/ missing data.

After completion of the trial the database will be retained on the servers of UCL for on-going analysis of secondary outcomes. All data storage will adhere to Data Protection Act 1998.

The identification, screening and enrolment logs, linking participant identifiable data to the pseudo-anonymised PIN, will be held locally by the trial site. This will either be held in written form in a locked filing cabinet or electronically in password protected form on hospital computers. After completion of the trial the identification, screening and enrolment logs will be stored securely by the sites for 10 years unless otherwise advised by CCTU.

6.10.3 Non-Adherence and Non-Retention

Participants will be provided with a drug diary to record uptake of trial medication 30 days leading to their next scheduled clinic visit. Reasons for non-adherence to protocol will be noted in the medical notes and CRF. Outcome data will continue to be collected on all contactable patients continuing to provide informed consent.

6.10.4 Statistical Methods

Statistical analysis will be undertaken by the Trial Statistician at Department of Medical Statistics at the London School of Hygiene and Tropical Medicine.

The primary analysis will be conducted on an Intention-to-Treat basis. A per protocol analysis will be considered including those who were compliant with their randomised intervention.

6.10.4.1 Statistical Analysis Plan

A detailed statistical analysis plan (SAP) will be produced prior to interim unblinded analysis and agreed by the Trial Steering Committee (TSC). This will detail the statistical methods used

for description of demographic and baseline characteristics, assessing treatment compliance, evaluation of effectiveness of simvastatin treatment on primary and secondary outcomes, and evaluation of safety.

The statistical analysis will be based on all participants as randomised, irrespective of subsequent compliance with allocated treatment (intention to treat analysis). A per protocol analysis including patients who received their randomised intervention as specified will be conducted.

A CONSORT diagram will be used to describe the course of patients through the trial. Baseline characteristics will be summarised by randomised group. Continuous variables will be summarized using summary statistics (mean, standard deviation, median, minimum, and maximum) by treatment group, and categorical variables will be presented using frequency distributions by treatment group.

6.10.4.2 Statistical Methods – Outcomes

The primary analysis will be a comparison of the time to confirmed disability progression between the simvastatin and placebo arms. Hazard ratios and 95% confidence intervals will be calculated using Cox proportional hazards modelling and Kaplan-Meier curves produced. The time scale used for survival analysis will be time since randomisation. Participants will be censored on the date at which the outcome occurs, if they die, are lost to follow-up, withdraw from the study, or at 36 months after randomisation. The model will allow for between centre variability by stratification by site. In addition other variables included in the minimisation process [sex - male/female), age (<45, ≥45), baseline EDSS (4.0-5.5 / 6.0-6.5) and newly licenced DMD for SPMS (≥2017) (Yes/No)] will be included as fixed effects.

The assumptions underlying the Cox model will be assessed and if there is clear non-proportionality hazard ratios will be presented separately for the relevant time periods.

In general, continuous variables for secondary outcome measures will be summarized using summary statistics (mean, standard deviation, median, minimum, and maximum) by treatment group, and categorical variables will be presented using frequency distributions by treatment group.

Time to disability progression on the composite outcome (25FW, 9HPT or EDSS), and on the individual outcomes making this composite, will be evaluated using time to event analysis using the same methods as outlined for the primary outcome (confirmed progression of EDSS).

Baseline (M0) to visit 10 (M36/week 156) change in continuous patient reported outcomes will be compared between groups using a linear mixed model adjusting for centre as random effects and baseline value and the minimisation variables as fixed effects. If parametric assumptions for the linear regression model are substantially violated, bias corrected and accelerated bootstrap confidence intervals will be used for inference. Poisson regression will be used to compare relapse rate between the treatment groups adjusted for the minimisation variables as fixed effects, with robust standard errors to account for clustering by centre.

6.10.4.3 Additional Analyses – Adjusted

As described above, analyses will adjust for the minimisation variables, sex (male/female), age (<45, ≥45), baseline EDSS (4.0-5.5 / 6.0-6.5) and newly licenced DMD for SPMS (≥2017) (Yes/No), as fixed effects and allowing for between centre variability by stratification by site. No other adjusted analyses are planned. In this protocol we allow for the possibility that we shall add more research arms to be evaluated. In doing this we shall fully address the issues of the potential impact on the family-wise error.

6.10.5 Analysis Population and Missing Data

The primary analysis will be performed on an Intention-to-Treat basis, including all patients where possible according to the group to which they were randomised irrespective of whether they complied with treatment. A secondary per protocol analysis will be considered including those who were compliant with their randomised intervention. The per protocol analysis population will include patients who received their randomised intervention as specified. These are patients who were either on high dose study IMP (80mg/2 tablets) (depending on the trial arm they are in) for three years and have reported taking, on average, at least 90% of the pills. This average will be calculated using the self-reported proportion of pills taken at each study visit. In addition to the per protocol analysis the causal effect of treatment for those who comply with their allocated treatment will also be estimated.

Missing data will be identified and an effort made to return to the original medical records to obtain the data. Total number of patients withdrawing and reasons for withdrawal will be tabulated by treatment group. The characteristics of the patients with missing data will be compared to those with complete data and patterns compared between the treatment groups.

In the event of substantial differences in withdrawal patterns being found, further sensitivity analyses will be carried out to investigate the robustness of the results.

6.10.5.1 Health Economic Analysis Plan/Evaluations

A treatment that slows progression could represent a highly cost-effective use of NHS resources with the high costs of SPMS and very low cost of simvastatin. A cost-utility study will be carried out to assess the incremental cost per quality adjusted life year (QALY) gained from the perspective of the NHS and personal social services (PSS). Cost utility will be estimated for a) the "within trial" period and b) for the lifetime of the patient using a model based approach. The lifetime model will take the form of a Markov model using EDSS states, including a death state, to model the progression of patients beyond the trial period. A secondary analysis from a societal perspective will be undertaken which will consider additional costs borne by the patient such as time off work.

Resource Use Data

Patient resource use will be assessed using a self-complete resource use form, the Client Services Receipt Inventory (CSRI) and using patient records. The CSRI will be modified according to the needs of people with SPMS and will be administered at baseline and six monthly intervals. The CSRI will ask for details of primary care and social care resource use. We will also apply for access to Hospital Episode Statistics to provide data on hospital admissions to further understand differences in resource use between arms.

Utility and Quality Of Life Data

QALYs will be estimated, 6 monthly, using the EQ-5D-5L using the area under the curve approach.[61,62] Utility scores will be calculated using UK-specific tariffs and adjusting for baseline differences in patients in the trial arms if necessary. In addition, given current uncertainties regarding the appropriateness of the EQ-5D-5L for people with SPMS,[63] the MSIS-29v2,[64] a condition-specific measure will be considered for estimating QALYs through methods available in the literature.[65]

6.10.5.3 Within-trial analysis

The within-trial economic evaluation will estimate cost-effectiveness of simvastatin for the trial period. We will estimate results as the incremental cost-effectiveness ratio where data will

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

6.10.5.4 Model based analysis

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

Good practice guidelines for economic evaluations will be used for the analysis.[66] Long term costs and health outcomes will be discounted using discount rates recommended by NICE. [66]

6.11 Data Monitoring

6.11.1 Data Monitoring & Ethics Committee

An Independent Data Monitoring and Ethics Committee (DMEC) constituting a minimum of 3 independent members will each provide expert knowledge/advice on different aspects notably clinical expertise on multiple sclerosis, conduct of clinical trials and statistical analysis of trial data.

DMEC members will convene at scheduled time points throughout the duration of the trial to review interim trial data and safety data. A formal interim analysis will be conducted on an annual basis (at month (M) M18, M30, M42, M54 and M66). Recommendations will be made

by the DMEC to the trial steering committee (TSC) regarding continuation/ stopping of the trial based on safety data.

MS-STAT2 is a milestone driven study and incorporates a STOP/GO progression 15 months after patient recruitment commences. The STOP/GO criteria for recruitment will be achievement of n=632 randomisations (equivalent to 53% of recruitment). We propose that an DMEC meeting will be convened to review recruitment against the STOP/GO progression criteria to allow the DMEC to advice on whether the progression criteria has been achieved The results from the formal STOP/GO analysis will demonstrate confidence in achieving MS-STAT2 key deliverables.

The Trial Statistician will generate the summaries of trial results for the DMEC to review, ensuring that the trial team remain blinded to treatment allocation. Further details of the roles and responsibilities of the DMEC, including membership, relationships with other committees, decision making processes, and the timing and frequency of interim analyses (and description of stopping rules and/or guidelines where applicable) are described in detail in the MS-STAT2 DMEC Terms of Reference (ToR).

6.11.2 Interim Analyses

The interim analyses will take place on an annual basis at M18, M30, M42, M54 and M66 from project activation. Safety data will be presented to the DMEC in addition to interim analyses for review. At each formal interim analyses, a hazard ratio comparing the two treatments and its 95% confidence interval will be presented along with a p-value, calculated using an Cox proportional hazards model adjusted for the minimisation variables; sex (male/female), age (<45, ≥45), baseline EDSS (4.0-5.5 / 6.0-6.5) and newly licenced DMD for SPMS (≥2017) (Yes/No), as fixed effects and allowing for between centre variability by stratification by site.

As a guideline, the DMEC may consider stopping for safety if there is evidence that high dose simvastatin treatment is worse than placebo alone with a p-value of <0.01 for all-cause deaths. The DMEC may consider stopping for efficacy based p-value of <0.001 for a difference between the treatment groups on primary outcome of 6 month confirmed EDSS progression. Use of the Haybittle–Peto stopping boundary of p<0.001 preserves the p<0.05 level for statistical significance in the final analysis. There will be no formal interim futility analysis. A DMEC recommendation for early stopping for either safety or effectiveness will be possible at

the first four interim analyses (M18, M30, M42, M54) as these take place while recruitment or follow-up is continuing.

These guidelines are not absolute stopping rules. The DMEC may consider the strength of any formal statistical comparison alongside the internal consistency of results, consistency with external evidence and ability of the results to influence clinical practice. The DMEC will be able to modify the number and timing of interim analyses based on patterns that emerge in the data as the trial progresses.

6.11.3 Data Monitoring for Harm

All Adverse Events (AEs) and SAEs occurring during the trial observed by the investigator or reported by the patient, whether or not attributed to the investigational drug, trial interventions or other trial-specific procedure will be recorded in the patient's medical records, and on the appropriate MS-STAT2 CRFs. UCL CCTU will keep investigators informed of any safety issues that arise during the course of the trial.

6.11.3.1 Safety reporting

Definitions of harm of the EU Directive 2001/20/EC Article 2 based on the principles of ICH GCP apply to this trial.

Table 2: 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 product.
Adverse Reaction (AR)	Any untoward and unintended response to an investigational medicinal product related to any dose administered
Unexpected Adverse Reaction (UAR)	An adverse reaction, the nature or severity of which is not consistent with the applicable product information (e.g. Investigator's Brochure for an unauthorised product or summary of product characteristics (SmPC) for an authorised product.

Serious Adverse Event (SAE) or Serious Adverse Reaction (SAR)	Any AE or AR that at any dose: • results in death • is life threatening* • requires hospitalisation or prolongs existing hospitalisation** • results in persistent or significant disability or incapacity • is a congenital anomaly or birth defect • or is another important medical condition***
* the term life threatening here refers to an event in which the patient is at risk of death at the time of the event; it does not refer to an event that might hypothetically cause death if it was more severe (e.g. a silent myocardial infarction) ** Hospitalisation is defined as an in-patient admission, regardless of length of stay, even if the hospitalisation is a precautionary measure for continued observation. Hospitalisation for pre-existing conditions (including elective procedures that have not worsened) do not constitute an SAE *** Medical judgement should be exercised in deciding whether an AE or AR is serious in other situations. Important AEs or ARs that may not be immediately life threatening or result in death or hospitalisation, but may seriously jeopardise the participant by requiring intervention to prevent one of the other outcomes listed in the table (e.g. a secondary malignancy, an allergic bronchospasm requiring intensive emergency treatment, seizures or blood dyscrasias that do not require hospitalisation, or development of drug dependency).	

Adverse events include:

- an exacerbation of a pre-existing illness
- an increase in the frequency or intensity of a pre-existing episodic event or condition
- a condition (regardless of whether PRESENT prior to the start of the trial) that is DETECTED after trial drug administration. (This does not include pre-existing conditions recorded as such at baseline – as they are not detected after trial drug administration.)

- continuous persistent disease or a symptom present at baseline that worsens following administration of the trial treatment

Adverse events do NOT include:

- Medical or surgical procedures: the condition that leads to the procedure is the adverse event
- Pre-existing disease or a condition present before treatment that does not worsen
- Hospitalisation where no untoward or unintended response has occurred e.g. elective cosmetic surgery
- Overdose of medication without signs or symptoms
- Events/Relapses related to SPMS

Expected events related to SPMS:

SPMS is a progressive neurological condition and as such deterioration in neurological symptoms is expected. Therefore natural changes in motor, sensory, balance, sphincter (including urinary tract infections), visual, cognitive and fatigue levels are excluded as AEs/SAEs/SARs and will not be reported as such. In addition, relapses will not be counted as AEs/SAEs/SARs, but will be collated separately.

They will be graded as follows:

Grade of relapse	**Description of event**
Grade 1	Relapse not treated with corticosteroids
Grade 2	Relapse treated with corticosteroids, but not requiring hospitalisation
Grade 3	Relapse treated with corticosteroids and requiring in-patient hospitalisation; or relapse not treated with corticosteroids but requiring in-patient hospitalisation *Please note: SAE forms must be completed for participants reporting a grade 3 relapse and sent to the MS-STAT2 trial team at CCTU no more than 24 hours of the investigator becoming aware of the event.*

Table 1: Grading of MS related relapses

Participants experiencing a relapse should be advised to contact their local MS team (nurse/consultant), or GP as per standard routine practice to ensure appropriate management can take place. The clinical investigating team at local sites should ask participants at each clinic follow up appointment if they have experienced any relapse in the intervening period to ensure that relapse is adequately documented. At the Investigator/nurse's discretion unscheduled visits can be organised for participants to be assessed.

Upon clinical review, if the investigator suspects that the disease has progressed faster due to the administration of the study IMP, this will be reported as an unexpected adverse event.

The "seriousness" of each event should be assessed by the PI. A non-serious adverse event is an AE not classified as serious. The MS-STAT2 adverse event log should be completed with details of each adverse event experienced by the participant.

The adverse event collection and reporting should begin at initiation of study drug. All AEs should be followed to resolution or stabilisation, or reported as SAEs if they become serious.

If a patient reports a relapse which is subsequently recorded as a grade 3 relapse, an SAE form should also be completed in addition. The completed SAE form must be sent to the MS-STAT2 trial team at CCTU no more than 24 hours of the investigator becoming aware of the event.

6.11.3.3 Other Notifiable Adverse Events

Confirmation of hepatotoxicity based on elevated levels of ALT/AST (≥3x ULN of local laboratory reference range) will require notification in an expedited manner in the same way as an SAE (CCTU to be notified immediately the investigator becomes aware of the event, in no circumstance should this notification take longer than 24 hours).

Confirmation of myalgia based on elevated levels of CK (≥ 3x ULN of local laboratory reference range) will require notification in an expedited manner in the same way as an SAE (CCTU to be notified immediately the investigator becomes aware of the event, under no circumstance should this notification take longer than 24 hours).

Pregnancy is not a serious adverse event. Following initiation of the study IMP, if a female participant becomes pregnant, the MS-STAT2 Pregnancy notification form should be completed by the investigator at the site and forwarded to the MS-STAT2 trial team at CCTU.

CCTU notification should take place immediately, but no longer than 24 hours of the investigator becoming aware of the pregnancy. The pregnancy outcome may or may not be considered a SAE.

6.11.3.4 Procedures following notification of pregnancy

6.11.3.4.1 Notification of pregnancy by female participants

Simvastatin is contraindicated during pregnancy as safety in pregnant women has not been established. Female patients with a positive pregnancy test at screening are not eligible for inclusion in this trial and should not be randomised. Women on simvastatin should not breast feed. Female participants of child bearing potential will be advised to use an effective form of contraception throughout the duration of the study. In the event that a female participant becomes pregnant during the course of the trial, the study IMP will be discontinued. Pregnant female participants will remain in the trial (receiving **no study IMP**) and complete all trial follow up assessments as per protocol.

The MS-STAT2 Pregnancy Notification Form must be completed and forwarded to the trial team at CCTU. Pregnancy should be followed until the outcome is known (including any premature termination of the pregnancy) and information on the status of the mother and child. Pregnant participants will be followed up until birth, the MS-STAT2 Pregnancy Follow-up Form (capturing information for up to 6 to 8 weeks after birth) should be completed and forwarded to the trial team at CCTU. Any congenital malformations and/or birth defects are reportable as SAE.

6.11.3.4.2 Notification by male participants in the event of partner becoming pregnant

Male participants will be advised to use an effective form of contraception throughout the duration of the study. The MS-STAT2 Pregnancy Notification Form should be completed and forwarded to the trial team at CCTU in the event that the partner of a male participant becomes pregnant.

The Pregnancy should be followed until the outcome is known (including any premature termination of the pregnancy) and information on the status of the mother and child.

Pregnant partners of male participants will be followed up until birth, the MS-STAT2 Pregnancy Follow-up Form (capturing information for up to 6 to 8 weeks after birth) should be completed and forwarded to the trial team at CCTU. Any congenital malformations and/or birth defects are reportable as SAE.

6.11.3.5 Investigator responsibilities relating to safety reporting

All relapses, non-serious AEs and ARs, whether expected or not, should be recorded in the patient's medical notes. SAEs and SARs should be notified to CCTU immediately the investigator becomes aware of the event (in no circumstance should this notification take longer than 24 hours).

6.11.3.5.1 Seriousness assessment

When an AE or AR occurs, the investigator responsible for the care of the participant must first assess whether or not the event is serious using the definition given in Table 2. If the event is classified as 'serious' then an SAE form must be completed and CCTU notified immediately (no longer than 24hours of investigator becoming aware of the event).

6.11.3.5.2 Severity or grading of Adverse Events

The severity of all AEs and/or ARs (serious and non-serious) in this trial should be graded using the toxicity gradings in National Institutes of Health Common Terminology Criteria for Adverse Events (CTCAE) version 4. SUSARs will be coded using via Medical Dictionary for Regulatory Activities (MedDRA) for expedited reporting to MHRA/REC.

6.11.3.5.3 Causality

The investigator must assess the causality of all serious events or reactions in relation to the study IMP using the definitions in Table 3.

Table 3: Causality definitions

Relationship	Description	Event type
Unrelated	There is no evidence of any causal relationship	Unrelated SAE
Unlikely to be related	There is little evidence to suggest that 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 or other concomitant treatment)	Unrelated SAE
Possibly related	There is some evidence to suggest a causal relationship (e.g. because the event occurs within a reasonable time after administration of the trial	SAR

	medication). However, the influence of other factors may have contributed to the event (e.g. the participant's clinical condition or other concomitant treatment)	
Probably related	There is evidence to suggest a causal relationship and the influence of other factors is unlikely	SAR
Definitely related	There is clear evidence to suggest a causal relationship and other possible contributing factors can be ruled out.	SAR

If an SAE is considered to be related to trial treatment, and treatment is discontinued, interrupted or the dose modified, refer to the relevant Interventions sections of the protocol.

6.11.3.5.4 Expectedness

If there is at least a possible involvement of the trial medications (including any comparators), the investigator and sponsor must assess the expectedness of the event. An unexpected adverse reaction is one that is not reported in the current IB or SmPCs, or one that is more frequently reported or more severe than previously reported. See the current SmPC for a list of expected toxicities associated with simvastatin. If a SAR is assessed as being unexpected it becomes a SUSAR (suspected, unexpected, serious adverse reaction) and MHRA and REC reporting guidelines apply (see Notifications sections of the protocol).

6.11.3.6 Notifications

6.11.3.6.1 Notifications by the Investigator to CCTU

CCTU must be notified of all SAEs no more than 24 hours of the investigator becoming aware of the event.

Investigators should notify CCTU of any SAEs and other Notifiable Adverse Events (NAEs) occurring from the time of randomisation until 30 days after the last protocol treatment administration, including SARs and SUSARs. From this point forward the site will not actively monitor SAEs or NAEs but will notify the CCTU of any SARs and SUSARs if they become aware of them until trial closure.

Any subsequent events that may be attributed to treatment should be reported to the MHRA using the yellow card system (https://yellowcard.mhra.gov.uk/the-yellow-card-scheme/).

The SAE form must be completed by the investigator (the clinician named on the delegation of responsibilities list who is responsible for the participant's care) with attention paid to the grading, causality and expectedness of the event. In the absence of the responsible investigator, the SAE form should be completed and signed by a member of the site trial team and emailed as appropriate within the timeline. The responsible investigator should check the SAE form at the earliest opportunity, make any changes necessary, sign and then email to CCTU. Detailed written reports should be completed as appropriate. Systems will be in place at the site to enable the investigator to check the form for clinical accuracy as soon as possible.

The minimum criteria required for reporting an SAE are the trial number and date of birth, name of reporting investigator and sufficient information on the event to confirm seriousness. Any further information regarding the event that is unavailable at the time of the first report should be sent as soon as it becomes available.

The SAE form must be scanned and sent via secure portal/encrypted to the trial team at CCTU on **ms-stat2@ucl.ac.uk**

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 CCTU as further information becomes available. Additional information and/or copies of test results etc. may be provided separately. The participant must be identified by trial number, date of birth and initials only. The participant's name should not be used on any correspondence and should be blacked out and replaced with trial identifiers on any test results.

6.11.3.6.2 CCTU responsibilities

Medically qualified staff at CCTU and/or the Chief Investigator (CI or a medically qualified delegate) will review all SAE reports received. In the event of disagreement between the causality assessment given by the local investigator and the CI, both opinions and any justifications will be provided in subsequent reports.

The delegated staff at CCTU will review the assessment of expectedness and, based on possible wider knowledge of the reference material for the treatment or comparator, and after discussion

with the CI, may over-rule the investigator assessment of expectedness for the purposes of onward reporting.

CCTU is undertaking the duties of trial sponsor and is responsible for the reporting of SUSARs and other SARs to the regulatory authorities (MHRA and competent authorities of other European member states and any other countries in which the trial is taking place) and the RECs as appropriate. Fatal and life threatening SUSARs must be reported to the competent authorities within 7 days of CCTU becoming aware of the event; other SUSARs must be reported within 15 days.

CCTU will keep investigators informed of any safety issues that arise during the course of the trial.

The trial manager or delegate at CCTU will submit Development Safety Update Reports (DSURs) to competent authorities.

6.11.4 Quality Assurance and Control

6.11.4.1 Risk Assessment

The Quality Assurance (QA) and Quality Control (QC) considerations for the MS-STAT2 trial are based on the standard CCTU Quality Management Policy that includes a formal Risk Assessment, and that acknowledges the risks associated with the conduct of the trial and proposals of how to mitigate them through appropriate QA and QC processes. Risks are defined in terms of their impact on: the rights and safety of participants; project concept including trial design, reliability of results and institutional risk; project management; and other considerations.

QA is defined as all the planned and systematic actions established to ensure the trial is performed and data generated, documented and/or recorded and reported in compliance with the principles of GCP and applicable regulatory requirements. QC is defined as the operational techniques and activities performed within the QA system to verify that the requirements for quality of the trial related activities are fulfilled.

Benefits: The purpose of this trial is to find a drug which slows down progression in SPMS, which is currently untreatable. The global community was greatly encouraged by the results of the MS-STAT trial, for example, as reported by the BBC, [67] which not only showed a clear and unambiguous effect of whole brain atrophy, but indicated a significant effect on two measures

of disability, one clinician and one patient orientated, despite the trial not being set up for this. Simvastatin is inherently safe, is repurposed and likely to be highly cost-effective if proven clinically successful at phase 3.

Risks: The trial will be conducted through Good Clinical Practice (GCP) from a highly experienced trials team and coordinated through the CCTU. The drug has a low side-effect profile, and will be monitored closely according to the protocol with close scrutiny of any adverse events.

6.11.4.2 Central Monitoring at CCTU

CCTU staff will review Case Report Form (CRF) data for errors and missing key data points. The trial database will also be programmed to generate reports on errors and error rates. Essential trial issues, events and outputs, including defined key data points, will be detailed in the MS-STAT2 trial Data Management Plan.

6.11.4.3 On-site Monitoring

The frequency, type and intensity of routine and triggered on-site monitoring will be detailed in the MS-STAT2 Quality Management and Monitoring Plan (QMMP). The QMMP will also detail the procedures for review and sign-off of monitoring reports. In the event of a request for a trial site inspection by any regulatory authority the CCTU must be notified as soon as possible.

6.11.4.3.1 Direct access to participant records

Participating investigators must agree to allow trial related monitoring, including audits, REC review and regulatory inspections, by providing access to source data and other trial related documentation as required. Participant consent for this must be obtained as part of the informed consent process for the trial.

6.11.4.4 Trial Oversight

Trial oversight is intended to preserve the integrity of the trial by independently verifying a variety of processes and prompting corrective action where necessary. The processes reviewed relate to participant enrolment, consent, eligibility, and allocation to trial groups; adherence to

trial interventions and policies to protect participants, including reporting of harms; completeness, accuracy and timeliness of data collection; and will verify adherence to applicable policies detailed in the Compliance section of the protocol. Independent trial oversight complies with the CCTU trial oversight policy.

In multi-centre trials this oversight is considered and described both overall and for each recruiting centre by exploring the trial dataset or performing site visits as described in the MS-STAT2 QMMP.

6.11.4.4.1 Trial Team

The Trial Team (TT) will be set up to assist with developing the design, co-ordination and day to day operational issues in the management of the trial, including budget management. The membership, frequency of meetings, activity (including trial conduct and data review) and authority will be covered in the TT terms of reference.

6.11.4.4.2 Trial Management Group

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.

6.11.4.4.3 Independent Trial Steering Committee

The Independent Trial Steering Committee (TSC) is the independent group responsible for oversight of the trial in order to safeguard the interests of trial participants. The TSC provides advice to the CI, CCTU, the funder and sponsor on all aspects of the trial through its independent Chair. The membership, frequency of meetings, activity (including trial conduct and data review) and authority will be covered in the TSC terms of reference.

6.11.4.4.4 Independent Data Monitoring & Ethics Committee

The Independent Data Monitoring & Ethics Committee (DMEC) is the only oversight body that has access to unblinded accumulating comparative data. The DMEC is responsible for safeguarding the interests of trial participants, monitoring the accumulating data and making recommendations to the TSC on whether the trial should continue as planned. The membership, frequency of meetings, activity (including review of trial conduct and data) and authority will be covered in the DMEC terms of reference. The DMEC will consider data in accordance with the statistical analysis plan and will advise the TSC through its Chair.

6.11.4.4.5 Trial Sponsor

The role of the sponsor is to take on responsibility for securing the arrangements to initiate, manage and finance the trial. UCL is the trial sponsor and has delegated the duties as sponsor to CCTU via a signed letter of delegation.

7 Ethics and Dissemination

7.1 Ethics Committee Approval

Before initiation of the trial at any clinical site, the protocol, all informed consent forms and any material to be given to the prospective participant will be submitted to the relevant EC for approval. Any subsequent amendments to these documents will be submitted for further approval. Before initiation of the trial at each additional clinical site, the same/amended documents will be submitted for local permissions.

The rights of the participant to refuse to participate in the trial without giving a reason must be respected. After the participant has entered the trial, the clinician remains free to give alternative treatment to that specified in the protocol, at any stage, if s/he feels it to be in the best interest of the participant. The reasons for doing so must be recorded. After randomisation the participant must remain within the trial for the purpose of follow up and data analysis according to the treatment option to which they have been allocated. However, the participant remains free to change their mind at any time about the protocol treatment and follow-up without giving a reason and without prejudicing their further treatment.

7.2 Competent Authority Approvals

This protocol will be submitted to the national CA (e.g. the MHRA in the UK), as appropriate in each country where the trial will be conducted.

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

The progress of the trial, safety issues and reports, including expedited reporting of SUSARs, will be reported to the Competent Authority, regulatory agency or equivalent in accordance with relevant national and local requirements and practices.

7.3 Other Approvals

The protocol will be submitted to the Health Research Authority (HRA) - or equivalent organisation if outside remit of NHS England) - for approval. A copy of the local permissions (or other relevant approval as above) and of the Participant Information Sheet (PIS) and consent form on local headed paper must be forwarded to the co-ordinating centre before participants are randomised to the trial.

The protocol has received formal approval and methodological, statistical, clinical and operational input from the CCTU Protocol Review Committee.

7.4 Protocol Amendments

The sponsor will ensure that essential documents namely - trial protocol, patient information sheet, consent form ,GP letter and submitted supporting documents have been approved by the appropriate regulatory body (MHRA), REC, and HRA prior to any patient recruitment. The protocol and all agreed substantial amendments will be documented and submitted for ethical and regulatory approval prior to implementation.

7.5 Consent or Assent

PwSPMS will be fully informed of purpose of the study, the potential benefits and possible risks of participating in the trial including possible improvement in disease control and advances in our understanding of SPMS disease pathogenesis.

A patient information sheet (PIS) will be provided to patient with sufficient time for them to consider participation in the trial. Following a discussion with a medically qualified investigator or suitably trained and authorised delegate, any questions will be satisfactorily answered and if the participant is willing to participate, written informed consent will be obtained.

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

In accordance with the UK Clinical Trial Regulations, the risk/benefit profile of the trial will be regularly monitored. Consent will be re-sought if new information becomes available that affects the participant's consent in any way. This will be documented in a revision to the patient information sheet and the participant will be asked to sign an updated consent form. These will be approved by the ethics committee prior to their use.

A copy of the approved consent form is available from the MS-STAT2 trial team.

7.5.1 Consent or Assent in Ancillary Studies

Consent will be sought from all eligible MS-STAT2 patients at site(s) participating in the sub-studies (in addition to main trial) to partake in either one, or any combination of three sub-studies outlined below to better understand the mechanism of action of simvastatin and for use of their clinical data to support further analysis for future research.

- Magnetic Resonance Imaging (MRI) sub-study [Appendix 1]
- Biomarker sub-study [Appendix 2]
- Optical Coherence Tomography (OCT) sub study [Appendix 3]

Participants interested in the Biomarker sub-study will be asked to consent to storage of biological specimens for future research purposes to enable the investigation of emerging biomarkers in MS. All stored biological specimens will retain unique assigned identifier.
Consent will also be sought from healthy participants (individuals with no Multiple Sclerosis diagnosis) to participate in the Biomarker sub-study only.

Withdrawal of participant from the trial or any of the associated sub-studies will not be accompanied by withdrawal of previously collected specimens. No individual information derived from this research will be communicated to the participants.
Additional details relating to the sub-studies is outlined in Section 8.

7.6 Confidentiality

Adequate measures will be in place to ensure all participant data collected are kept secure. The web-based randomisation service provider – Sealed Envelope, will provide a unique trial identification code for each participant and their name will be thus replaced by a depersonalised code using an unrelated sequence of characters. The service provided by Sealed Envelope is secure and is recognised as such by the MHRA.

7.7 Declaration of Interests

The investigators named on the protocol have no financial or other competing interests that impact on their responsibilities towards the scientific value or potential publishing activities associated with the trial.

7.8 Indemnity

UCL holds insurance to cover 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 in the clinical trial. UCL does not accept liability for any breach in the hospital's duty of care, or any negligence on the part of hospital employees. This applies whether the hospital is an NHS Trust or not. This does not affect the participant's right to seek compensation via the non-negligence route.

Participants may also be able to claim compensation for injury caused by participation in this clinical trial without the need to prove negligence on the part of UCL or another party. Participants who sustain injury and wish to make a claim for compensation should do so in writing in the first instance to the Chief Investigator, who will pass the claim to UCL'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 UCL, upon request.

7.9 Finance

MS-STAT2 is fully funded by an NIHR-HTA project number 15/57/143. It is not expected that any further external funding will be sought.

7.10 Archiving

The investigators agree to archive and/or arrange for secure storage of MS-STAT2 trial materials and records for a minimum of 5 years after the close of the trial unless otherwise advised by the CCTU.

7.11 Access to Data

Requests for access to trial data will be considered, and approved in writing where appropriate, after formal application to the TSC. Considerations for approving access are documented in the TSC Terms of Reference.

7.12 Ancillary and Post-trial Care

There are no arrangements to provide simvastatin to participants' post-trial.

7.13 Publication Policy

It is anticipated that all results from this work will be published in high-impact journals. Publication and dissemination of the study results will be coordinated by MS-STAT2 trial team in collaboration with the Chief Investigator and Investigators as per the MS-STAT2 publication policy.

7.13.1 Trial Results

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

7.13.2 Authorship

Authorship will be granted to individuals making a substantial contribution to the design, setup or conduct of the trial and/or analysis and interpretation of trial data.

7.13.3 Reproducible Research

The latest version of the trial protocol will be made available as Supplementary material upon publication of the final trial report.

8 Ancillary Studies

The sub - studies outlined here will provide additional insight into the effect of simvastatin on the following areas;

1. MRI sub-study (Appendix 1) – Explore the rate of brain atrophy using MRI at different time points

2. Biomarker sub-study (Appendix 2) – Measure the serum levels of lactate dehydrogenase (LDH) and serum neurofilament light chains (NFL) and explore their potential role as novel surrogate markers for axonal damage. Examine the effect of osmotic and or mechanical stress on erythrocytes in people with SPMS

3. OCT sub-study (Appendix 3) – Examine the degree of thinning of the peripapillary retinal nerve fibre layer (pRNFL) over the course of the trial period

9 Protocol Amendments

Protocol Version Number	Protocol Date	Summary of Changes
1.0	1- Aug- 2017	New Protocol
2.0	24-Jan-2018	**1.** Addition of a new exclusion criteria – Patients with rare hereditary problems of galactose intolerance, the lapp lactase deficiency or glucose-galactose malabsorption may experience a serious reaction to use of simvastastin as each 40mg film-coated tablet contains 116.4 mg lactose per film-coated tablet. Exclusion criteria to be amended to ensure patients with lactose intolerance as a result of rare hereditary problems of galactose intolerance, the lapp lactase deficiency or glucose-galactose malabsorption are not enrolled to the trial **2.** Inclusion of trial identifiers - ClinicalTrials.gov unique identifier - Clinical Trial Authorisation (CTA) number **3.** Use of two new questionnaires at all participating sites a. Modified Fatigue Index Scale – 21 (MFIS-21) b. Chalder Fatigue Questionnaire (CFQ) **4.** Addition of three sub-studies at participating site(s) only - MRI sub-study (Appendix 1) - Biomarker sub-study (Appendix 2) - OCT sub-study (Appendix 3) **5.** Recruitment of healthy blood donors for the biomarker sub-study **6.** Change from ABILHAND-56 to ABILHAND-23 **7.** Section 7.5.1 has been revised to outline process of obtaining consent from sub-study participants **8.** SAE form to be sent to trial team via secure portal/encrypted **9.** Change in wording – Oversight group changed from Independent Data and Monitoring Committee (IDMC) to Data Monitoring and Ethics Committee (DMEC) in line with funder (NIHR) terminology **10.** Editing of section 6.11.3.4: Procedures following notification of pregnancy **11.** Addition of section 6.11.3.4.2 Notification by male participants in the event of partner becoming pregnant **12.** Addition of new terms to Glossary (section 4) **13.** Minor edits and formatting throughout the protocol

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11 Appendices

APPENDIX 1: MAGNETIC RESONANCE IMAGING (MRI) SUB-STUDY

AIM

This study will aim to confirm the effect of simvastatin on whole brain atrophy over a 3 year period.

The effect of simvastatin on other important measures of neurodegeneration including grey matter, deep grey matter (in particular the thalamus) and spinal cord atrophy will be examined.

In addition, the team will seek to determine if there is an anti-inflammatory component on new and enlarging T2 lesions and T2 lesion volume.

Data on the longitudinal sensitivity and clinical correlation of the imaging measures will inform their utility as viable outcome measures for future trials in secondary progressive MS (SPMS). These could form the basis for exploratory analysis as summarized below:

1. To confirm the simvastatin-related reduction in whole brain atrophy progression, which was detected in MS-STAT[13,68], in an independent sample, and extend the follow-up to 3 years. This will cement the role of atrophy measurement as being central to trials in SPMS.
2. To investigate the effect of treatment on secondary imaging outcome measures of neuroprotection that are clinically relevant in SPMS (spinal cord, grey matter and thalamus), which may be able to reflect the therapeutic effects of simvastatin more efficiently than changes in clinical scores of disability.
3. To assess the potential anti-inflammatory effect of simvastatin on changes in T2 lesion load.
4. To enhance trial performance by more robust and quantitative analysis of the relationships of earlier MRI outcomes and later clinician- and patient-reported end-points.
5. To explore the performance of secondary MRI outcome measures, such as brain grey matter atrophy, thalamic atrophy and upper cervical cord atrophy, to better understand the mechanism of action of simvastatin.

RATIONALE FOR SPECIFIC MRI OUTCOME MEASURES

MRI has been vital in the development of new disease modifying treatments (DMTs) in relapsing-remitting multiple sclerosis (RRMS), and has the potential to play a similar pivotal role in SPMS trial design. In phase 2 trials in RRMS, reduction in inflammatory activity, inferred by the prevention of new gadolinium enhancing or T2 weighted lesions, has come to be a mandatory step in demonstrating surrogate efficacy before proceeding to the much larger phase 3 trials, in which the primary outcome measure is reduction in relapse rate.[69] During the last decade, this strategy has been highly successful as demonstrated by the trials using natalizumab (phase 2, n=213[70] and phase 3 , n=942)[71] and fingolimod (phase 2 , n=281[72] and phase 3, n=1272) [73].

In RRMS trials there is also a correlation of treatment effect on brain atrophy with the effect on disability.[74] The stronger correlation of clinical treatment effect with the combined effect on brain atrophy and MRI lesion activity[75] has therefore supported the use of change in brain volume as additional outcome measure in RRMS trials. Several phase 3 treatment trials in RRMS have indeed included reduction in brain atrophy as a secondary efficacy end point.

In SPMS, whilst there is still a role for investigating the development of new lesions as a marker of inflammatory activity (and the increase in T2 lesion load will be quantified), the main MRI metric for investigating neurodegeneration - the substrate of progressive and irreversible disability – is the change (reduction) in brain volume which can be expressed as the percentage brain volume change (PBVC).[75] Compared with age-matched healthy controls, there is a greater decrease in brain volume over time in SPMS than healthy controls and patients with relapsing-remitting MS, which can be quantified by MRI. On average there is 0.5-1% loss of brain volume/year in SPMS, as opposed to 0.1-0.2%/year in age-matched controls. Amongst all types of MS, SPMS shows the fastest rate of brain atrophy per year, which in large, multi-centre settings has been estimated to be 0.64%/year.[76]

In our previous phase 2 double-blind, placebo-controlled trial (MS-STAT), we investigated the effects of simvastatin 80 mg per day in 140 patients with SPMS patients by comparing the annualised rate of whole-brain atrophy between treated and placebo patients, and found that there was a 43% reduction in annualised rate in the simvastatin-treated group (the annualised brain atrophy rate in the placebo arm was 0.58%/year),[68] demonstrating that brain atrophy may have the same pivotal role in SPMS trials as lesion activity in RRMS trials.

Whole Brain Atrophy

Whole brain atrophy has been measured with a variety of methods. The most popular tools are the BSI (Boundary Shift Integral)[77,78] and SIENA (Structural Image Evaluation, using Normalisation, of Atrophy),[79] which are applied after brain extraction has been undertaken using automated methods. Both methods are based on registration of repeated scans: in BSI the repeat scan is registered to the halfway, in the SIENA method the baseline and follow-up scans are aligned and then resampled into mid-space. MS-STAT used serial 2D-T1 multi-slice scans, which were analysed with the BSI methodology.[68]

More recently, trials have started to calculate PBVC from SIENA applied to 3D T1 volumetric scans.[80] The advantage of using 3D scans is the improved (isotropic) spatial resolution and therefore reduction of partial volume effect, which allows better grey/white matter and CSF segmentation, allowing additional analysis of tissue/areas of interest, such as cortical and deep grey matter regions – relevant in SPMS. 3D SIENA will be used to analyse results generated for the primary outcome.

Other MRI Outcome Measures For SPMS Trials

Despite the importance of using brain atrophy in clinical trials to estimate the effect of neuroprotective strategies, the correlation between whole brain atrophy and clinical measures in SPMS tends to be modest.[14] Other MRI measures, including grey matter volume, thalamic volume, and spinal cord cross-sectional area, correlate better with clinical progression than whole brain atrophy, and can be considered as additional, secondary efficacy endpoints in SPMS trials. These will therefore also be examined in this study.

Normalised grey matter (GM) volume, which is obtained by the segmentation of high resolution, brain 3D imaging, is significantly associated with long-term disability in SPMS,[81,82] and explains physical disability better than white matter atrophy.[82,83] The placebo arm of the 2-year lamotrigine trial in SPMS demonstrated that the GM atrophy was greater and more responsive than white matter atrophy (-1.18%/year vs. 0.12%/year), and was the only regional brain atrophy measure that correlated with clinical changes.[21]

Within the GM compartments, thalamic atrophy seems to be particularly important in contributing to disability. In SPMS, thalamic atrophy correlates with long-term disability,[84] including cognitive dysfunction.[85] The result from a recent multi-centre study showed that the

yearly rate of thalamic atrophy in SPMS is 2.3%, which is higher than the mean whole GM rate (1.6%), suggesting that the estimation of thalamic volume can become a useful outcome measure.[86] The thalamus is the largest of the deep grey structures and deep grey matter (DGM) atrophy as a whole will also be derived.

The reduction of cervical cord cross-sectional area at C2-C3 reflects spinal cord atrophy. This measure is significantly associated with disability in SPMS and has been used before in neuroprotective trials in patients with progressive MS such as the lamotrigine trial, where the spinal cord demonstrated the highest atrophy rate (1.63%/year).[84,87] From a methodological point of view, upper cervical cord area measurement can be reliably measured from volumetric brain imaging with careful placement of the field of view during 3D T1 acquisition.[88]

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, 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.[89-91] It has been demonstrated that NODDI has higher sensitivity and specificity than standard DTI.[92]

ASSESSMENTS

Imaging (MRI) will take place on an annual basis to fit in with the main study schedule. The total MRI acquisition time will not exceed 1 hour.

MRI acquisition will take place at these times points;

- Baseline (M0 / week 0)
- Visit 6 (M12/week 52)
- Visit 8 (M24 / week 104)
- Visit 10 M36/week 156)

OUTCOME

Primary outcome measure

The percentage brain volume change (PBVC) measured using the SIENA technique, applied to T1-weighted volumetric 3D scan (magnetisation-prepared gradient echo sequence, voxel size 1x1x1 mm[70]).

The use of 3D pulse sequences and automated image segmentation methods are recommended in longitudinal and treatment studies of MS.[93]

SIENA is a fully-automated method that is applied after extracting the brain from the two time-point whole-head input data. The brain is extracted using an automated brain extraction tool (BET) with additional manual editing when required. [79] The two brain images are then aligned to each other (using the skull images to constrain the registration scaling); [94,95] both brain images are resampled into the halfway space between the two. Next, tissue-type segmentation is carried out, [96] in order to find brain/non-brain edge points, and then the perpendicular edge displacement (between the two time-points) is estimated at these edge points. Finally, the mean edge displacement is converted into a global estimate of PBVC between the two time-points, using self-calibration based on automated image rescaling and re-estimation of displacement.

Secondary Outcome Measures

1. Brain grey matter (GM) volume and thalamic volume

Reduction in the rate of change of these two MRI measures of grey matter atrophy would provide supportive evidence of a treatment that prevents cortical demyelination and neurodegeneration**.** A series of software developments have taken place at UCL over the past years as part of the NifTK software programme. These developments will prove highly beneficial in terms of analysis. Firstly, lesion masks will be automatically created on 3D-T1 and FLAIR space using an in-house automatic lesion segmentation and parcellation technique.[97] Then a lesion-filling technique will be applied to reduce the impact of white matter lesion misclassification on GM volume.[98] The lesion-filled images will be segmented using Geodesic Information Flows method (GIF) version 2, which is a multi-atlas segmentation propagation and fusion technique, available in the NiftyWeb platform (http://cmictig.cs.ucl.ac.uk/niftyweb/).[99]

2. Cross-sectional cord area

Cord atrophy is an important measure of axonal degeneration that occurs especially in patients with progressive MS and is a major determinant of clinical disability.[84]

The cross sectional cord area will be measured to determine treatment effect on spinal cord atrophy.

3. Increase in T2 lesion load

Although this measure appears to be less relevant than brain atrophy as a measure of neuroprotection in SPMS, it has proved sensitive in detecting efficacy of immunomodulatory drugs in preventing new lesion formation in previous trials over 2 years in SPMS.[100,101] Changes in T2 total lesion load will be automatically calculated using T1 and FLAIR images (using the Bayesian Model Selection (BaMoS) method)[97] and included as a secondary outcome measure in order to detect an unanticipated immunomodulatory effect. Moreover, at baseline, to determine the proportion of patients with active enhancement (i.e. at least one enhancing lesion) gadolinium will be given for any differential therapeutic effect. This method jointly models different modalities (T1, and FLAIR) to segment lesions, and is known as has been previously validated against other automatic segmentation methods and manual lesion segmentation of white matter lesions in MS.

4. Multi-shell diffusion weighted imaging

Multi-shell DWI allows us to derive quantitative measures that will provide in-vivo information on the integrity and structure connectivity of neuronal fibres in the brain.

SAMPLE SIZE

The sample size calculation used for this sub-study is based on similar studies that have reported measurement of PBVC using SIENA in PwSPMS[14,102] which are very similar to the annualised rate of whole brain atrophy measured using BSI of 0.584%/year in the placebo group of the MS-STAT trial.[68] Kapoor reported that the rate of change in PBVC was 0.59%/year in 56 SPMS patients in the placebo group of the Lamotrigine clinical trial[21] and De Stefano reported mean PBVC of 0.64%/ year (SD 0.68%) in a cohort of 139 patients with SPMS.[14] These studies were over two years of follow-up, so it is necessary to make further assumptions in order to determine the sample size for a longer 3 year study. Based on the

previous study by Altmann,[103] we assumed that PBVC measured using SIENA will have minimal residual measurement error, and that the variance of between participant differences in annualised rate of PBVC will be approximately 1.6 times the variance of the within participant visit specific departures from linear rate of change. Under these assumptions, and with SD of 0.68%/year over 2 years, it is predicted that the SD of PBVC will be 0.63%/year over 3 years.

It is assumed that the mean annualised rate of PBVC will be 0.64%/year in the placebo group and 0.3648%/year in the Simvastatin treatment group, reflecting the 43%/year reduction previously seen in the MS-STAT trial. For analysis using a mixed effect model of the repeated measures of directly measured change[104] to provide 90% power to demonstrate a statistically significant difference (two sided $p<0.05$), 110 patients are required in each treatment group. Assuming drop-out of 7%, as in the MS-STAT2 study, 120 participants per arm are required: 240 in total.

ANALYSIS PLAN

A CONSORT flow diagram will be reported. Exploratory summary methods will be used to describe baseline characteristics (including gadolinium status): continuous variables will be summarized using summary statistics (mean, standard deviation, median, minimum, and maximum) by treatment group, and categorical variables will be presented using frequency distributions by treatment group. A detailed statistical analysis plan (SAP) will prepared which will include details of methods for calculating derived variables, methods for handling missing data and withdrawals, any sensitivity analyses and approaches to testing the assumptions in the statistical analyses.

The primary analysis will be by intention to treat with participants compared according to the treatment group to which they were randomised irrespective of which treatment they may have received (intention-to-treat). A secondary analysis will also be performed on the sub-set of patients who were treated per protocol. A sub-group analysis will be performed to compare the treatment effect according to gadolinium baseline status (exploratory analysis).

STATISTICAL METHODS – OUTCOMES

Primary Outcome Measure

The primary endpoint will be the PBVC measured using the SIENA method. For each participant, PBVC will be calculated between baseline and each follow-up visit giving three values for those attending all visits (0-12, 0-24, 0-36). Mean rates of PBVC in the two groups will be compared using the family of linear mixed models developed for the analysis of repeated direct measures of change[104] with adjustment for the baseline normalised brain volume and the minimisation variables (sex, age, baseline EDSS). All patients for whom there is at least one measure of PBVC (i.e. have at least one follow-up scan) will be included as this method permits participants with multiple measures of atrophy, and those with only a single change measure, to contribute to the analysis in an appropriately weighted fashion. The distribution of the PBVC will be investigated for non-normality before analysis and if necessary a data transformation will be made or a non-parametric statistical analysis will be conducted.

Secondary Outcomes

1. Brain grey matter (GM) volume and thalamic volume

Grey matter and thalamic volumes will be compared between the treatment groups using a mixed effects linear regression for repeated measures, adjusting for the minimisation variables (sex, age, baseline EDSS) and baseline normalised grey matter and thalamic volume.

2. Cross-sectional cord area

This will be compared between the treatment groups using a mixed effects linear regression models for repeated measures, adjusting for the minimisation variables (sex, age, baseline EDSS).

3. Changes in T2 lesion load

The treatment group will be compared with placebo in terms of changes in T2 lesion load using a mixed effects linear regression models for repeated measures, adjusting for the minimisation variables (sex, age, baseline EDSS).

4. Multi-shell DWI

Quantitative measures of structural connectivity and neuronal integrity will be analysed at baseline and compared between treatment and placebo groups at each of the pre-specified time points and the differences in the rate of changes in these measures over time between the treated and untreated group will be estimated using a mixed effects linear regression models for repeated measures, adjusting for the minimisation variables (sex, age, baseline EDSS).

APPENDIX 2: BIOMARKER SUB-STUDY

Eligibility Criteria - Healthy Donors Only

Inclusion Criteria

1. Aged 25 to 65 years old
2. Male or Female
3. Written informed consent provided

Exclusion Criteria

1. Confirmed diagnosis of Multiple Sclerosis
2. Significant organ co-morbidity e.g. cardiac failure, renal failure, malignancy

Data Collection - Healthy Donors only

Basic information will be collected - Name, Age, Gender, Ethnicity, Medication history, and Concomitant medication

AIM

There are currently no biomarkers in Multiple Sclerosis (MS) that can predict outcome, disability progression or treatment response. There is a clear unmet need to identify biomarkers both in relapsing remitting and progressive MS.

The aim of this sub-study is to evaluate the effect of simvastatin on serum levels of lactate dehydrogenase (LDH) and serum neurofilament light chains (NFL).

We will examine the utility of serum NFL as a marker of axonal loss. In addition, we will explore potential use of LDH as a biomarker and the probable role of haemolysis in the pathophysiology of secondary progressive MS test by testing whether erythrocytes from people with SPMS are abnormally fragile in response to osmotic stress, in comparison to healthy age- and sex-matched controls.

BACKGROUND

The pathological substrate that results in the acquisition of non-reversible or permanent disability in MS is axonal loss. Axonal loss occurs by two mechanisms; firstly, as a result of axonal transection in acutely inflamed focal lesions and secondly as the delayed consequence

of earlier damage that renders axons vulnerable to degeneration when compensatory mechanisms fail.[105,106]

Assessing the efficacy of neuroprotective agents in the setting of delayed axonal loss is proving problematic. Most investigators have until now used clinical or MRI outcomes. MRI outcomes include whole brain or regional brain atrophy measurements, typically over a period or 2 years or longer. Unfortunately, the use of whole brain atrophy has proven problematic due to the effect of pseudo-atrophy.[107] Another problem is the responsiveness of whole brain atrophy as an outcome measure. Most trials use a parallel design with an active and comparator placebo arm and typically run for a period of at least 2 years.

Studies using clinical outcomes, namely the Expanded Disability Status Scale (EDSS), need much larger numbers of subjects and take longer. For example, the CUPID study (Cannabinoid Use in Progressive Inflammatory brain Disease) in the UK, which evaluated whether THC, a cannabinoid from the cannabis plant, might slow the development of disability in progressive MS, used the EDSS as its primary outcome over 3 years.[60] Proof-of-concept studies of 2 to 3 years duration with a typical recruitment period of 6 to 12 months take at 3 to 4 years, or longer, to complete.

Therefore we are proposing to test a new and novel trial design based on serum levels of lactate dehydrogenase (LDH) and neurofilament light chain (s-NFL) as a read-out for axonal damage and hence neuroprotection. We aim to determine whether serum levels of LDH and NFL, surrogate markers of axonal damage, prove to be responsive to neuroprotective therapies within the first year which will allow studies to be powered to provide readouts within 12 months.

In addition, we propose testing the hypothesis whether erythrocytes are abnormally fragile to osmotic or mechanical stress in patients with SPMS, compared with erythrocytes from healthy age- and sex-matched controls.

RATIONALE

In the MS-STAT trial, a sub study was conducted that used mass spectrometry to identify potential biomarkers of progressive MS. Lewin et al identified two protein peaks that were correlated with brain atrophy rates. Further analysis identified these two protein peaks as alpha and beta haemoglobin. Free serum haemoglobin levels were thus assayed and found to be significantly higher than in control groups. Statistical modelling showed a significant

correlation between free serum haemoglobin rates and brain atrophy rates in SPMS. Further statistical analysis showed that this correlation was independent of the effect of simvastatin on decreasing the rate of brain atrophy.

This unexpected observation on free serum haemoglobin suggests the hypothesis that erythrocytes are abnormally fragile to osmotic or mechanical stress in patients with MS. This effect has been observed by studies[108,109] who reported that erythrocytes are abnormally fragile to osmotic or mechanical stress in patients with active MS. However, this phenomenon has not been followed up, and the cause of this fragility is currently unknown.

Following the identification of increased free haemoglobin in SPMS patients, serum LDH levels were measured to look for evidence of haemolysis. Median LDH levels were significantly greater in patients with MS than in each of the 3 control groups. Based on this finding, it was hypothesised that intravascular haemolysis could be directly involved in the process of neurodegeneration via the direct effect of free haemoglobin entering CNS parenchyma or its breakdown products. These findings from MS-STAT have provided a potential insight into the pathophysiology of SPMS and provide the basis for further research on the viability of serum levels of LDH as a biomarker of disease progression.

Neurofilaments (NF) are the structural scaffolding proteins of neurons as axons and dendrites are composed of light (NFL), medium (NFM) and heavy (NFH) chain subunits. Due to their abundance and specificity for neurons they are a marker of neuronal injury. All pathological processes that cause neuroaxonal damage release NF proteins into the extracellular space, CSF and depending on the extent of damage, the peripheral blood. A recent long-term study has confirmed the utility of CSF NFL levels as a prognostic marker in MS; CSF NFL levels measured at baseline correlated with MS severity score (MSSS) with a median follow-up of 14 years. Patients with CSF NFL above the median had a higher risk of developing severe MS, defined as a MSSS of greater than 3.25, compared to subjects with a more benign course (odds ratio 5.2; 95% CI 1.8-15) . Several other studies have confirmed that CSF NFL and NFH are raised in MS and correlate with disability.[110-114] More recent studies suggest that serum NFL is preferable to measuring NFH as it correlates better with disability and shows a more significant decrease in MS.[114,115] Owing to the fact that obtaining CSF by lumbar puncture is invasive and impractical in a clinical setting, serum NFL has also been studied as a surrogate marker of MS activity.

Amor et al studied serum NFL antibodies in a several groups of patients including RRMS, SPMS, healthy controls and RRMS on natalizumab.[116] They demonstrated that NFL antibodies were higher in MS clinical groups than healthy controls and that NFL antibody levels were higher in RRMS compared with SPMS. NFL antibody levels were also shown to be lower in natalizumab treated patients than in untreated RRMS patients.[116] Disanto et al more recently showed that serum NFL were increased in patients with clinically isolated syndrome. They also found that higher serum NFL levels were associated with several MR measures and higher disability scores at CIS diagnosis.[117] Following on from this Kuhle et al compared serum and CSF NFL levels in 31 patients with RRMS over a median period of 3.6 years.[118] They found that serum NFL levels were highly correlated with CSF levels ($r = 0.62$, $p = 0.0002$). Serum NFL remained higher in MS patients than healthy controls at baseline and at follow up ($p = 0.0009$) and was associated with several MRI measures including white matter lesion volume, T1 and T2* relaxation times.[118]

The most recent publication from this group examined serum NFL from participants in a randomised double blinded trial of neuroprotection with riluzole vs placebo as an-add on to weekly IFN-beta. There was no treatment effect with riluzole thus both cohorts were analysed together. The group showed that serum NFL decreased at the 1 and 2 year time points (Serum NFH showed no significant change). A positive correlation between increasing serum NFL levels and increasing EDSS ($p = 0.009$) was also observed.

Increase in serum NFL was also associated with several cognitive measures including poorer judgement of line orientation, lower CVLT-II and BVMT-R scores. High baseline serum NFL was associated with an increased rate of brain atrophy.[119]

Earlier this year, Piehl et al published their study on NFL levels in CSF and serum/plasma in a first cohort of MS patients and neurological disease controls and a second cohort that consisted of patients from a post-marketing study of fingolimod. Firstly they confirmed the previous finding by Kuhle et al that plasma/serum and CSF NFL levels were highly correlated ($n = 66$, $r = 0.672$, $p < 0.0001$). Secondly they showed that in patients switching to fingolimod, mean plasma NFL levels were reduced between baseline (20.4) and at 12 months (13.5, $p < 0.00003$).[120] The evidence supporting the use of serum NFL as a biomarker of disease progression in MS continues to accumulate and thus forms the basis for its study in MS-STAT2.

STUDY OBJECTIVES

As a result of these considerations, we aim to test:

a. Whether axonal degeneration, and thereby the release of neurofilaments into peripheral blood, can be reduced by simvastatin;

b. Whether erythrocytes are abnormally fragile in response to osmotic or mechanical stress in people with SPMS, compared to healthy age- and sex-matched controls;

c. Whether intravascular hemolysis and thereby release of LDH into serum can be reduced by simvastatin;

d. The utility of both serum LDH and serum NFL as biomarkers of disease activity and progression in SPMS;

The principal research questions underpinning this sub-study are therefore:

Q1. Does simvastatin prevent axonal damage in SPMS?

The primary outcome will be the longitudinal change in serum NFL levels.

Q2. Exploratory analysis into the effect of simvastatin on serum LDH in SPMS?

The primary outcome will be effect on serum LDH levels. This will be correlated with clinical (EDSS) and MRI measures (core and exploratory analyses) to look for further insights into pathophysiology of SPMS.

Q3. Can serum NFL and LDH be used as biomarkers of disease activity and progression in SPMS?

The primary outcome will be examining the correlation between serum LDH and NFL, clinical disability (EDSS) and MRI measures (brain atrophy rates).

Q4. Are erythrocytes in people with SPMS abnormally fragile in response to osmotic or mechanical stress, compared with erythrocytes from healthy age- and sex-matched controls?

OUTCOMES

Primary Outcome(s)

1. The relative reduction of serum NFL levels from baseline to 12 months (week 52) between the simvastatin and placebo treated arms.
2. The relative reduction of serum LDH levels from baseline to 12 months (week 52) between the simvastatin and placebo treated arms.
3. Erythrocyte Fragility measurement

Secondary Outcomes

1. The relative reduction of serum NFL levels from baseline to 36 months (week 156), 12 months (week 52) to 24 months (week 104), and 24 months (week 104) to 36 months (week 156).

2. The relative reduction of serum LDH levels from baseline to 36 months (week 156), 12 months (week 52) to 24 months (week 104) and 24 months (week 104) to 36 months (week 156).

Exploratory outcomes

1. To determine the correlation between serum NFL levels, EDSS and MRI brain atrophy measures. This will be completed within each group at baseline, 12 months (week 52), 24 months (week 104) and 36 months (week 156).

   Our rational for using these time points is based on data from several studies: Kuhle et al showed that serum NFL was decreasing at month 24 and was associated with EDSS in a cohort of patients with early RRMS or CIS.[119] Kuhle et al also showed serum NFL levels to be higher than controls at baseline and after a median time period of 3.6 years.[118] Amor showed statistically significant reductions in NFL antibodies at baseline and 24 months in MS patients.[116] These studies show that changes were occurring at the 24 months and up to median 3.6 years thereby providing surrogate evidence that axonal damage is still occurring after many months and that amelioration of this could be achieved as measured by a reduction in serum NFL at the aforementioned study time points.
2. To determine the correlation between serum LDH levels, EDSS and MRI brain atrophy measures. This will be completed within each group at baseline, 12 months (week 52), 24

months (week 104) and 36 months (week 156).

3. To study the composition and the metabolic profile of erythrocytes and test specific hypotheses on the cause of the red cell fragility. The results may suggest new avenues to treat and prevent the disabling neurodegeneration that accompanies the progressive disease.

ASSESSMENTS

Blood samples will be taken at these time points;

- Baseline (M0/ week 0)
- Visit 3 (M1/ week 4)
- Visit 5 (M6/Week 26)
- Visit 6 (M12/week 52)
- Visit 7 (M18/ week 78)
- Visit 8 (M24/week 104)
- Visit 9 (M30/week 130)
- Visit 10 (M36/ week 156)

ANALYSIS PLAN

Primary analysis will be by intention-to-treat, but per protocol analyses will also be reported.

Spearman's rank correlation coefficients will be calculated to assess the bivariate correlation of serum NFL levels with PBVC and EDSS score at 36 months (week 156). A further analysis plan will be developed.

APPENDIX 3: OPTICAL COHERENCE TOMOGRAPHY (OCT) SUB-STUDY

AIM

To determine if OCT parameters can be a marker of cognitive impairment in patients with MS in a longitudinal study.

BACKGROUND

OCT is a non-invasive imaging technique that uses back-scattered infrared light to detect the retinal layers. Pulicken et al first showed that patients with multiple sclerosis (MS) whose eyes were previously unaffected by optic neuritis had thinning of the retinal nerve fibre layer and decreased macular volume as progressive MS ensued (as well as relapsing remitting MS).[121]

Thinning of the peripapillary retinal nerve fibre layer (pRNFL) is seen in progressive MS and the degree of thinning, reflecting axonal loss, is associated with quantitative measures of visual impairment. Atrophy of the temporal region of the RNFL has also been shown to demonstrate highly significant thinning over time in patients with relapsing remitting multiple sclerosis (RRMS).[122,123] Although serial OCT-measured RNFL thickness has been proposed as a measure of neurodegeneration for clinical trials in MS, longitudinal observations are largely confined to relapsing remitting.[124]

The more recently introduced high resolution spectral-domain (SD) OCT can also measure the retinal nerve ganglion cell and inner plexiform layer (GCIPL) thickness with thinning of this layer reflecting ganglion cell loss. Thinning of the GCIPL is seen in MS and is significantly correlated with measures of visual dysfunction and disability. [125] [126-129] Furthermore, GCIPL thinning was also shown to have a strong association with multiple MRI metrics including whole brain, grey matter, white matter and thalamic atrophy in patients with progressive MS.[130]

The International Multiple Sclerosis Visual (IMSVISUAL) System Consortium used SD-OCT in 664 patients with MS (all types) showing that pRNFL $\leq$ 87µm doubled the risk of disability worsening after at any after first year and up to the third year of follow up.[131] Furthermore, it has been shown that OCT metrics including pRNFL thickness and total macular volume are lower in progressive MS when compared to patients with RRMS.[132] A recent meta-analysis examining studies using SD-OCT in mixed cohorts of MS patients confirmed that when

compared to healthy controls - pRNFL and GCIPL were both decreased in both multiple sclerosis optic neuritis (MSON) and non-optic neuritis (MSNON).[133] In terms of OCT and cognitive impairment, a cross-sectional study from 2017 showed a strong relationship between cognitive impairment and atrophy of pRNFL and mean GCIPL.[134]

Inclusion of serial SD-OCT in MS-STAT2 will elucidate the extent and evolution of both RNFL thinning, RGC+IPL and macular volume loss in secondary progressive MS. It will provide further information on both axonal and neuronal cell body degeneration in this form of MS. It will investigate the longitudinal sensitivity and clinical relevance (by correlating with low contrast visual acuity and neurological function measures) of these OCT parameters, providing further evidence of its potential use as a surrogate marker of axonal loss or neuroprotection that will inform future trial design in secondary progressive MS.

RATIONALE & RISKS/BENEFITS

Secondary progressive MS is a form of MS exhibiting slowly increasing disability after an earlier relapsing remitting phase that is thought to be caused by progressive neuroaxonal loss affecting key CNS pathways and regions. There is a pressing need for sensitive and clinically meaningful new outcome measures that can be used to detect effective neuroprotective treatments. OCT measurement of the retinal neural layers is one such potential approach. Its utility will be analysed in this cohort of patients with SPMS being treated with active drug (simvastatin) or placebo.

OCT has also recently shown a strong relationship with cognitive impairment in a cross sectional study. This interesting finding warrants further examination in a longitudinal study to determine if OCT parameters can be a marker of cognitive impairment in patients with MS.

There are no side-effects associated with this imaging technique and as such risk minimisation is minimal. Eye drops may be required to dilate the pupil for the OCT examination in participants with a small pupil. These drops may cause mild stinging sensation which lasts for a few seconds. There may be transient but mild blurring of vision or glare, and participants will be advised not to drive a vehicle for 2 hours after completing the visit if eye drops are needed.

STUDY OBJECTIVES

1. To use OCT to measure:

- Retinal nerve fibre layer thickness

- Retinal ganglion cell layer thickness

- Macular thickness and volume

2. Evaluate the sensitivity of OCT to detect on-going retinal neuroaxonal loss in secondary progressive MS, and whether such loss can be prevented by simvastatin.

3. To investigate the utility of OCT as a biomarker of cognitive impairment in patients with SPMS

STUDY DESIGN

Optical coherence tomography generates high resolution, cross-sectional as well as 3 dimensional images of the internal microstructure of the posterior ocular structures including the retinal nerve fibre layer (RNFL), retinal ganglion cell layer (RGCL), optic disc and macula. It is the optical analogue of ultrasound B mode imaging but instead of using echoes created by acoustic waves, it uses light reflections to acquire images. A laser generated beam is scanned across the retina and the magnitude and echo time delay of backscattered light is measured. As the direct detection of light echoes is not possible because of their speed, a correlation technique must be used and OCT systems are based on low coherence tomography.

There are two types of OCT techniques that are commercially available. Time domain OCT uses a fibre-optic Michelson interferometer that operates by creating interference between the back-scattered light from the tissue and a beam of light variable length reference arm. In this way a series of A-scans are sequentially acquired one after another. A number of adjacent A scans produce a final cross-sectional image or B scan with a resolution of approximately 10um vertically and 20 um horizontally. This data is processed and displayed as 2D or volumetric grey scale or false colour image.

Spectral domain (SD)-OCT is based on fast fourier transformation which eliminates the need for a moving mirror in the path of a reference beam. In SD-OCT the interference signal is a function of the wavelength and all echoes of light from the various layers of the retina can be measured simultaneously. SD-OCT has significantly improved image acquisition and is able

to acquire around 27,000 scans per second with a resolution of between 3-10 μm. There is also a significant reduction of artefact from ocular movements.

ASSESSMENTS

Optical coherence tomography (OCT) measurements will be performed on all consented participants. The same OCT machine and software (Heidelberg Engineering Spectralis Software Version 5.4) will be used for acquisition of SD-OCT images at these time points;

- Baseline (M0/week 0)
- Visit 6 (M12/week 52)
- Visit 8 (M24/week 104)
- Visit 10 (M36/week 156)

OUTCOME

Outcome measures and analysis:

The following parameters will be measured:

- Global average retinal nerve fibre layer thickness
- Segmented retinal nerve fibre layer thickness
- Average macular thickness and volume
- Macular retinal ganglion-cell/inner plexiform layer thickness

Primary Analysis

The analysis will be of the global average RNFL thickness and will exclude eyes with optic neuritis. The analysis will use a multiple linear regression method adjusting for baseline and the minimisation variables, to calculate adjusted mean differences and 95% confidence intervals for the individual pairwise comparisons between each active treatment and placebo. Specific sectors of each eye will also be analysed using the same approach, for each sector separately.

The same analysis as above will be performed for the macular retinal ganglion cell layer volume measured from the OCT at 36 months. Other variables from the peripapillary circular scan and the macula volume scan, such as the average macular thickness and volume will be analysed using similar regression methodology.