UCL COMPREHENSIVE CLINICAL TRIALS UNIT

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

Version	V4.0
Date	22nd July 2019
Sponsor	University College London (UCL)
Sponsor R & D ID#	17/0158
Comprehensive Clinical Trials Unit (CCTU)	CTU/2014/107
Trial Adoption Group #	
EudraCT #	2017-003328-56
CTA #	20363/0381/001-0001
REC #	17/LO/1509

Authorisation: Chief Investigator

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Date	22nd July 2019

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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 2018, the EU General Data Protection Regulation (GDPR) 2016 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 the 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	29th December 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
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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>LOW DOSE (INITIAL)</u>**: - 40mg Simvastatin (1x 40mg tablet taken once daily at night) *for 1 month* from Baseline (Month 0). ***OR*** - Placebo (1x tablet taken once daily at night *for 1 month* from Baseline (Month 0). *Dose escalation at Visit 3 (Month 1)* **<u>HIGH DOSE:</u>** - 80mg Simvastatin (2x 40mg tablet taken once daily at night) *for 35 months* from Visit 3 (Month 1) to Visit 10 (Month 36), or Visit 11 (where needed to confirm initial disability progression). ***OR*** - Placebo (2x tablet taken once daily at night) *for 35 months* from Visit 3 (Month 1) to Visit 10 (Month 36), or Visit 11 (where needed to confirm initial disability progression).
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[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 1 point if on the Expanded Disability Status Scale (EDSS) score <6, or an increase of 0.5 point if EDSS score ≥6, or clinical documentation of increasing disability. 2. EDSS 4.0 - 6.5 (inclusive). 3. Aged 25 to 65 years old. 4. Patients must be able and willing to comply with the terms of this protocol. 5. 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 creatine kinase (CK) ≥3 x 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, elbasvir, grazoprevir, 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, dimethyl fumarate, teriflunomide, cladribine 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.
Date of First Enrolment	May 2018
Target Sample Size	1180
Primary Outcome	Time to initial disability progression between the simvastatin and placebo arms. The initial disability progression event is finalised as positive if disability is sustained and confirmed ≥6* months later. **Participants presenting with an initial disability progression (based on EDSS scores) at Month 36 (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, at an additional Visit 11.* This will be measured using the Expanded Disability Status Scale (EDSS). The EDSS will be measured on a 6 monthly basis from baseline until last available EDSS score recorded at last attended clinic appointment. Progression of disability is defined as an increase of at least 1 point if EDSS score at baseline visit is <6, or an increase of 0.5 point if EDSS score at baseline visit is ≥6.

Secondary Outcomes	1. To examine the clinical effect of neuroprotection based on clinician and patient reported outcome measures:
	
	Clinician reported outcome measures
	• 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.
	  ○ Timed 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
	• Modified Rankin Scale (mRS)
	• Brief International Cognitive Assessment For Multiple Sclerosis (BICAMS), a composite cognitive assessment tool comprising of the three components:
	  ○ Symbol Digit Modalities Test (SDMT)
	  ○ California Verbal Learning Test - II (CVLT- II)
	  ○ Brief Visuospatial Memory Test - Revised (BVMT-R)

	Patient reported outcome measures • Multiple Sclerosis Impact Scale-29 v2 (MSIS-29v2) • Multiple Sclerosis Walking Scale-12 v2 (MSWS-12v2) • Modified Fatigue Impact Scale – 21 (MFIS-21) • Chalder Fatigue Questionnaire (CFQ) 2. To estimate the incremental cost and cost-effectiveness of simvastatin versus standard care for the trial period and for the lifetime horizon: • EQ-5D-5L Health Questionnaire • Client Services Receipt Inventory (CSRI)
Sub-Studies	5 Sub-Studies are being conducted at the lead site (UCLH) only: • MRI Sub-Study • OCT Sub-Study • Biomarkers Sub-Study • ABILHAND-23 Sub-Study • FAB Sub-study

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
Professor Jeremy Chataway	University College London (UCL) Institute of Neurology (IoN)	Chief Investigator
Professor Chris Frost	London School of Hygiene and Tropical Medicine (LSHTM)	Statistician/Co-applicant
Dr Jennifer Nicholas	LSHTM	Trial Statistician/Co-applicant
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Professor Sue Pavitt	University of Leeds	Co-applicant
Professor Siddharthan Chandran	University of Edinburgh	Co-applicant
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Professor Gavin Giovannoni	Queen Mary University of London	Co-applicant
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Professor John Greenwood	UCL IoN	Co-applicant
Professor Nick Freemantle	University College London Comprehensive Clinical Trials Unit (UCL CCTU)	Director CCTU/ Co-applicant
Dr Martha Bajwa Joseph	UCL CCTU	Clinical Trial Manager
Mr James Blackstone	UCL CCTU	Clinical Trial Manager
Ms Elizabeth Deane	UCL CCTU	Clinical Project Manager

1.4.2 Trial Sponsor and Funders

Organisation	Role
University College London	Sponsor
NIHR-HTA	Funder

1.4.3 Trial Team

Name	Affiliation	Role
Mr James Blackstone	UCL CCTU	Clinical Trial Manager
Ms Marie Braisher	UCL IoN	Research Manager
Professor Jeremy Chataway	UCL IoN	Chief Investigator
Ms Elizabeth Deane	UCL CCTU	Clinical Project Manager
Professor Chris Frost	LSHTM	Senior Statistician
Ms Georgia Marley	UCL CCTU	Data Manager

Name	Affiliation	Role
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1.4.4 Trial Management Group

Name	Affiliation	Role
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Mr Stuart Nixon	UK Multiple Sclerosis Society (UK-MSS)	Lay Representative

1.4.5 Trial Steering Committee

Name	Affiliation	Role
Dr Brendan McLean	Royal Cornwall Hospitals NHS Trust	Chair (Independent)
Professor Jeremy Chataway	UCL	Chief Investigator (Observer)
Professor Thomas Jaki	Lancaster University	Statistician (Independent)
Dr Victoria Williams	Guy's and St Thomas's NHS Trust	Neurologist (Independent)
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Professor Chris Frost	LSHTM	Senior Statistician (Observer)
Dr Jennifer Nicholas	LSHTM	Trial Statistician (Observer)

1.4.6 Independent Data Monitoring Committee

Name	Affiliation	Role

Professor Graeme McLennan	University of Aberdeen	Professor of Statistics (Independent Chair)
Professor Emeritus Michael Hutchinson	University College Dublin	Professor of Neurology (Independent Member)
Dr Heather Wilson	Royal Free Hospital	Neurologist (Independent Member)
Professor Chris Frost	LSHTM	Senior Statistician (Observer)
Dr Jennifer Nicholas	LSHTM	Trial Statistician (Observer)

1.4.7 Recruitment Management Group

Name	Affiliation	Role
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Professor Jeremy Chataway	UCL IoN	Chief Investigator
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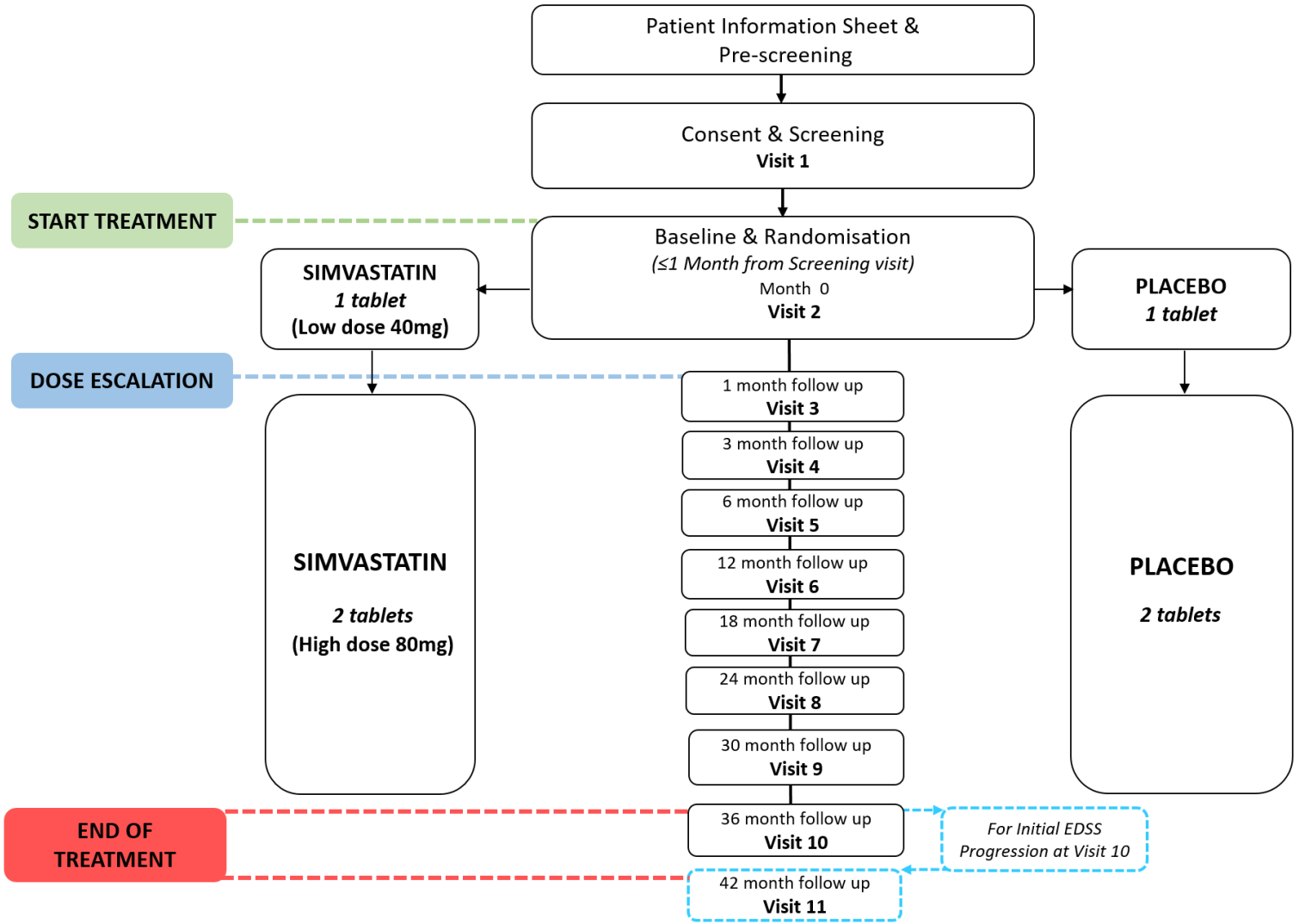
Ms Marie Braisher	UCL IoN	Research Manager
Mr James Blackstone	UCL CCTU	Clinical Trial Manager
Ms Elizabeth Deane	UCL CCTU	Clinical Project Manager
Ms Georgia Marley	UCL CCTU	Data Manager

2 Trial Diagram



3 Abbreviations

9HPT	9-Hole Peg Test
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
BSI	Boundary Shift Integral
CA	Competent Authority
CCTU	Comprehensive Clinical Trials Unit
CI	Chief Investigator
CK	Creatinine Kinase
CNS	Central Nervous System
CRF	Case Report Form
CFQ	Chalder Fatigue Questionnaire
CSF	Cerebrospinal Fluid
CSRI	Client Services Receipt Inventory
CTA	Clinical Trial Authorisation
CVLT-II	California Verbal Learning Test - Second Edition
DKI	Diffusion Kurtosis Imaging
DM	Diabetes Mellitus
DMD	Disease Modifying Drug
DMT	Disease Modifying Treatment
DSUR	Development Safety Update Report
DWI	Diffusion Weighted Imaging
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
GCIPL	Ganglion Cell and Inner Plexiform Layer
GCP	Good Clinical Practice
GM	Grey Matter
HMG-CoA	3-Hydroxy-3-methylglutaryl-coenzyme A
HTA	Health Technology Assessment
HRA	Health Research Authority
ICH	International Conference on Harmonisation
IDMC	Independent Data Monitoring Committee
IMP	Investigational Medicinal Product
IoN	UCL Institute of Neurology
ITT	Intention to Treat
LDH	Lactate Dehydrogenase
LFT	Liver Function Test
LSHTM	London School of Hygiene and Tropical Medicine
MFIS-21	Modified Fatigue Impact Scale – 21 Item (MFIS-21)
MHRA	Medicines and Healthcare products Regulatory Agency
MRI	Magnetic Resonance Imaging
mRS	Modified Rankin Scale
MS	Multiple Sclerosis
MS-CTN	Multiple Sclerosis Clinical Trials Network
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]
MSFC	Multiple Sclerosis Functional Composite
MSS	Multiple Sclerosis Society
MSSS	Multiple Sclerosis Severity Score
MSWS-v2	Multiple Sclerosis Walking Scale – version2
NAE	Notifiable Adverse Event
NFL	Neurofilament Light Chains
NODDI	Neurite Orientation Dispersion and Density Imaging
OCT	Optical Coherence Tomography
PBVC	Percentage Brain Volume Change
PI	Principal Investigator

PIS	Participant Information Sheet
PPE	Patient Public Engagement
PPI	Patient Public Involvement
pRNFL	Peripapillary Retinal Nerve Fibre Layer
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
QP	Qualified Person
RCT	Randomised Controlled Trial
REC	Research Ethics Committee
RNFL	Retinal Nerve Fibre Layer
RRMS	Relapsing Remitting Multiple Sclerosis
s-NFL	Serum Neurofilament Light Chain
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan

SAR	Serious Adverse Reaction
SD	Standard Deviation
SD-OCT	Spectral Domain Optical Coherence Tomography
SDMT	Single Digit Modality Test
SIEBA	Structural Image Evaluation, using Normalisation, of Atrophy
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.
- **Peripapillary 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.
- **Secondary progressive multiple sclerosis (SPMS):** Secondary Progressive MS (SPMS) is defined as the progressive accumulation of disability after an initial relapsing course. Disability progression can be defined as; Clinical: steadily increasing objectively documented neurological dysfunction/disability without unequivocal recovery; fluctuations and phases of stability may occur, or on Imaging (MRI): no standardized imaging measures of disease progression are currently established. Progressive disease (SPMS or PPMS) can be defined over 'n' time, e.g. 1 year, although there is currently no defined time. This is subdivided into; active and with progression, active but without progression, not active with progression, or not active and without progression (stable) progressive disease (SPMS or PPMS).[6, 7]

- **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 minimised.

5 Introduction

5.1 Background and Rationale

Multiple sclerosis (MS) is the most common 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.[8]

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,[9] 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.[10] The review concluded that there is no current 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 dimethyl fumarate (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.[11-13]

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, was 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.[14] 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 imaging (MRI) were done off-medication. This technique supports the contention that the noted reduction was due to a real effect on the 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.[15]

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% (SD 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% [SD 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.[16, 17]

This effect on brain atrophy rate is positive, given that longitudinal studies have shown a relation between atrophy progression and disability.[18] 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,[19] it remains the favoured outcome of regulators for trials,[20] 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 patients with SPMS with higher atrophy rates had on average greater progression of disability.[21] 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,[22, 23] 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.[20, 24]

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.[25-27] 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%.[25]
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.[28] 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.[16] 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, 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.[29-32]

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.[11, 32] Statins also block adhesion molecule expression and inhibit leucocyte migration through the blood-brain barrier.[29, 33, 34]

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[29, 35-37] and improve cerebrovascular haemodynamics,[38] outcomes which are likely to benefit PwSPMS. This is consistent with growing evidence that patients with later stage MS exhibit vascular,[12, 39] and brain parenchymal cell dysfunction.[36, 37, 40, 41] 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,[36, 42] resulting in attenuated cytotoxic damage to neurons and oligodendrocytes. In addition, statins may exert a neuroprotective effect by preventing glutamate-mediated excitotoxicity.[43] Statins also have a beneficial effect on vascular function[12] and are increasingly seen as vasculoprotective.[12, 44-47] As such, use of statins have been reported to improve vascular perfusion[38, 48] and maintain/enhance blood vessel function[49] 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[50-53] 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[54] and inhibiting endothelin-1.[55]

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,[4, 54, 55] 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.[56, 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.[4] 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 ratio active to placebo) in patients with 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 patients with SPMS, based on change in EDSS score compared to baseline.

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

**Participants presenting with an initial disability progression (based on EDSS score) 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.*

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 SPMS.

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:

Clinician Reported Outcome Measures

- A modified Multiple Sclerosis Functional Composite (MSFC) comprising:
    - Timed 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)
- Modified Rankin Scale (mRS)
- Brief International Cognitive Assessment For Multiple Sclerosis (BICAMS) comprising:
    - Symbol Digit Modalities Test (SDMT)
    - California Verbal Learning Test - II (CVLT- II)

- Brief Visuospatial Memory Test - Revised (BVMT-R)

Patient Reported Outcome Measures

- Multiple Sclerosis Impact Scale-29 v2 (MSIS-29v2)
- Multiple Sclerosis Walking Scale-12 v2 (MSWS-12v2)
- Modified Fatigue Index Scale - 21(MFIS-21)
- Chalder Fatigue Questionnaire (CFQ)

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 the 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:

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

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.

LOW DOSE (INITIAL):

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

OR

- Placebo (1x tablet taken once daily at night) *for 1 month* from Baseline (Month 0).

Dose escalation at Visit 3 (Month 1)

HIGH DOSE:

- 80mg Simvastatin (2x 40mg tablets taken once daily at night) *for 35 months* from Visit 3 (Month 1) to Visit 10 (Month 36), or Visit 11 (where needed to confirm initial disability progression).

OR

- Placebo (2x tablet taken once daily at night) *for 35 months* from Visit 3 (Month 1) to Visit 10 (Month 36), or Visit 11 (where needed to confirm initial disability progression).

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

- Visit 1 - Screening (-1 Month)
- Visit 2 - Baseline/Randomisation (Month 0)

- Visit 3 - (Month 1)
- Visit 4 – Telephone & Safety bloods (Month 3)
- Visit 5 - (Month 6)
- Visit 6 - (Month 12)
- Visit 7 - (Month 18)
- Visit 8 - (Month 24)
- Visit 9 - (Month 30)
- Visit 10 - (Month 36)*

**Participants with an initial disability progression based on EDSS score recorded at visit 10 will have an additional Visit 11 scheduled up to 6 months later. Participants will continue taking trial medication until Visit 11.*

Additional visit

- Visit 11 - (Month 42)

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 the 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).

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, conduct assessments and 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[6, 7] who fulfil the revised McDonald criteria for MS[3-5] in addition to ALL inclusion criteria and NONE of the exclusion criteria set out in 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. 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 1 point if EDSS score <6, or an increase of 0.5 point if EDSS score ≥6, or clinical documentation of increasing disability;
2. EDSS 4.0 - 6.5 (inclusive);
3. Aged 25 to 65 years old;
4. Patients must be able and willing to comply with the terms of this protocol;
5. 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 creatine kinase (CK) ≥3 x 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, clrithromycin, 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, elbasvir, grazoprevir, 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, dimethyl fumarate, teriflunomide, cladribine 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 Co-enrolment Guidance

Concurrent participation in another clinical trial of an investigational medicinal product or medical device is not allowed.

6.3.1.5 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 the 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: Full Blood Count (FBC), Liver Function Tests (ALT/AST, Alkaline Phosphatase), Creatine Kinase (CK), Lipid profile (HDL, LDL, Total Cholesterol, Triglycerides), Renal Function (potassium, sodium, creatinine, and eGFR), Glucose, Thyroid Function (TSH and Free T4).
- Urine samples from all women of child bearing potential (WOCBP) will be tested to determine pregnancy status.

If any of the screening blood test results are classified as clinically significant (CS), these should be repeated. The repeat safety blood result(s) should be used to assess eligibility. If the patient is considered to be eligible based on the repeat safety blood results they can proceed to the baseline visit (Visit 2 – Month 0).

The baseline visit (Visit 2 – Month 0) must occur within 1 month of the screening visit (Visit 1 – Month -1). If the baseline visit does not occur within this window (e.g. for CS blood test result(s) or logistical reasons) then the patient should be given a new participant identification number, be re-consented and re-screened using the new participant identification number, with safety bloods also redone.

If a patient is ineligible at screening due to other factors aside from CS blood test result(s), they can be re-screened at a later date where appropriate. If a patient is re-screened they should be given a new participant identification number, be re-consented and re-screened using the new participant identification number.

Prior to a baseline assessment commencing, **all** blood tests described above must be completed and deemed not clinically significant (NCS) within the previous month.

6.4 Intervention

6.4.1 Products

- Simvastatin
- Placebo

6.4.2 Treatment Schedule (Simvastatin/Placebo)

Participants will follow the treatment schedule outlined below (see Figure 1).

LOW DOSE (INITIAL):

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

OR

- Placebo (1x tablet taken once daily at night) *for 1 month* from Baseline (Month 0).

Dose escalation at Visit 3 (Month 1)

HIGH DOSE:

- 80mg Simvastatin (2x 40mg tablets taken once daily at night) *for 35 months* from Visit 3 (Month 1) to Visit 10 (Month 36), or Visit 11 (where needed to confirm initial disability progression).

OR

- Placebo (2x tablet taken once daily at night) *for 35 months* from Visit 3 (Month 1) to Visit 10 (Month 36), or Visit 11 (where needed to confirm initial disability progression).

6.4.3 Dispensing

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

- Visit 2 - Baseline/Randomisation (Month 0)
- Visit 3 - (Month 1)
- Visit 5 – (Month 6)
- Visit 6 – (Month 12)
- Visit 7 – (Month 18)
- Visit 8 – (Month 24)
- Visit 9 – (Month 30)

Additional dispensing

- Visit 10 (Month 36) - Participants with an initial disability progression based on EDSS scores recorded at this visit will receive additional supply of trial medication to ensure adequate provision until their additional visit (Visit 11). The timing of Visit 11 should be 6 months after

Visit 10, except where there is less than 6 months prior to the end of the trial (in which case Visit 11 may occur a minimum of 3 months after Visit 10).

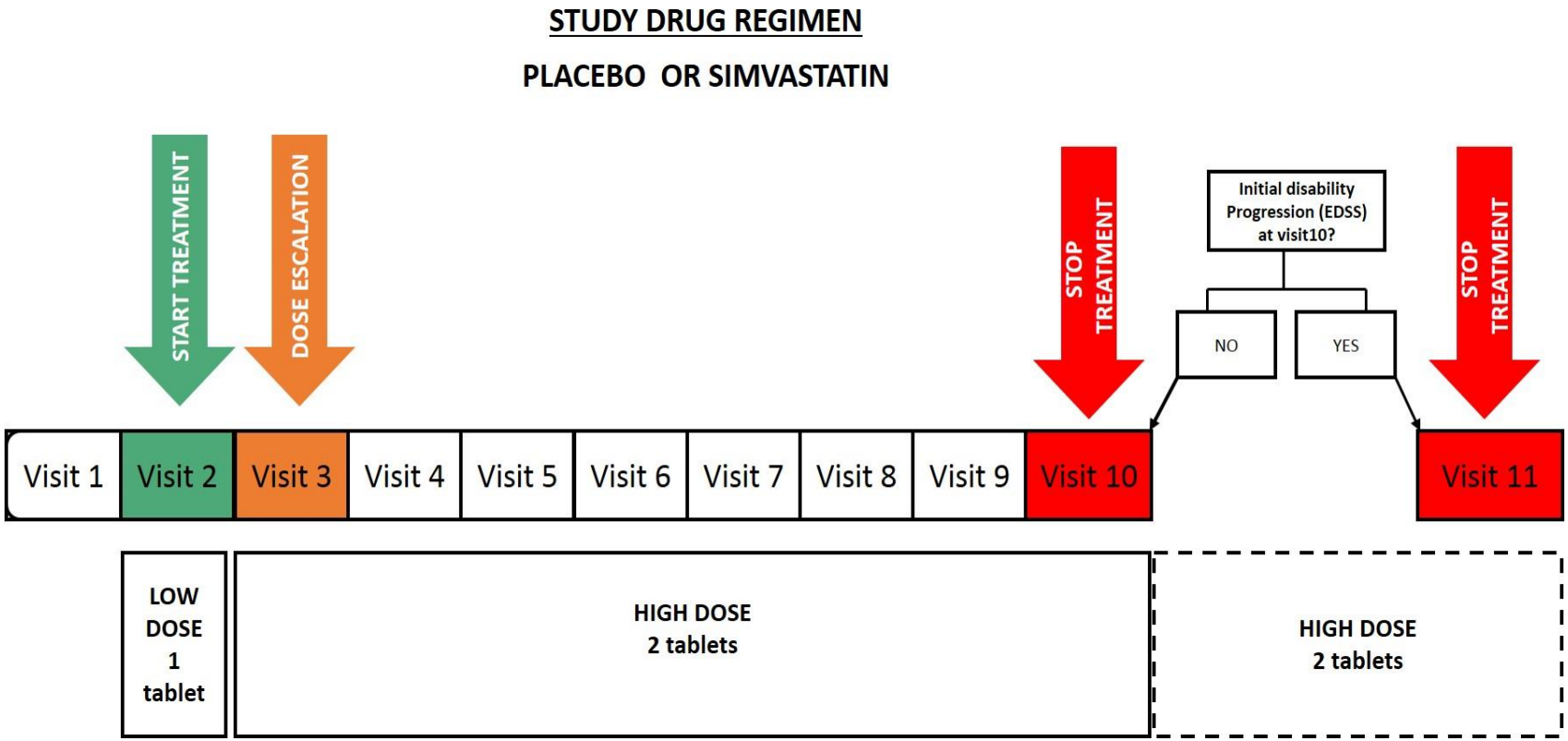


Figure 1: Dosing regimen for MS-STAT2. The schematic above depicts the dosing regimen for participants on trial medication (simvastatin or placebo) from baseline until end of follow up at Visit 10 (or additional Visit 11) when participants are required to stop trial medication and resume standard medical care. Participants with an initial disability progression based on EDSS score recorded at Visit 10 (Month 36) will continue to take trial medication for an additional 6 months until the end of follow up at their additional Visit 11 when they will stop the trial medication and resume standard medical care.

6.4.4 Dose Modifications, Interruptions and Discontinuations – Simvastatin/Placebo

6.4.4.1 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 trial medication.

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

Patients presenting with elevated ALT/AST levels ≥5 x ULN should have their trial medication discontinued. These patients should remain in trial and continue all clinic follow up with no trial medication. In cases where the elevated ALT/AST levels ≥5 x ULN have a clear non-causal relationship to the IMP, it is at the Principal Investigator's discretion as to whether the patient may be rechallenged.

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. Use of these drugs is contraindicated.

The risk of myopathy, incuding rhabdomyolosis, may be increased by concomitant administration of fusidic acid with statins and as such its use is contraindicated.

Simvastatin is a substrate of the Breast Cancer Resistant Protein (BCRP) efflux transporter. Concomitant administration of products that are inhibitors of BCRP (e.g., elbasvir and grazoprevir) may lead to increased plasma concentrations of simvastatin and an increased risk of myopathy; therefore 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.

There have been very rare reports of immune-mediated necrotizing myopathy (IMNM), an autoimmune myopathy, during or after treatment with some statins. IMNM is clinically characterized by: persistent proximal muscle weakness and elevated serum creatine kinase, which persist despite discontinuation of statin treatment; muscle biopsy showing necrotizing myopathy without significant inflammation; improvement with immunosuppressive agents (see section 4.4 of the current SmPC).

Patients experiencing myalgia with elevated levels of creatine kinase (CK ≥3 x ULN according to local practice) will continue to take trial 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 trial medication (80mg/2 tablets). Patients currently on low dose of trial medication (40mg/1 tablet) with persisting elevated CK levels (≥3 x ULN) will have their trial medication stopped.

If parameters assessed return to baseline levels in patients on low dose trial medication (40mg/1 tablet) within 6 months of monitoring, patients may be placed back on high dose trial medication (80mg/2 tablets). Where parameters return to baseline in patients who have stopped trial medication within 6 months of monitoring, patients may be rechallenged, initially at the low dose (40mg/1 tablet).

Patients experiencing myalgia with elevated CK levels (≥5 x ULN) should have their trial medication discontinued. These patients should remain in trial and continue all clinic follow up with no trial medication. In cases where the elevated CK levels ≥5 x ULN have a clear non-causal relationship to the IMP, it is at the Principal Investigator's discretion as to whether the patient may be rechallenged.

6.4.4.2 Dose Modification as a Result of Adverse Events

Patients on low dose trial medication (40mg/1 tablet) reporting serious adverse events (with the exception of MS related relapses) prior to dose escalation at Visit 3 (Month 1) may remain on the low dose (40mg/1 tablet) at the discretion of the clinical investigator.

However, this does not prevent a subsequent increase to high dose trial medication (80mg/2 tablets) once the adverse event/s reported are resolved, and following clinical evaluation by the clinical investigator.

If a participant cannot tolerate the low dose trial medication (40mg/1 tablet) due to frequency of statin related common side effects experienced, trial medication should be stopped. The patient should continue with all clinical follow up assessments. The participant can be re-challenged at a later time point with low dose of trial medication at the discretion of the clinical investigator.

Upon re-challenge, if the participant is unable to tolerate low dose trial medication, they should discontinue trial medication for the remaining duration of the trial. The participant should remain in trial follow-up and complete all clinical assessments.

If a participant cannot tolerate high dose trial medication (80mg/2 tablets), the dose should be reduced to the low dose (40mg/1 tablet). The participant can be re-challenged at a later time point with high dose trial medication (80mg/2 tablets).

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

Upon challenge on high dose (80mg/2 tablets) of trial medication on a second occasion, if participant cannot tolerate the high dose again, the investigator should consider reducing to low dose trial medication (40mg/1 tablet) for the remaining duration of the trial. All dose modification must be recorded on the CRFs and in the medical notes.

6.4.4.3 General rules for Dose Modification

It is acceptable for the patient to move between the high and low dose, and to temporarily discontinue trial medication according to the investigator's discretion.

Dose modifications can be made at trial visits, where there is a clinical need. Modification may also occur between visits, where the clinical trial team consider this necessary.

All dose modification should be recorded on the trial CRFs and documented in the patient's medical notes.

In cases where patients have a dose modification for logistical (non-clinical) reasons, e.g. inability to attend clinic to receive IMP, patients may restart on IMP initially at the low-dose (40mg/1 tablet), followed by increasing to the high-dose (80mg/2 tablets) where the participant can tolerate this regimen.

6.4.5 Accountability

The trial pharmacist at each participating site will be responsible for accountability of trial medication supplies. Accountability must include tracking all IMP received at site, dispensed to patients and destroyed as unused or expired.

Participants should return all bottles of unused IMP at each visit. The number of bottles returned should be recorded on the CRF. Pill counts of returned unused IMP are not required. Returned IMP can be destroyed as per standard local procedures.

6.4.6 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 card to record whether they have taken their trial medication since their last visit.

Compliance will also be assessed by direct questioning of participants at each follow up visit. The number of missed doses should be recorded on the CRFs. Site staff may wish to review the patients diary card to facilitate the conversation (if they have completed one), but the diary card is intended as an aide memoire for patients. Reasons for non-compliance will be sought and addressed where appropriate.

6.4.7 Concomitant Care

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

Should a Diease Modifying Drug (DMD) be newly licensed for SPMS during the course of the MS-STAT2 trial (e.g. siponimod) it is acceptable for patients already in the MS-STAT2 trial to commence treatment while continuing to participate. For patients who have not yet been randomised to the trial, it will be required to record whether the patient is taking newly licensed DMDs (≥2017) during the randomisation process.

6.4.8 Contraindicated Medications

The following drugs have been found to interact unfavourably with simvastatin (please refer to the current approved SmPC for a full 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
- Elbasvir
- Grazoprevir

- Grapefruit juice
- Alcohol abuse

If it is necessary for the patient to take one these contraindicated medications for a short period of time then the patient should discontinue trial medication temporarily. Once the patient has stopped taking the contraindicated medication they can resume trial medication according to the investigator's discretion. The patient should restart trial medication at the low dose (40mg/1 tablet) for 2 weeks, and can then increase to the high dose (80mg/2 tablets) if the low dose (40mg/1 tablet) is tolerated.

6.4.9 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 should discontinue trial medication for the remaining duration of the trial and no further supply of trial medication given.

To date, a few cases of Simvastatin overdose 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, symptomatic and supportive measures should be adopted.

6.4.10 Protocol Treatment Discontinuation

In consenting to the trial, participants are consenting to trial treatment, trial follow-up and data collection. However, an individual participant may stop treatment 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 unless they specifically withdraw their consent to do so.

6.5 Outcomes

6.5.1 Primary Outcome

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

placebo arms is based on change in EDSS score compared to baseline. Progression of disability is defined as an increase of at least 1 point if EDSS score at screening visit <6, or an increase of 0.5 point if EDSS score at screening visit is ≥6.

**Participants presenting with an initial disability progression (based on EDSS score) 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.*

The classical measurement tool and industry standard for measuring the progression of disability is the Expanded Disability Status Scale (EDSS).[5] It is based largely on neurological examination (with some history). The EDSS quantifies disability in eight functional systems (pyramidal, bowel, bladder, cerebellar, visual, brainstem, cerebral, and sensory) and allows neurologists to assign a functional system score (FSS) in each of these. The EDSS scale ranges from 0 to 10, and each 0.5 unit increment represents increasing levels of disability.

A 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.[58]

The initial screening EDSS assessment (Visit 1) will be conducted by the treating clinician, or delegate(s) of the clinical team. Subsequent EDSS assessments from the baseline visit (Visit 2 – Month 0) until the end of study will be conducted by the assessing clinician, or delegated member(s) of the clinical team who are independent to the treating clinician. The assessing clinician should not be familiar with the patient's medical or MS history. The EDSS will be measured at multiple time points at 6 monthly intervals (refer to section 6.6 - Participant Timeline) in clinic or by telephone.

The *initial* disability progression event is finalised as positive if it is confirmed ≥6 months later*. Participants with initial EDSS progression recorded at the last scheduled clinic visit (Visit 10 – Month 36) will have an additional appointment scheduled up to 6 months later (additional Visit 11) to confirm disability progression. The timing of the additional Visit 11 should be 6 months after Visit 10 (Month 36) but may be as soon as 3 months after Visit 10 (Month 36) depending on how close it is to the end date of the trial.

**Participants presenting with an initial disability progression (based on EDSS score) 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: increase in EDSS (0.5 point increase if baseline ≥6 or 1.0 point increase if baseline <6), ≥20% increase in time taken to complete the T25FW, or ≥20% increase in time taken to complete 9HPT. 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 (Month 36).

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

6.5.2.1 Clinician Reported Outcomes

- **A Modified Multiple Sclerosis Functional Composite (MSFC)** - Score comprised of 3 components, the Timed 25 Foot Walk (T25FW), 9 Hole Peg Test (9HPT) and Symbol Digit Modalities Test (SDMT). The SDMT will replace the Paced Auditory Serial Addition Test (PASAT), one of the 3 components in the Standard MSFC:

    - *Timed 25 Foot Walk (T25FW)* - The T25FW is a quantitative mobility and leg function performance test based on a timed 25 foot walk. 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 but this must be recorded.

    - *9-Hole Peg Test (9HPT)* - 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 9HPT 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 9 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)* – This is a brief measure of cognitive processing speed. It measures information processing speed for visually presented stimuli, but is self-paced, with at least equal reliability and sensitivity to the presence of worsening cognitive impairment. Participants are presented with a series of 9 symbols, each paired with a single digit in a key. When prompted, participants are asked to voice the digit associated with each symbol as quickly as possible for 90 seconds. The single outcome measure is the total number correct over the 90 second time span.

- **Sloan Low Contrast Visual Acuity (SLCVA)** - Sloan chart testing is a reliable, quantitative, and clinically practical measure of visual function. The Sloan flipchart consists of rows of grey letters on a white background (60 letters in total). The chart should be used with the room lights on and the patient should stand 2 metres away from the chart. Letters are displayed in decreasing size order from the top of the chart to the bottom. The patient is asked to read the letter with both eyes (binocular vision). If the patient normally wears vision aids (e.g. glasses or contact lenses) then these should be worn during the test. Testing will be conducted at 3 different contrast levels (100%, 2.5% and 1.25%). For each of the 3 contrast levels the chart will be scored based on the number of letters correctly identified out of 60 letters.

- **Brief International Cognitive Assessment For Multiple Sclerosis (BICAMS)** – This is a composite cognitive assessment tool comprising of the 3 components:

- *Symbol Digit Modalities Test (SDMT)* – This is a brief measure of cognitive processing speed. It measures information processing speed for visually presented stimuli, but is self-paced, with at least equal reliability and sensitivity to the presence of worsening cognitive impairment. Participants are presented with a series of 9 symbols, each paired with a single digit in a key. When prompted, participants are asked to voice the digit associated with each symbol as quickly as possible for 90 second. The score is the total 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 aloud a list of 16 words and patients are required to listen and recall as many of the items as possible. Participants are not required to recall items in any particular order. The number of items correctly recalled out of 16 is recorded. This constitutes one trial; a further 4 trials will completed. A total learning score out of 80 will be recorded.

- *Brief Visuospatial Memory Test- Revised (BVMT-R)* – This assessment tool is used to evaluate immediate visual learning. The examiner presents a visual display of 6 abstract designs (Form 1 of the BVMT-R) to the participant for 10 seconds. The abstract designs are then removed from view and the participant will be asked to draw as many designs as they can using a pencil. The designs must be drawn as accurately as they can and in the correct location. Each design scores 0 to 2 points depending on accuracy and location. Each trial can therefore score a maximum of 12 points. The drawn shapes must be scored using the BVMT-R Professional Manual. The learning trial will be repeated 2 more times using the same visual display of 6 abstract designs. The total score is the total number of points earned over the 3 learning trials.

- **Modified Rankin Scale (mRS)** – This is used to evaluate the degree of disability in daily activities for patients with neurological disability. Scores range 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 will have been preceded by a period of clinical stability of at least 30 days, with no other explanation other than MS. Grade 1 and 2 relapses will be excluded as AEs/SAEs/SARs and will not be reported as such, however grade 3 relapses should be reported as an SAE. Relapses should be documented on the Relapse Assessment Log CRF. Relapses will be graded as described in Table 1 below. The number of relapses and severity of each relapse will be compared between the treatment groups.

Table 1: Grading of MS related relapses

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

6.5.5.2 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 4 point response categories for each item: 'not at all', 'a little', 'moderately', and 'extremely'. Scores on the physical impact scale can range from 20 to 80 and on the psychological impact scale from 9 to 36. Lower scores indicate little impact of MS and higher scores indicate greater impact.

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

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

- **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. 7 items represent physical fatigue (items 1–7) and 4 represent mental fatigue (items 8–11).

- **Client Services Receipt Inventory (CSRI)** – Questionnaire that collects information on service utilisation, income, accommodation and other cost-related variables. Its primary purpose is to allow resource use patterns to be described and support costs to be estimated for health economics purposes.

6.5.5.3 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 the relevant outcome measures used as part of the MS-STAT2 trial. It is the responsibility of the PI to delegate tasks to appropriately trained members of site staff. PI delegated roles and responsibilities in this trial will be documented on 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.

6.6 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	**SCREENING**	**Month 0 BASELINE**	**Month 1**	**Month 3 TELEPHONE**	**Month 6**	**Month 12**	**Month 18**	**Month 24**	**Month 30**	**Month 36**	**Month 42**
Protocol window		**(within 1 month of screening)**	**(+/-1 week)**	**(+/-1 week)**	**(+/- 2 weeks)**	**(+/- 2 weeks)**	**(+/-2 weeks)**	**(+/-2 weeks)**	**(+/-2 weeks)**	**(+/-2 weeks)**	**(+/-2 weeks)**
Informed consent	X										
Inclusion/exclusion criteria review	X	X									
Demography	X										
Review of medical and MS history	X										
EDSS – Treating clinician	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[B]	X	X[C]	X	X[D]	X	X	X	X	X	X	X
Lipid profile	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
Randomisation		X									
Dispense trial medication		X	X		X	X	X	X	X	X[E]	
Trial medication - dose escalation			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	**SCREENING**	**Month 0 BASELINE**	**Month 1**	**Month 3 TELEPHONE**	**Month 6**	**Month 12**	**Month 18**	**Month 24**	**Month 30**	**Month 36**	**Month 42**
Protocol window		**(within 1 month of screening)**	**(+/-1 week)**	**(+/-1 week)**	**(+/- 2 weeks)**	**(+/- 2 weeks)**	**(+/-2 weeks)**	**(+/-2 weeks)**	**(+/-2 weeks)**	**(+/-2 weeks)**	**(+/-2 weeks)**
Clinician reported outcome measures											
EDSS – Independent Assesssing clinician		X[F]			X	X	X	X	X	X[FG]	X
9HPT		X			X	X	X	X	X	X	X
T25FW		X			X	X	X	X	X	X	X
SDMT[H]		X				X		X		X	
CVLT-II		X								X	
BVMT-R		X								X	
SLCVA		X				X		X		X	
mRS		X				X		X		X	
Patient reported outcome measures											
MSIS-29v2		X				X		X		X	
MSWS-12v2		X				X		X		X	
EQ-5D 5L		X			X	X	X	X	X	X	
CSRI		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] **Screening safety bloods** to include Full Blood Count (FBC), Liver Function Tests (ALT/AST, Alkaline Phosphatase), Creatine Kinase (CK), Lipid profile (HDL, LDL, Total Cholesterol, Triglycerides), Renal Function (potassium, sodium, creatinine, and eGFR), Glucose, Thyroid Function (TSH and Free T4). **All other safety bloods** to include Full Blood Count (FBC), Liver Function Tests (ALT/AST, Alkaline Phosphatase), Creatine Kinase (CK), Renal Function (creatinine and eGFR). Patients should **not** be fasted for safety bloods, including at screening visit.

[C] Repeat safety blood tests if any parameter measured at screening visit is clinically significant (CS).

[D] Visit 4 can be a telephone visit and patients can have safety bloods at their local GP surgery if they prefer. Blood tests should be requested from the GP by the research team at study site.

[E] Additional dispensing for participants with an initial disability progression (based on EDSS scores) at Visit 10.

[F] EDSS at Visit 2 (Baseline – Month 0) and Visit 10 (Month 36) must be an observed EDSS e.g. if the patient says they can walk 200m they must be observed to walk 200m.

[G] Additional visit 11 scheduled 6 months after visit 10 for participants with an initial disability progression at visit 10 (based on EDSS scores). Note that a small number of participants with less than 6 months to the end of trial may have Visit 11 scheduled between 3-6 months after Visit 10.

[H] SDMT to be recorded once at each indicated visit; the data from which should make up the modified MSFC and BICAMS.

Sub- studies (UCLH - lead site only)

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	**SCREENING**	**Month 0 BASELINE**	**Month 1**	**Month 3 TELEPHONE**	**Month 6**	**Month 12**	**Month 18**	**Month 24**	**Month 30**	**Month 36**	**Month 42**
Protocol window		**(within 1 month of screening)**	**(+/-1 week)**	**(+/-1 week)**	**(+/- 2 weeks)**	**(+/- 2 weeks)**	**(+/-2 weeks)**	**(+/-2 weeks)**	**(+/-2 weeks)**	**(+/-2 weeks)**	**(+/-2 weeks)**
MRI[I]		X[J]				X		X		X	
Biomarker - bloods sLDH , sNFL and free serum haemoglobin		X[k]				X		X		X	
OCT		X				X		X		X	
ABILHAND-23		X				X		X		X	
FAB		x				x		x		x	

[I] Female participants of childbearing potential should have a pregnany test prior to all MRI scans.
[J] Baseline MRI scan can occur at any time between Visit 1 –screening and Visit 2 – baseline providing the participant has been confirmed as eligible for the study.
[K] Baseline biomarkers sample can be takem at any time between Visit 1 – screening and Visit 2 – baseline providing the participant has been confirmed as eligible for the study.

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 according to the follow-up schedule defined in the protocol, providing they are willing. They should be encouraged and facilitated to remain in the trial, even if they are no longer taking 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 a participant specifically withdraws consent for their data to be used.

Participants who withdraw from the trial or stop trial treatment or follow up early will not be replaced. All randomised patients (except those who have specifically withdrawn consent) will be analysed according to the principles of 'intention to treat'.

6.6.2 Participant Transfers

If a participant moves from the area making continued follow up at their consenting site inappropriate, every effort should be made for them to be followed at another participating trial site. Written consent should be taken at the new site and then a copy of the completed CRFs for the participant should be provided to the new site. Responsibility for the participant remains with the original consenting site until the new consent process is complete. The original site remains responsible for resolving data queries relating to data collected prior to the point of transfer. Further detail on the transfer process is provided in the Patient Management Plan.

6.6.3 Loss to Follow-up

Every effort will be made to follow up participants. If a patient does not attend a clinic visit the site should attempt to contact the patient by telephone on at least 3 occasions.

If the patient is not willing or able to return to clinic for visits then a telephone assessment of EDSS should be completed at the relevant timepoints, and the patient reported outcome measures should be posted to the patient for completion.

If it is not possible to make contact with the patient by phone their next of kin or General Practitioner should be contacted. Only after all 3 of these avenues have been exhausted should the patient be deemed as lost to follow up.

6.6.4 Trial Closure

The end of the trial will be defined as the date of database lock. Database lock will only occur once the last patient's last clinic visit has occurred, data cleaning has been competed and all data queries are closed.

The REC and MHRA will be notified within 90 days of trial closing. 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 a 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 Visit 10 - Month 36, based on a review of all previous phase 3 trials in SPMS,[10] and the recent 3 year trials, which revealed 6 months confirmed progression rates of between 35-44%.[59-61] 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 call from a member of the research team at site to explain the trial and to ensure that the patient is likely to fulfill the general criteria to enter the trial. If the patient is likely to be suitable and interested in hearing more they will be sent a PIS.

Patients should be given at least 24 hours to consider the information in the PIS and discuss the trial with their family and friends. If they choose to take part in the trial they can then attend a screening visit.

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 trialists.

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 site. More importantly, it will provide the possibility of adopting strategies to maintain and increase patient recruitment across sites. Recruitment will be managed and reviewed by the MS-STAT2 Recruitment Management Group.

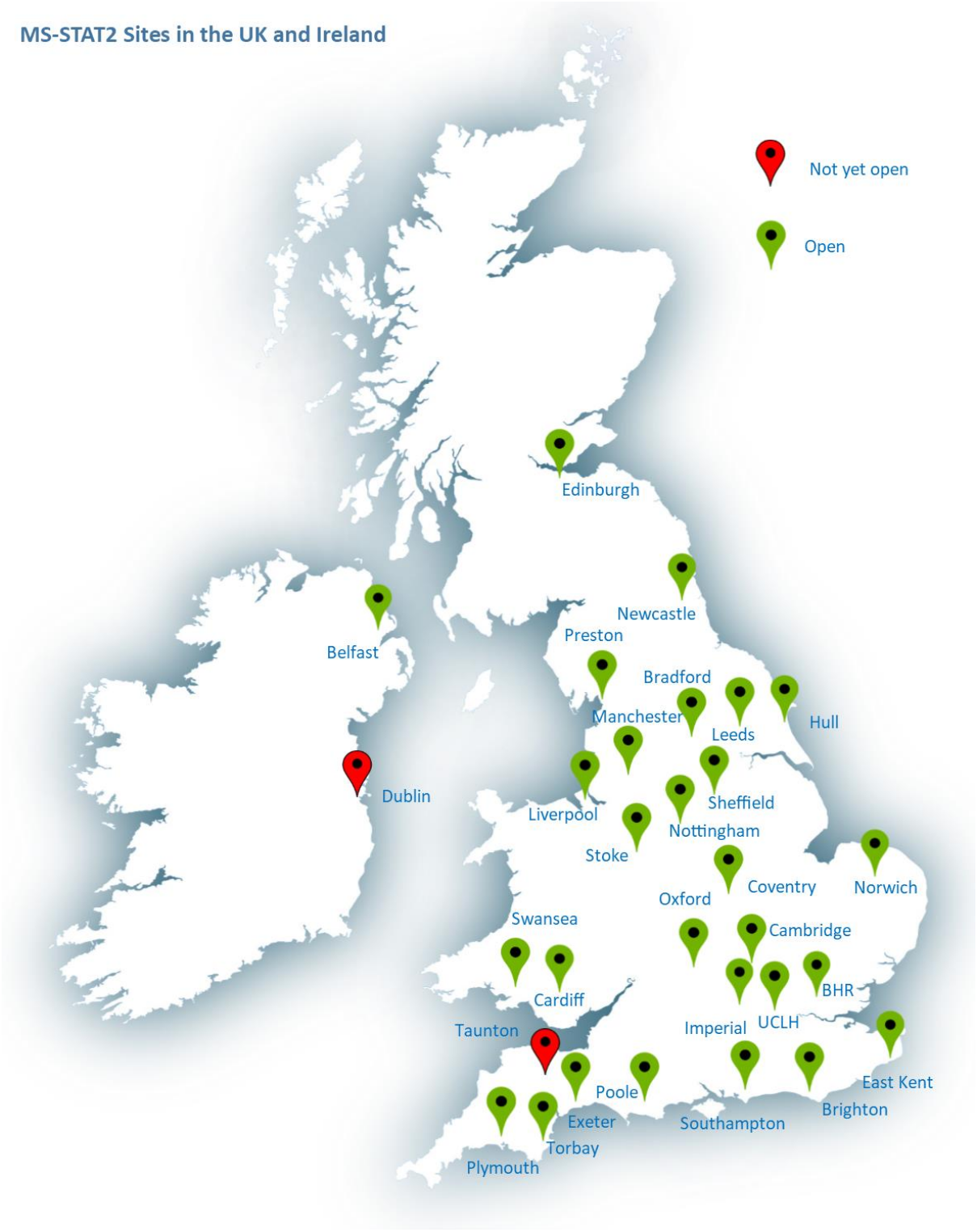


Figure 2: Map of expected MS-STAT2 sites

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 representatives and members of the UK MSS-PPI forum to maximise patient benefit. 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. This important PPI input should facilitate retention in the trial.

The UK MSS and forum have agreed to work closely with the research team to maximise participant retention by co-developing a tailored communication strategy 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. They will also explain the 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 team at local sites using the web-based randomisation service, Sealed Envelope. Each patient will be randomised using their unique participant identification number that was allocated sequentially at screening.

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

- Sex (Male / Female)
- Age (<45 years old / ≥45 years)
- 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.

The Trial Statistician will generate unique identifier 'kit codes' for every bottle of trial medication. The kit codes will be provided to Sealed Envelope and the Qualified Person (QP) at drug manufacturing site who will ensure that trial medication is labelled appropriately, and that the trial team and participants remain blind to treatment allocation. Drug will be dispensed at baseline (Visit 2 – Month 0) and subsequent clinic follow up visits. A delegated member of the site team will enter the patient's unique participant identification number into the SealedEnvelope.com website which will then provide the kit code of the trial medication to be dispensed. Sufficient number of trial medication will be provided to each site to ensure availability of adequately labelled kits for Pharmacy dispensing.

6.9.1.2 Allocation Concealment Mechanism

A sufficient number of labelled bottles of trial medication will be dispensed following randomisation at baseline (Visit 2 - Month 0), and at subsequent clinic follow up appointments where dispensing is due to take place (Section 6.4.2 Dispensing).

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

The investigator will provide details of the allocated kit code(s) assigned to each participant to enable dispensation of trial medication by the pharmacy department. Trial medication will only be dispensed upon receipt of the prescription form and printed copy of the confirmation from Sealed Envelope showing the allocated kit code(s).

A full accountability trail will be maintained from receipt of trial medication in pharmacy, up to the point of dispensing and destruction of undispensed trial medication. The site pharmacist will remain blinded to trial arm and trial medication (simvastatin/placebo) allocation.

6.9.1.3 Allocation Implementation

The responsibility for enrolling participants and prescribing trial medication 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 trial medication 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 and have the delegation of responsibility for a specific task signed off by the PI.

6.9.2 Blinding

The trial medication kit 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 medication packs occur in the correct manner. Adequate safeguards will be 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 allocation of kit codes to trial medication and 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 an emergency contact available out of hours 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 SealedEnvelope.com. It will occur for any participant experiencing a serious adverse event (SAE) for which the clinical management of the SAE will require the unblinding of the participant's treatment allocation. 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.

6.9.4 Unblinding Following Trial Closure

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

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 UK Data Protection Act 2018 and the EU General Data Protection Regulation 2016.

Clinical trial team members across all participating sites will receive adequate training on MS-STAT2 protocol and clinician led assessments used as part of the trial. The PI is responsible for ensuring site staff are adequately trained for the roles and responsibilities they are delegated. PIs remain responsible for ensuring appropriate staff training for all of the clinician led assessments. The EDSS is the primary outcome measure and should be completed by a clinician (or delegated staff member) with appropriate training, such as Neurostatus certification.

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 Procedures.

The source data for the trial is usually the patients' medical records. The preferred method of data collection is completion of paper case report forms (CRFs). Some of the clinician led assessments will require the completion of trial Worksheets. Summary scores will then be transcribed from the Worksheets on to the paper CRFs. Data from the paper CRFs should then be entered 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. All data should be verifiable from the patients' medical records except the patient reported outcome measures where the completed questionnaires are considered the source data.

Data collected	Source documentation
Clinician led outcome measures	MSFC (T25FW, 9HPT, SDMT), SLCVA, mRS, BICAMS (SDMT, CVLT-II, BVMT-R) CRFs and associated worksheets
Patient reported outcome measures	MSIS-29v2, MSWS-12v2, MFIS-21, CFQ, EQ5D-5L, CSRI CRFs
All other data	Medical records

Trial specific paper case report forms (CRFs) will be designed by the MS-STAT2 trial team. The approved MS-STAT2 CRFs will be provided to all participating sites. Data must be recorded on the MS-STAT2 paper CRFs prior to entry onto the database. The CRFs will not bear the patient's name, instead the patient's initials, date of birth and unique participant identification number will be recorded, and used for identification.

6.10.2 Data Management

A custom designed MACRO 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 an individual 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 UCL. The database will be password protected and only accessible to members of the MS-STAT2 trial team at CCTU, trained and authorised site staff 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 failures/missing data.

After completion of the trial the database will be retained on UCL servers for on-going analysis of secondary outcomes. All data storage will adhere to UK Data Protection Act 2018 and the EU General Data Protection Regulation (GDPR) 2016.

The MS-STAT2 Screening Log that links 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 Screening Logs will be stored securely by the sites for 10 years unless otherwise advised by UCL CCTU.

6.10.3 Non-Adherence and Non-Retention

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.

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 Independent Data Monitoring Committee (IDMC) and Trial Steering Committee (TSC). The results of the interim unblinded analysis will only be available to the IDMC. The SAP 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 summarised using summary statistics (mean, standard deviation, median, minimum, and maximum) by treatment group, and categorical variables will be presented using frequency distributions by treatment group.

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 summarised using summary statistics (mean, standard deviation, median, minimum, and maximum) by treatment group, and categorical variables will be presented using frequency distributions by treatment group.

Time to disability progression on the composite outcome (T25FW, 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 (Visit 2 – Month 0) to Visit 10 (Month 36) 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.

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 on high dose trial medication (80mg/2 tablets) for three years and have reported taking, on average, at least 90% of the pills. This average will be calculated using the self-reported number of missed doses 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.

6.10.6 Health Economic Analysis Plan/Evaluations

6.10.6.1 Cost Utility

A treatment that slows progression could represent a highly cost-effective use of NHS resources with the high costs of SPMS and very low cost of 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.

6.10.6.2 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.

6.10.6.3 Utility and Quality Of Life Data

QALYs will be estimated, 6 monthly, using the EQ-5D-5L using the area under the curve approach.[62, 63] 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,[64] the MSIS-29v2,[65] a condition-specific measure will be considered for estimating QALYs through methods available in the literature.[66]

6.10.6.4 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.

6.10.6.5 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.[67]

6.11 Data Monitoring

6.11.1 Independent Data Monitoring Committee

An Independent Data Monitoring Committee (IDMC) 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.

IDMC 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. Recommendations will be made by the IDMC 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 IDMC meeting will be convened to review recruitment against the STOP/GO progression criteria to allow the IDMC to advise 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 IDMC to review, ensuring that the trial team remain blinded to treatment allocation. Further details of the roles and responsibilities of the IDMC, 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 IDMC Terms of Reference (ToR).

6.11.2 Interim Analyses

The interim analyses will take place on an annual basis from project activation. Safety data will be presented to the IDMC in addition to interim analyses for review. At each formal interim analysis, 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 IDMC 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 IDMC may consider stopping for an efficacy based p-value of <0.001 for a difference between the treatment groups on the 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. An IDMC recommendation for early stopping for either safety or effectiveness will be possible for any interim analyses that take place while recruitment or follow-up is continuing.

These guidelines are not absolute stopping rules. The IDMC 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 IDMC 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. If the investigator attributes an AE solely to the patients MS symptoms or relapse it does not need to be reported as an AE on the AE Log. 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 medication administration. (This does not include pre-existing conditions recorded as such at baseline – as they are not detected after trial medication 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.

- Adverse events that do not meet the criteria to be considered 'serious' and deemed solely due to progression of the patient's SPMS condition

6.11.3.2 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 expected.

These are excluded as adverse events if they do not meet the seriousness criteria and are solely considered to be related to the particpant's multiple sclerosis (and therefore unrelated to the administration of the IMP). If all of these critera are met then the event does not need to be reported as an adverse event on the adverse event log.

For clarity, all adverse events considered by an appropriately delegated investigator as 'possibly,' 'probably' or 'definitely' a reaction to the IMP must be reported on the AE log, and where meeting the seriousness criteria, also an SAE report.

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

The 'seriousness' of each event should be assessed by the PI or delegated clinician. 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, except as outlined previously within this section.

The adverse event collection and reporting should begin from the date of informed consent. All AEs should be followed to resolution or stabilisation, or reported as SAEs if they become serious.

6.11.3.2.1 Relapses

Relapses will be graded as per Table 1 in S.6.5.2.1.

Grade 1 and 2 relapses that are not considered serious will not be counted as adverse events, but will be collated separately on the Relapse Assesment Log. Grade 3 relapses that result in hospitalisation meet the seriousness critera and should be reported as an SAE.

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 since their last trial visit to ensure that relapse is adequately documented. At the investigator/nurse's discretion unscheduled visits can be organised for participants to be assessed.

If a patient reports a relapse which is subsequently recorded as a grade 3 relapse, an SAE form should also be completed in addition to recording the relapse on the Relapse Assessment Log. 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 (≥3 x 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 trial medication, if a female participant becomes pregnant, or female partner of a male participant becomes pregnant then 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. Female participants should also not breast feed while on trial medication. 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 trial medication will be discontinued. Pregnant female participants will remain in the trial (receiving **no trial medication**) and complete all trial follow up assessments as per protocol.

The MS-STAT2 Pregnancy Notification Form must be completed, entered on the database 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 Notification Form (capturing information for up to 6 to 8 weeks after birth) should be updated, entered on the database and forwarded to the trial team at CCTU. Any congenital malformations and/or birth defects are reportable as an 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 female partner of a male participant becomes pregnant.

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

Pregnant partners of male participants will be followed up until birth, the MS-STAT2 Pregnancy Notification Form (capturing information for up to 6 to 8 weeks after birth) should be updated,

entered on the database and forwarded to the trial team at CCTU. Any congenital malformations and/or birth defects are reportable as an 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 (within 24 hours of the 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 5. 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 trial medication 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 medication). However, the influence of other factors may have contributed to the event (e.g. the participant's clinical condition or other concomitant treatment)	SAR
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 sponsor will assess the expectedness of the event. . If information on expectedness is provided by the investigator this should also be taken into consideration by the sponsor. An unexpected adverse reaction is one that is not reported in the current approved version of the IB or SmPC for the trial, or one that is more frequently reported or more severe than previously reported. The reference safety information is the current version of the SmPC (specifically section 4.8 'Undesirable effects'). Please refer to this 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 protocol section 6.11.3.6 Notifications).

6.11.3.6 Notifications

6.11.3.6.1 Notifications by the Investigator to CCTU

CCTU must be notified of all SAEs within 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 (a clinician named on the delegation of responsibilities list who is responsible for the participant's care) who will provide the grading and causality for 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 it 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 participant's trial number, month and year 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 email 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 their trial number on any test results.

6.11.3.6.2 CCTU Responsibilities

A medically qualified member of staff will be appointed as the sponsor clinical reviewer (usually the Chief Investigator (CI) or a medically qualified delegate), and will perform a clinical review of all SAE reports received. The sponsor clinical reviewer will complete the assessment of expectedness in light of the Reference Safety Information (RSI).

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 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 the 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 the 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. This acknowledges the risks associated with the conduct of the trial and includes 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,[68] 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 electronic Case Report Form (CRF) data on the trial database 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 (section 1.1) 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.

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 Committee

The Independent Data Monitoring Committee (IDMC) is the only oversight body that has access to unblinded accumulating comparative data. The IDMC 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 IDMC terms of reference. The IDMC 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 REC 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 and of the Participant Information Sheets (PIS) and consent form on local headed paper must be forwarded to the CCTU 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 bodies (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

Patients with SPMS will be fully informed of the 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 patients 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 (UCLH site only)

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

The 5 sub-studies are:

- Magnetic Resonance Imaging (MRI) sub-study [Appendix 1]
- Biomarker sub-study [Appendix 2]
- Optical Coherence Tomography (OCT) sub-study [Appendix 3]
- ABILHAND-23 sub-study [Appendix 4]
- FAB sub-study [Appendix 5]

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 be retained under the participant's identification number. Consent will also be sought from healthy participants (individuals with no Multiple Sclerosis diagnosis) to participate in the Biomarker sub-study only.

Withdrawal of a 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. Each participant will be assigned a unique trial Participant Identification Number (PIN). CRFs will record the patients initials and month/year of birth but not the patient's name. The only link between the PIN and the patient's name will be on the screening log kept at site and accessed only by the patient's direct clinical care team.

Data will be recorded on the CRFs and entered onto MS-STAT2's custom-designed database under this identification number. The database will be password protected and only accessible to members of the MS-STAT2 trial team at CCTU, trained and authorised site staff, 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 randomisation 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 the 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 the 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 (UCLH site only)

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. It will also 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.

4. ABILHAND-23 sub-study (Appendix 4) – Examine manual ability over the course of the trial period.

5. Frontal Assessment Battery (FAB) sub-study (Appendix 5) – for assessing change in executive dysfunction over the trial period.

9 Protocol Amendments

Protocol Version Number	Protocol Date	Summary of Changes
1.0	1- Aug- 2017	N/A
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 (IDMC) 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
3.0		1. New logo for UCL CCTU (front page) 2. Addition of reference to EU General Data Protection (GDPR) 2016 in section 1.1, 6.10 3. Inclusion criteria edited to remove: - that patients must have entered the secondary progressive stage 'at randomisation' - inclusion criteria for being male or female 4. Date of first enrolment amended to May 2018 (structured summary section 1.3)

		5. Addition of CSRI form as a secondary outcome measure (structured summary section 1.3) 6. List of sub-studies added to structured summary (section 1.3) 7. Protocol contributors (section 1.4.1), Trial sponsor and funders (section 1.4.2), Trial team (section 1.4.3), Trial Management Group (section 1.4.4), Trial Steering Committee (section 1.4.5), Independent Data Monitoring Committee (section 1.4.6), and Recruitment Management Group (section 1.4.6) edited due to staff changes and to add clarity and consistency. 8. References to DMEC changed to IDMC throughout 9. Inclusion criteria (section 1.3, 6.3.1.2 and 6.5.1) updated to remove reference to screening EDSS 10. Addition of new terms to Abbreviations (section 3) 11. Addition of new terms to Glossary (section 4) 12. Secondary objectives (section 5.2.2.2) updated for clarity, to add CSRI form, be clear which outcomes relate to Health Economics, and to remove SF-36 and ABILHAND-23 13. Visit numbers edited to refer to month numbers only (week numbers removed) 14. Eligibility criteria for individuals performing the interventions clarified and moved to section 6.5.5.3 15. Co-enrolment guidance (section 6.3.1.5) clarified 16. Blood samples taken during screening procedures (section 6.3.1.6) clarified 17. Clarification added that if screening blood tests are clinically significant these should be repeated prior to the baseline visit (section 6.3.1.6) 18. Clarification around re-screening patients under new patient identification numbers added (section 6.3.1.6) 19. Drug referred to as 'trial medication' consistently 20. Clarification around additional visit 11 added (section 6.4.2 and figure 1) 21. Accountability (section 6.4.5) updated to state patients should return all unused trial medication at each visit, and that destruction can occur as per standard local policy 22. Compliance and adherence (section 6.4.6) updated to clarify that the diary card will record doses trial medication taken since the last visit 23. Concomitant care (section 6.4.7) updated for clarity in relation to statins and DMDs 24. Contraindicated medications (section 6.4.8) updated regarding re-starting trial medication after taking a contraindicated medication for a short period of time 25. Overdose (section 6.4.9) updated to state that patients who overdose should discontinue trial medication but remain in follow up and not be withdrawn 26. Protocol treatment discontinuation (section 6.4.10) updated to state that patients should remain in follow up unless they specifically withdraw consent to do so 27. Primary outcome (section 6.5.1) updated to clarify when the EDSS should be done by a treating or assessing clinician 28. SLCVA, CVLT-II, BVMT-R (section 6.5.2.1) guidance updated for clarity and to specify which subsets of the CVLT-II and BVMT-R are being completed as part of BICAMS

		29. Relapse assessment guidance (section 6.5.1) updated to be clear that grade 3 relapses should be reported as an SAE 30. Participant timeline (section 6.6) updated to increase the number of timepoints the 9HPT and T25FW completed at 31. Participant timeline (section 6.6) updated to reduce the number of timepoints the SLVCA, mRS, MSIS-29v2, MSWS-12v2, EQ-5D-5L and Lipid profile completed at, and to remove the SF-36 32. Loss to follow-up (section 6.6.3) updated to include methods to attempt to contact patients before considered lost to follow up, and the use of telephone assessment EDSS and posted patient reported outcome measure for patients that are unable to attend clinic 33. Participant timeline (section 6.6) updated to reduce the number of timepoints bloods are taken for the biomarkers sub-study 34. Additional footnotes added to participant timeline (section 6.6) for clarity 35. Participant timeline (section 6.6) updated to move ABILHAND-23 to sub-study section as now being using only at the lead site (UCLH) as a sub-study 36. Participant timeline (section 6.6) additional footnote added regarding timing of baseline MRI scan for MRI sub-study 37. Early stopping of follow up (section 6.6.1) updated in regards to intention-to-treat 38. Participant transfers (section 6.6.2) updated in regards to responsibility for resolution of data queries 39. Loss to follow-up (section 6.6.3) updated to clarify procedures for preventing loss to follow up 40. Recruitment (section 6.81) updated to specify when PIS should be provided to potentially interested patients 41. Figure 2 updated with a more accurate map of expected sites 42. Assignment of intervention (section 6.9) updated to clarify that the patient identification number will be the screening number, and the patient will be randomised under this number. References to drug identification codes replaced with 'kit codes' 43. New section 6.9.4 added for unblinding following trial closure 44. Data collection methods (section 6.10.1) updated regarding training required for EDSS as the primary outcome measure. 45. Data collection methods (section 6.10.1) updated clarifying which documentation is considered as source documentation 46. Non-adherence and non-retention (section 6.10.3) updated in regards to how compliance is assessed 47. Statistical analysis plan (section 6.10.4.1) updated to clarify that only the IDMC will see the result of interim unblinded analyses 48. Analysis population and missing data (section 6.10.5) updated to clarify that compliance will be assessed on reported missed doses 49. Health economics (section 6.10.6) sections numbered for clarity

		50. Health Economics (section 6.10.6.2) updated to remove that an application will be made for Hospital Episode Statistics 51. Timing of interim analyses (section 6.11) updated due to annually 52. Data monitoring for harm (section 6.11.3) updated in regard to requirements for reporting AEs solely related to MS 53. Other notifiable AEs (section 6.11.3.3) updated to include reporting pregnancies for female partners of male participants 54. Notification of SAEs by investigators to CCTU (section 6.11.3.6.1) updated to state month and year of birth will be collected not full date of birth 55. CCTU responsibilities for clinical review of SAEs (section 6.11.3.6.2) clarified 56. Confidentiality (section 7.6) updated to provide additional information 57. Appendix 1 MRI sub-study, Appendix 2 Biomarkers sub-study, Appendix 3 OCT sub-study have had eligibility criteria added 58. Appendix 1 MRI sub-study eligibility (section 1) state that patients that cannot tolerate gadolinium can still participate without gadolinium 59. Appendix 1 MRI sub-study the secondary outcomes (section 5.1.2) have been updated to correct the minimisation variables 60. Appendix 1 MRI sub-study secondary outcomes (section 7.1.2) clarified 61. Appendix 2 Biomarkers sub-study data collection for healthy donor (section 1.3) updated to state initials not name will be collected 62. Appendix 2 Biomarkers sub-study Aims (section 2) updated to specify exactly what samples will be tested 63. Appendix 2 Biomarkers sub-study objectives (section 5) clarified 64. Appendix 2 Biomarkers sub-study outcomes (section 6) updated to clarify outcomes and include additional exploratory outcome 65. Appendix 4 ABILHAND-23 sub-study added
4.0	22-Jul-2019	1. Exclusion criteria updated to exclude patients taking elbasvir, grazoprevir and recent cladribine (structured summary section 1.3, section 6.3.1.3) 2. Exclusion criteria updated to state dimethyl fumarate instead of just fumarate (structured summary section 1.3, section 6.3.1.3) 3. Structured summary (section 1.3) updated primary outcome should be change in EDSS in comparison to baseline visit (not screening visit) 4. Creatinine kinase corrected to creatine kinase throughout 5. Laboratory abnormalities (section 6.4.4.1) updated to include further information about myopathy 6. Laboratory abnormalities (section 6.4.4.1) updated to provide greater clarity on the dose modification strategy due to AEs and other reasons. 7. Contraindicated medications (section 6.4.8) updated to include elbasvir and grazoprevir

		8. Trial closure (section 6.6.4) definition of end of trial updated 9. SLCVA guidance (section 6.5.2.1) updated to state that the SLVCA should only be tested binocularly. 10. Participant timeline (section 6.6) updated to remove the FAB. The FAB will only be completed at baseline and visit 10 at UCLH as a separate sub-study 11. Participant timeline (section 6.6) footnote B edited to state that safety bloods do not required fasting and to remove potassium and sodium for safety bloods test except at screening 12. Map (section 6.8.1) updated to show currently open sites 13. Clarification that only AEs which are both non-serious AND can be attributed solely to the progression of the patient's SPMS condition can be excluded from reporting (section 6.11.3.2). 14. Section 6.11.3.5.2 updated from CTCAE V4 to CTCAE V5 15. Section 6.11.3.5.4 updated in relation to sponsor assessing expectedness for SAEs 16. Section 6.11.3.6.1 updated to remove investigator assessing expectedness for SAEs 17. Section 6.11.3.5.2 updated in relation to sponsor assessing expectedness for SAEs 18. References corrected for minor duplication and entered into Endnote system. 19. Appendix 2 Biomarkers sub-study aims (section 2) updated, frozen serum and plasma samples will be stored to allow future analysis of novel biomarkers. Order of paragraphs changed to improve fluidity of reading. 20. Appendix 3 OCT sub-study updated to include Sloan Low Contrast (100/2.5/1.25%) assessment for OS/OD (removed from main study for other sites). 21. Appendix 5 added for FAB sub-study

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11 Appendices

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

1 Eligibility Criteria

The eligibility criteria for the MRI Sub-Study are identical to the inclusion and exclusion criteria of the main MS-STAT2 trial.

If patients cannot tolerate gadolinium contrast they are still able to participate in the MRI sub-study and have the MRI scans without gadolinium.

The MRI Sub-Study is only being conducted at a single site, UCLH, which is the lead site for the MS-STAT2 trial.

2 Aim

This study will aim to confirm the effect of simvastatin on whole brain atrophy over a 3 year period. It will examine effect of simvastatin on other important measures of neurodegeneration including grey matter, deep grey matter (in particular the thalamus) and spinal cord atrophy. 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 SPMS. These could form the basis for exploratory analysis as summarised below:

1. To confirm the simvastatin-related reduction in whole brain atrophy progression, which was detected in MS-STAT[14], 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.

3 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[20] 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).[20] Compared with age-matched healthy controls, there is a greater decrease in brain volume over time in SPMS than healthy controls and patients with RRMS, which can be quantified by MRI. On average there is 0.5-1% loss of brain volume per year in SPMS, as opposed to 0.1-0.2% per 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% per year.[15]

In a previous phase 2 double-blind, placebo-controlled trial (MS-STAT), the effects of 80mg simvastatin per day was investigated in 140 patients with SPMS by comparing the annualised rate of whole-brain atrophy between treated and placebo patients. The study 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% per year),[14] demonstrating that brain atrophy may have the same pivotal role in SPMS trials as lesion activity in RRMS trials.

3.1 Whole Brain Atrophy

Whole brain atrophy has been measured with a variety of methods. The most popular tools are the BSI (Boundary Shift Integral)[75, 76] and SIENA (Structural Image Evaluation, using Normalisation, of Atrophy),[77] 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.[14]

More recently, trials have started to calculate PBVC from SIENA applied to 3D T1 volumetric scans.[78] 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.

3.2 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.[15] 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,[79, 80] and explains physical disability better than white matter atrophy.[81, 82] 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% per year vs. 0.12% per 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,[83] including cognitive dysfunction.[84] 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.[22] The thalamus is the largest of the deep grey structures and deep grey matter 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% per year).[22, 82] 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.[85]

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.[86-88] It has been demonstrated that NODDI has higher sensitivity and specificity than standard DTI.[89]

4 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 time points;

- Baseline Visit (Month 0)*
- Visit 6 (Month 12)
- Visit 8 (Month 24)
- Visit 10 Month 36)

*The baseline scan can be taken at anytime between Visit 1 – screening and Visit 2 – baseline, providing the participant has been confirmed as eligible for the MS-STAT2 study and eligible for the MRI sub-study.

4.1 Outcome measures

4.1.1 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[69]).

The use of 3D pulse sequences and automated image segmentation methods are recommended in longitudinal and treatment studies of MS.[90]

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.[77] The two brain images are then aligned to each other (using the skull images to constrain the registration scaling);[91, 92] both brain images are resampled into the halfway space between the two. Next, tissue-type segmentation is carried out,[93] 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.

4.1.2 Secondary Outcome Measures

1. Brain grey matter 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.[94] Then a lesion-filling technique will be applied to reduce the impact of white matter lesion misclassification on GM volume.[95] 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/).[96, 97]

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**.**[80]

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.[96-98] Changes in T2 total lesion load will be automatically calculated using T1 and FLAIR images (using the Bayesian Model Selection (BaMoS) method)[94] 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.

6 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 people with SPMS[15, 99] which are very similar to the annualised rate of whole brain atrophy measured using BSI of 0.584% per year in the placebo group of the MS-STAT trial.[14] Kapoor reported that the rate of change in PBVC was 0.59% per year in 56 SPMS patients in the placebo group of the Lamotrigine clinical trial[22] and De Stefano reported mean PBVC of 0.64% per year (SD 0.68%) in a cohort of 139 patients with SPMS.[15] 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,[100] 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 a standard deviation (SD) of 0.68% per year over 2 years, it is predicted that the SD of PBVC will be 0.63% per year over 3 years.

It is assumed that the mean annualised rate of PBVC will be 0.64% per year in the placebo group and 0.3648% per year in the Simvastatin treatment group, reflecting the 43% per year reduction previously seen in the MS-STAT trial. For analysis using a mixed effect model of the repeated measures of directly measured change[101] 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.

7 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 summarised using summary statistics (mean, standard deviation, median, minimum, and maximum) by treatment group, and categorical variables will be presented using frequency distributions by treatment group. A detailed statistical analysis plan (SAP) will be 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).

7.1 Statistical Methods - Outcomes

7.1.2 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[101] with adjustment for the baseline normalised brain volume and 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)] and study site included as a random slope. 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.

7.1.2 Secondary Outcomes

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

Rate of change in 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 (male / female), age (<45 / ≥45), baseline EDSS (4.0-5.5 / 6.0-6.5) and newly licenced DMD for SPMS (≥2017) (Yes / No)] and baseline value of the outcome of interest. Study site will be included as a random effect.

2. **Cross-sectional cord area**

The rate of change in cross-sectional cord area will be compared between the treatment groups using a mixed effects linear regression model for repeated measures, adjusting 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)] and baseline value. Study site will be included as a random effect.

3. **Changes in T2 lesion load**

Changes in T2 lesion volume will be compared between the treatment groups using a mixed effects linear regression models for repeated measures, adjusting 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)]. Study site will be included as a random effect.

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 follow-up.

APPENDIX 2: BIOMARKER SUB-STUDY

1 Eligibility Criteria for MS-STAT2 Pariticipants

The eligibility criteria for the Biomarkers Sub-Study are identical to the inclusion and exclusion criteria of the main MS-STAT2 trial.

The Biomarkers Sub-Study is only being conducted at a single site, UCLH, which is the lead site for the MS-STAT2 trial.

2 Eligibility Criteria for Healthy Donors

2.1 Inclusion Criteria

1. Aged 25 to 65 years old.
2. Written informed consent provided.

2.2 Exclusion Criteria

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

2.3 Data Collection - Healthy Donors only

Basic information will be collected - initials, date of birth, gender, ethnicity, medical history, and concomitant medications.

3 Aim

There are currently no fluid 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. Additionally, the mechanisms by which simvastatin may work to slow disability progression in SPMS are currently unclear, and warrant further investigation.

The aim of this sub-study is to evaluate the effect of simvastatin on blood neurofilament light chain (NFL), markers of haemolysis (serum levels of lactate dehydrogenase (LDH), plasma free haemoglobin (PHB), serum haptoglobin (HAP) and red cell osmotic fragility) and to conduct further immunological investigations on blood samples to further investigate the mechanisms by which simvastatin may work in SPMS. Comparison will be made to samples from healthy age and sex-matched controls.

Both frozen serum and plasma samples will be stored to allow future analysis of novel biomarkers when they become available.

4 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.[102, 103]

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.[104] 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 tetrahydrocannabinol (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.[61] 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 on serum neurofilament light chain (sNFL) as a read-out for axonal damage and hence neuroprotection. We aim to determine whether serum levels of NFL, a surrogate marker 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 of whether erythrocytes are abnormally fragile in patients with SPMS, quantified using osmotic fragility and metrics of haemolysis, and whether we can detect immunological changes between treatment groups. Results will be compared with samples from healthy age and sex-matched controls.

5 Rationale

Neurofilament light chain as a marker of axonal damage

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.[105-109] 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.[109, 110] 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.[110] 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.[111] 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.[112] 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.[113] 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.[114]

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.[113]

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, $p<0.00003$).[115] 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.

Haemolysis in MS

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 changes in two protein peaks that were correlated with brain atrophy rates.[116] 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 changes in free serum haemoglobin 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 in previous studies[117, 118] 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 central nervous system (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.

Immunological mechanisms of simvastatin

Pre-clinical studies in animal models of MS identified possible immunomodulatory functions of simvastatin. Observations included a reduction in MHC class II antigen presentation, reduced T-cell activation, a switch from Th1 to Th2 proliferation phenotypes and a reduction in leukocyte adhesion molecules. Earlier clinical studies have also suggested possible changes on MRI metrics of inflammatory activity. In the STAyCIS study of simvastatins in CIS, a 50% reduction in new T2 lesions was noted. In MS-STAT, a non-significant reduction in new or enlarging T2 lesions was again noticed. In the MS-STAT study, however, no significant differences were noticed between treatment groups on a panel of serum immunological markers. By performing further immunological investigations in the MS-STAT2 study, we aim to clarify the potential immunological mechanisms of simvastatin.

6 Study Objectives

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

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

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

3. Whether intravascular hemolysis and thereby release of LDH and haemoglobin into serum/plasma can be reduced by simvastatin;

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

5. The phenotype and function of the innate and adaptive immune system before and after simvastatin treatment.

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

1. Does simvastatin prevent axonal damage in SPMS?

   The primary outcome will be the mean serum NFL levels.

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

   The primary outcome will be mean serum LDH levels, which will be compared between the treatment groups.

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

   The primary analysis will be examining the correlation between serum LDH and NFL, and clinical disability (EDSS) and MRI measures (brain atrophy rates) to look for further insights into pathophysiology of SPMS.

4. 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?

5. Does treatment with simvastatin result in changes in the phenotype and function of the innate or adaptive immune system?

7 Outcomes

7.1 Primary outcomes

1. The relative difference in serum NFL levels at 36 months between the simvastatin and placebo treated arms.
2. The relative change in serum LDH levels at 36 months between the simvastatin and placebo treated arms.
3. Erythrocyte fragility measurements, comparing SPMS to healthy controls.

7.2 Secondary outcomes

1. The relative change in serum NFL levels from baseline to 36 months, 12 months to 24 months, and 24 months to 36 months.
2. The relative reduction of serum LDH levels from baseline to 36 months, 12 months to 24 months,

and 24 months to 36 months.

7.3 Exploratory outcomes

1. To determine the correlation between serum NFL levels, EDSS and MRI brain atrophy measures. The association between serum NFL and EDSS will be examined across both treatment groups and within each group at baseline, 12 months, 24 months, and 36 months. The association between serum NFL levels at the follow-up visit and MRI brain atrophy between baeline and each follow-up visit will be examined.

   Our rationale 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.[114] 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.[113] Amor showed statistically significant reductions in NFL antibodies at baseline and 24 months in MS patients.[111] 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. The association between serum LDH and EDSS will be examined across both treatment groups and within each group at baseline, 12 months, 24 months, and 36 months. The association between serum LDH levels at the follow-up visit and MRI brain atrophy between baseline and each follow-up visit will be examined.
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.
4. To determine the degree of intravascular haemolysis by measuring free haemoglobin and serum haptoglobin at baseline, 12 months, 24 months and 36 months. In conjunction with LDH levels, these results may provide greater insight into the potential role of intravascular haemolysis in the pathogenesis of SPMS.
5. To study changes in the phenotype and function of the innate and adaptive immune system before and after initiation of simvastatin treatment, comparing with patients on placebo treatment and healthy controls.
6. To store frozen serum and plasma samples to allow future analysis of novel biomarkers when they become available.

8 Assessments

Blood samples will be taken at the following time points:

- Pre-treatment (Either screening or baseline study visit, Month -1 to month 0). Healthy controls will not be iniated on any treatment, and hence may enter the biomarker substudy, giving their first blood sample, at any time point during the study.
- Visit 6 (Month 12, or equivalent for healthy control)
- Visit 8 (Month 24, or equivalent for healthy control)
- Visit 10 (Month 36, or equivalent for healthy control)

9 Analysis Plan

Primary analysis will be by intention-to-treat, but per protocol analyses will also be reported. A detailed statistical analysis plan will be developed.

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

1 Eligibility Criteria

The eligibility criteria for the OCT Sub-Study contain all the inclusion and exclusion criteria of the main MS-STAT2 trial. Additionally, participants with ophthalmological diseases-or causes of vision loss or retinal damage not attributable to multiple sclerosis or high refractive errors (>±6) were also excluded.

The OCT Sub-Study is only being conducted at a single site, UCLH, which is the lead site for the MS-STAT2 trial.

2 Aim

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

3 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 (RNFL) and decreased macular volume as progressive MS ensued (as well as relapsing remitting MS (RRMS)).[119]120

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 RRMS.[120, 121] 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 RRMS.[122]

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.[123-127] 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.[128]

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.[129] 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.[130] 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).[131]

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.[132]133

Inclusion of serial SD-OCT in MS-STAT2 will elucidate the extent and evolution of both RNFL thinning, GCIPL, 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 SPMS.

MS patients have significantly lower low constrast visual acuity than healthy controls. Low contrast visual acuity is often assessed using the Sloan visual charts. Deficits in Sloan low contrast visual acuity (SLCVA) are found independently from the clinical occurrence of optic neuritis, even when high contrast visual acuity is normal. SLCVA correlates with RNFL and GCIPL thickness on OCT, as well as with clinical and MRI outcome measures in MS.[133]

4 Rationale & Risks/Benefits

SPMS 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 is minimal.

5 Study Objectives

1. To use OCT to measure:
    a. Retinal nerve fibre layer thickness
    b. Retinal ganglion cell layer thickness
    c. Macular thickness and volume

2. Evaluate the sensitivity of OCT to detect on-going retinal neuroaxonal loss in SPMS, 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.

6 Study Design

OCT 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, retinal ganglion cell layer, 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 20um horizontally. This data is processed and displayed as 2D or volumetric grey scale or false colour image.

Spectral domain OCT (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 3-10µm. There is also a significant reduction of artefact from ocular movements.

7 Assessments

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 (Month 0)
- Visit 6 (Month 12)
- Visit 8 (Month 24)
- Visit 10 (Month 36)

In the commencement of each OCT measurement, in addition to the trial protocol SLCVA testing, more detailed visual acuity testing will be performed using an Early Treatment Diabetic Retinopathy Study (ETDRS) illuminator cabinet. SLCVA 100%, 2.5% and 1.25% will be consecutively tested initially binocularly, and after that monocularly for each eye. If the patient normally wears vision aids (e.g. glasses or contact lenses), then these should be worn during the test. Additionally, when testing the right and left eye separately, an occluder should be used to cover the other eye, and the right and left eyes should be tested both with and without a pinhole occluder. The best corrected visual acuity should be recorded (with or without the pinhole occluder).

8 Outcomes

8.1 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

9 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 [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)], 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.

APPENDIX 4: ABILHAND-23 SUB-STUDY

1 Eligibility Criteria

The eligibility criteria for the ABILHAND-23 Sub-Study are identical to the inclusion and exclusion criteria of the main MS-STAT2 trial.

The ABILHAND-23 Sub-Study is only being conducted at a single site, UCLH, which is the lead site for the MS-STAT2 trial.

2 Aim

To determine whether simvastatin has an effect on manual ability in SPMS using the ABILHAND-23 questionnaire in a longitudinal study.

3 Background

The ABILHAND-23 questionnaire is a measure of manual ability as perceived by the patient. The 23 item scale measures an individual's ability to manage daily activities which require the use of the upper limbs. The ABILHAND-23 is administered on an interview basis (patients do not actually complete the activities). Patients are asked to rate their reception of difficulty for each activity on a 3-level response scale. The 3-level response scale includes 'impossible', 'difficult' and 'easy'.

The activities of the ABILHAND questionnaire are presented in random order to prevent any systematic effect. Ten different random orders are used, and the rate selects the next one of the 10 random orders for each new assessment, no matter which patient is tested.

4 Rationale & Risks/Benefits

The application of the ABILHAND-23 questionnaire will provide a subjective measure of activities of daily living in relation to manual ability in an SPMS population of EDSS scores of 4.0 to 6.5 (inclusive). Doing so would support the clinician-led and patient-reported outcome measures of the MS-STAT2 trial.

Due to the nature of patients with SPMS, it is possible that the questionnaire may not be completed due to patient factors.

5 Assessments

The ABILHAND-23 questionnaire will be given to all patients that have consented to participate in the ABILHAND-23 sub-study. The questionnaire will be completed at these time points:

- Baseline (Month 0)
- Visit 6 (Month 12)

- Visit 8 (Month 24)
- Visit 10 (Month 36)

6 Outcomes

6.1 Outcome measures and analysis

The raw data will be converted into a score by the ABILHAND website. The ABILHAND specific to chronic stroke patients will be used. This can be accessed via the following link:

http://www.rehab-scales.org/abilhand-rasch-analysis-chronic-stroke.html

Raw data from the completed ABILHAND-23 questionnaire will be entered into the website. Any missing answers on the ABILHAND-23 quetsionnaire will be recorded in the '?' column on the website. The Rasch analysis will be run and an ABILHAND Evaluation Report will be produced. This report provides the patient evaluation results. The primary outcome will be the Patient Measure which is measured in logits (ranges from -10 to 10).

7 Primary Analysis

The ABILHAND Patient Measure summary statistics (mean, standard deviation, median, minimum, and maximum) will be presented by treatment group.

The mean value of the Patient Measure at Visit 10 (Month 36) will be compared between groups using a mixed effects linear regression model for repeated measures, adjusting for the baseline value and 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)]. Site will be included as a random effect. If parametric assumptions for the linear regression model are substantially violated, then non-parametric methods (such as bootstrapping) will be used for inference.

APPENDIX 5: Frontal Assessment (FAB) SUB-STUDY

1 Eligibility Criteria

The eligibility criteria for the FAB Sub-Study are identical to the inclusion and exclusion criteria of the main MS-STAT2 trial.

The FAB Sub-Study is being conducted only at a single site, UCLH, which is the lead site for the MS-STAT2 trial.

2 Aims

To determine whether simvastatin has an effect on executive function in SPMS as indicated by the change in the FAB score over 36 months.

3 Background

The FAB was originally developed as a brief 10 minute bedside assessment of overall frontal lobe function by Dubois *et al*.[134] There are six components to the battery which test the following behaviours and cognitive functions; conceptualisation, mental flexibility, motor programming, sensitivity to interference, inhibitory control, and environmental autonomy, which together allow the identification of executive dysfunction.[134] The individual subtests were chosen as they significantly correlated with pathologies resulting in frontal lobe dysfunction in an 18-flurodeoxyglucose PET study.[135] Additionally, each component function described by the subtests has been shown to be associated with a specific area of the frontal lobe using different neuroimaging techniques, and so together the FAB is purported to comprise a measure of global frontal lobe function.[135-137] The FAB has good inter-rater reliability and discriminant validity for the original use in terms of identifying patients with frontal lobe dysfunction and controls.[134]

Multiple sclerosis is a disease characterised by the dissemination of neuroinflammatory lesions in time and space. The frontal cortex can therefore be affected with resultant executive dysfunction.[138] There have not been any specific studies of the FAB in multiple sclerosis, however this sub-study follows on from the cognitive sub-study of the 24 month MS-STAT phase II trial of simvastatin in SPMS which used the FAB to assess executive function. At baseline 45% of subjects (60 of 133) had executive impairment on the FAB. At 24 months the only cognitive outcome measure with a significant difference between placebo and simvastatin arms was the FAB (difference 1·2 points, 95% CI 0·2 to 2·3). Overall there was an increase in the FAB score in the simvastatin arm and a decrease in the placebo group.[139]

4 Rationale and Risks/Benefits

Following on from the MS-STAT cognitive sub-study, this specific study will explore the use of the FAB in a larger cohort of SPMS subjects. There is a need to develop sensitive and meaningful clinical outcome measures for the assessment of neuroprotective agents in SPMS. The FAB provides a potential non-invasive brief measure of this. The utility of the FAB will be assessed by comparing score changes in simvastatin treatment and placebo arms.

The application of the FAB battery will provide an objective measure of executive function in an SPMS population with EDSS scores of 4.0 to 6.5 (inclusive) at baseline. Doing so will support the clinician-led and patient-reported cognitive and clinical outcome measures of the MS-STAT2 trial.

There is no expected side effect associated with the FAB. If a patient cannot use the stated hand for the Luria subtest, the alternate hand can be used with the assessor adapting the task by using their alternate hand to provide a mirror image, thus preventing any alteration to the assessment function.

5 Assessments

The FAB will be undertaken by all patients that have consented to participate in the FAB sub-study at the UCLH site. The battery will be completed at these time points:

- Baseline (Month 0)
- Visit 10 (Month 36)

Content, instructions, and scoring of the FAB[134]:

1. Similarities (conceptualization)

"In what way are they alike?"

A banana and an orange (In the event of total failure: "they are not alike" or partial failure: "both have peel," help the patient by saying: "both a banana and an orange are..."; but credit 0 for the item; do not help the patient for the two following items)

A table and a chair

A tulip, a rose and a daisy

Score (only category responses [fruits, furniture, flowers] are considered correct) Three correct: 3 Two correct: 2 One correct: 1 None correct: 0

2. Lexical fluency (mental flexibility)

"Say as many words as you can beginning with the letter 'S,' any words except surnames or proper nouns."

If the patient gives no response during the first 5 seconds, say: "for instance, snake." If the patient pauses 10 seconds, stimulate him by saying: "any word beginning with the letter 'S.' The time allowed is 60 seconds. Score (word repetitions or variations [shoe, shoemaker], surnames, or proper nouns are not counted as correct responses) More than nine words: 3 Six to nine words: 2 Three to five words: 1 Less than three words: 0

3. Motor series (programming)

"Look carefully at what I'm doing."

The examiner, seated in front of the patient, performs alone three times with his left hand the series of Luria "fist–edge– palm." "Now, with your right hand do the same series, first with me, then alone."

The examiner performs the series three times with the patient, then says to him/her: "Now, do it on your own." Score Patient performs six correct consecutive series alone: 3 Patient performs at least three correct consecutive series alone: 2 Patient fails alone, but performs three correct consecutive series with the examiner: 1 Patient cannot perform three correct consecutive series even with the examiner: 0.

4. Conflicting instructions (sensitivity to interference)

"Tap twice when I tap once."

To be sure that the patient has understood the instruction, a series of three trials is run: 1-1-1.

"Tap once when I tap twice."

To be sure that the patient has understood the instruction, a series of three trials is run: 2-2-2.

The examiner performs the following series: 1-1-2-1-2-2-2-1-1-2.

Score No error: 3 One or two errors: 2 More than two errors: 1 Patient taps like the examiner at least four consecutive times: 0

5. Go–No Go (inhibitory control)

"Tap once when I tap once."

To be sure that the patient has understood the instruction, a series of three trials is run: 1-1-1.

"Do not tap when I tap twice."

To be sure that the patient has understood the instruction, a series of three trials is run: 2-2-2.

The examiner performs the following series: 1-1-2-1-2-2-2-1-1-2. Score No error: 3 One or two errors: 2 More than two errors: 1 Patient taps like the examiner at least four consecutive times: 0

6. Prehension behaviour (environmental autonomy)

"Do not take my hands." The examiner is seated in front of the patient. Place the patient's hands palm up on his/her knees. Without saying anything or looking at the patient, the examiner brings his/her hands close to the patient's hands and touches the palms of both the patient's hands, to see if he/she will spontaneously take them. If the patient takes the hands, the examiner will try again after asking him/her:

"Now, do not take my hands."

Score Patient does not take the examiner's hands: 3 Patient hesitates and asks what he/she has to do: 2 Patient takes the hands without hesitation: 1 Patient takes the examiner's hand even after he/she has been told.

An overall cut off score of 12 has previously been shown to have the highest sensitivity and specificity when differentiating subjects with frontotemporal dementia, with predominantly executive dysfunction, and Alzheimer's disease.[140]

6 Outcomes

6.1 Outcome measures and analysis

The FAB has an overall maximum score of 18 made up of the individual sub-test scores which are out of a maximum of 3 (see section above).

7 Primary Analysis

Total FAB scores will be presented raw as they are not normally distributed in healthy controls and so cannot be converted to z-scores. The FAB score summary statistics (mean, standard deviation, median, minimum, and maximum) will be presented by treatment group.

The mean value of the FAB score at Visit 10 (Month 36) will be compared between groups using a mixed effects linear regression model for repeated measures, adjusting for the baseline value and 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)]. Site will be included as a random effect. If parametric assumptions for the linear regression model are substantially violated, then non-parametric methods (such as bootstrapping) will be used for inference.