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

STATISTICAL ANALYSIS PLAN

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APPROVED BY:

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HISTORY OF CHANGES				
VERSION NUMBER	**EFFECTIVE DATE**	**CHANGE**	**REASON FOR CHANGE**	**CHANGE APPROVED BY (NAME)**
2.0	03-Jul-2024	Amending dates for COVID-19 pandemic subgroup analysis for patient reported outcomes: MSIS-29V2, MSWS-12V2, MFIS-21, CFQ	Period during which COVID-19 restrictions may have impacted data collection did not take into account the recall period for the questions. This was corrected.	Jennifer Nicholas
		Use random effects instead of fixed effects to adjust for site in analysis of binary and count outcomes: progression on EDSS at 36 months (sensitivity analysis), multicomponent measure of disability progression, progression on MSFC 25ft walk, progression on MSFC 9HPT, progression on MRS and relapse rate.	Some sites had small numbers of patients and therefore no patients at the site had the outcome of interest. This made it impossible to include all data while adjusting for site as a fixed effect, as had been specified in the Protocol v8.0 and v1.0 of the SAP. Instead, random effects for site were used to allow inclusion of data at all study sites.	Jennifer Nicholas

		Specifying that analysis of continuous outcomes with two time points (baseline and 36 months) will use an unstructured covariance matrix for the residuals to allow for correlation between repeated measures on an individual. These analyses are of: MSFC, on MSFC 25ft walk, MSFC 9HPT, SLCVA, BICAMS, COVID-19 sensitivity analyses for MSIS-29V2, MSWS-12V2, MFIS-21, CFQ.	The description of these models in V1.0 of the SAP specified that a random effect for individual would be included in a way that would make the model essentially equivalent to allowing adjustment for the baseline, but did not give details on how this would be done. This has now been clarified to properly describe the approach.	Jennifer Nicholas

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1 INTRODUCTION

This Statistical Analysis Plan (SAP) describes the planned analysis and reporting for the clinical trial Multiple Sclerosis – Simvastatin Trial 2 (MS-STAT2). A separate plan will be prepared for the health economic analysis and analysis of sub-studies.

The following documents were reviewed in preparation of this SAP:

- MS-STAT2 trial protocol version 8.0. Dated 26th February 2024

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

2 STUDY SYNOPSIS

MS-STAT2 is being undertaken to test the effectiveness of repurposed simvastatin (80mg) in slowing the progression of disability in secondary progressive multiple sclerosis (SPMS). It is a phase 3 multicentre interventional clinical trial including randomisation, double blinding, and placebo control. The planned sample size was 1050 participants who were to be randomised with 1:1 ratio to one of two groups: simvastatin (active) or matching placebo (control).

Simvastatin (Active)

- Low dose (Initial): 40mg Simvastatin (1x 40mg 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 optionally* to Visit 11, 12 or 13 (Month 42, 48, 54) for those patients who have not had a confirmed EDSS progression event by Visit 10.

Placebo (control)

- Low dose (Initial): Placebo (1x tablet taken once daily at night) for 1 month from Baseline (Month 0).
  Dose escalation at Visit 3 (M1/week 4)
- High dose: Placebo (2x tablet taken once daily at night) for 35 months from Visit 3 (Month 1) to Visit 10 (Month 36), or optionally* to Visit 11, 12 or 13 (Month 42, 48, 54) for those patients who have not had a confirmed EDSS progression event by Visit 10.

*Patients who have not had a confirmed EDSS progression event by Visit 10 (Month 36), will be invited to an optional series of additional visits, as detailed below:

- Visit 11 – (Month 42); for patients with at least 42 months from their randomisation to the Last Patient Last Visit date (LPLV).
- Visit 12 – (Month 48); for patients with at least 48 months from their randomisation to LPLV
- Visit 13 - (Month 54); for patients with at least 54 months from their randomisation to LPLV

Note that LPLV is the date that the last patient randomised into the trial will have their final scheduled visit. The final follow-up time point will vary between patients, with those randomised later in the trial not completing the full follow-up extension to month 54.

Participants will continue taking trial medication until their final clinic follow up appointment. All study IMP is dispensed by pharmacy departments within participating sites to coincide with participants' trial follow up visits. The visit schedule is outlined in Figure 1.

3 STUDY OBJECTIVES

3.1 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 the duration of the trial treatment period.

3.2 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 scores compared to baseline.

Progression of disability is 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.

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

3.3 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 outcomes

- A modified Multiple Sclerosis Functional Composite (MSFC) comprising
  - Timed 25 Foot Walk (T25FW)
  - 9 Hole Peg Test (9HPT)
  - Symbol Digit Modalities Test (SDMT)
- Multi-component measure of disability progression comprising either:
  - Increase in EDSS (0.5 point increase if baseline ≥6 or 1.0 point increase if baseline <6), or
  - ≥20% increase in time taken to complete the T25FW, or
  - ≥20% increase in time taken to complete 9HPT
- 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 outcomes

- MS Impact Scale-29 v2 (MSIS-29v2)
- MS Walking Scale-12 v2 (MSWS-12v2)
- Modified Fatigue Index 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:

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

A separate analysis plan will be prepared for health economic analysis to address objective 2.

4 STUDY DESIGN

4.1 General Design and Plan

A phase 3 double-blind randomised placebo-controlled trial of the effectiveness of repurposed simvastatin (80mg) in slowing the progression of disability in people with secondary progressive multiple sclerosis (SPMS). This is a multi-centre trial with centres in the United Kingdom.

4.2 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, the trial requires a total of 330 progression events. The original sample size was 1180 patients (590 patients per arm) with fixed follow-up of 36 months. With the revised schedule to follow patients for up to 54 months, the sample size was revised to 1050 patients (525 patients per arm). This sample size was estimated to be sufficient to observe a total of 330 progression events over the extended follow-up and so retain 90% power to demonstrate 30% relative reduction in disability progression, at the conventional 5% significance level. It is noted that if 950 patients are recruited, a power of more than 85% would be achieved.

Table 1 shows the assumed progression rate and losses to follow-up for the revised sample size calculation. The revised sample size calculation assumes that the placebo progression rate will be 8.2% per 6 months, resulting in cumulative event rate up to 48 months as shown in. Note that any initial progression events that occur in month 54 cannot be confirmed, so these events are not included. This is equivalent to an assumption of 40% progression by Visit 10 - Month 36, which is based on a review of all previous phase 3 trials in SPMS (Ontaneda et al., 2015) and recent 3 year trials in secondary progressive MS, which had confirmed progression rates of between 35-44% (Ball et al., 2015, Andersen et al., 2004, Panitch et al., 2004).

It is assumed that loss to follow-up will be 20% by month 36 and that there will be an additional 12% losses to follow-up by month 48. The allowance for loss to follow-up anticipates that the analysis will

include any progression events that are observed before the patient leaves the study. This means that although cumulative loss to follow-up of up to 32% by 4 years is assumed, this will result in loss of 18% of potential progression events.

Table 1: Assumed progression rate and losses to follow up for revised sample size calculation

Month	Placebo event rate	Simvastatin event rate	Combined event rate	Cumulative losses to follow-up
0	0%	0%	0%	0%
6	8%	6%	7%	10%
12	16%	11%	13%	12%
18	23%	16%	19%	14%
24	29%	21%	25%	16%
30	35%	26%	30%	18%
36	40%	30%	35%	20%
42	45%	34%	40%	26%
48	49%	38%	44%	32%

4.3 Randomisation and Blinding

Randomisation is by the web-based randomisation service, Sealed Envelope. Study arm allocation into the two treatment arms (1:1) takes these minimisation factors into consideration:

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

All investigators, participants and the pharmacy staff at site are blind to trial arm and study IMP (simvastatin/placebo) kit allocation.

4.4 Study Assessments

Patients have an initial screening visit (visit 1) to assess eligibility and return within 1 month for the baseline visit (visit 2) at which randomisation takes place. There is a dose escalation visit one month after randomisation (visit 3) and a safety telephone visit at month 3 (visit 4). Following this, participants will have study visits at month 6 (visit 5) and then at 6 monthly intervals up to 54 months post-randomisation (visits 6 to 13). Figure 1 indicates the outcome measures that are assessed at each visit.

In the original study design all visits except visit 4 required participant attendance at a study site. After the onset of the COVID-19 pandemic in March 2020 a protocol amendment was made to allow remote collection of outcome data. EDSS was collected over the telephone and patients were sent the patient reported outcome measures for completion at home. Other clinician reported outcome measures were not collected remotely.

Figure 1: **Visit schedule and schedule for collection of outcome data in MS-STAT2**

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[A]	VISIT 12[A]	VISIT 13[A]
Month	**SCREENING**	**Month 0 BASELINE**	**Month 1**	**Month 3 TELEPHONE**	**Month 6**	**Month 12**	**Month 18**	**Month 24**	**Month 30**	**Month 36**	**Month 42**	**Month 48**	**Month 54**
Clinician reported outcome measures													
EDSS – Independent Assesssing clinician		X[B]			X	X	X	X	X	X[B]	X	X	X
9HPT		X			X	X	X	X	X	X	X	X	X
T25FW		X			X	X	X	X	X	X	X	X	X
SDMT[C]		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			
Adverse events and compliance													
Compliance assessment			X	X	X	X	X	X	X	X	X	X	X
Relapse assessment (count & grade)	X	X	X	X	X	X	X	X	X	X	X	X	X
Adverse events		X	X	X	X	X	X	X	X	X	X	X	X

[A] Additional visits Participants who do not have confirmed EDSS progression by visit 10 may be invited for 1-3 additional visits (Visits 11-13). The number of additional visits will be based on available duration between their randomisation date and the trial's last patient last visit (LPPV) date.

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

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

5 STUDY POPULATION

Patients aged between 25 and 65 years with progressing SPMS (Lublin et al., 2014, Lublin and Reingold, 1996) who fulfil the revised McDonald criteria for MS (Thompson et al., 2018, Polman et al., 2011, Polman et al., 2005) in addition to **ALL** inclusion criteria and **NONE** of the exclusion criteria set out below.

5.1 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 baseline score <6, or an increase of 0.5 point if baseline EDSS score is ≥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.

5.2 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, clarithromycin, telithromycin, telaprevir, nefazodone, fibrates (including fenofibrates), nicotinic acid (or products containing niacin), azole anti-fungal preparations, macrolide antibiotics, protease inhibitors, verapamil, amiodarone, amlodipine, gemfibrozil, ciclosporin, danazol, diltiazem, rifampicin, fusidic acid, grapefruit juice or alcohol abuse;
7. Primary progressive MS;
8. Diabetes mellitus type 1;
9. Uncontrolled hypothyroidism;
10. Female participants that are pregnant or breast feeding. Women of child bearing potential (WOCBP) who are unwilling or unable to use an acceptable method to avoid pregnancy for the entire study period, and up to 4 weeks after the last dose of study drug;

11. Use of immunosuppressants (e.g. azathioprine, methotrexate, ciclosporine) or disease modifying treatments (avonex, rebif, betaferon, glatiramer) within the previous 6 months;
12. Use of mitoxantrone, natalizumab, alemtuzumab, daclizumab or other monoclonal antibody treatment, if treated within the last 12 months;
13. Use of fingolimod, fumarate, teriflunomide within the last 12 months;
14. Use of other experimental disease modifying treatment within the last 6 months;
15. Commencement of fampridine ≤6 months from day of randomisation;
16. Concurrent participation in another clinical trial of an investigational medicinal product or medical device;
17. Patients with rare hereditary problems of galactose intolerance, the lapp lactase deficiency or glucose-galactose malabsorption.

5.3 Withdrawals

If a participant chooses to discontinue their trial treatment, they should continue to be followed up according to the follow-up schedule defined in the protocol, providing they are willing. However, if a participant exercises the view that they no longer wish to be followed–up they will be withdrawn entirely from the trial. Data already collected will be kept and included in analyses for all participants who stop follow up early, unless the participant withdraws consent for all data being held.

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

5.4 Missing Data

Missing data will be identified and an effort made to return to the original medical records to obtain the data.

5.5 Populations for Sub-Group Analyses

Subgroup analyses will be conducted to examine whether the effectiveness of treatment was impacted by the COVID-19 pandemic, as outlined in section 10. No other subgroup analyses are planned.

6 STATISTICAL ANALYSIS

6.1 General

The final statistical analysis will be performed as pre-specified in this SAP. Any, post-hoc, exploratory analyses completed to support planned analyses, which were not identified in this SAP, will be documented and reported in the relevant trial reports. Any results from unplanned analyses will be clearly identified as such in the text of the trial reports.

6.2 Pooling of Sites

The data from each participating centre will be pooled for all primary and secondary analyses.

6.3 Interim Analyses

An Independent Data Monitoring Committee (IDMC) constituting a minimum of 3 independent members convened at scheduled time points throughout the duration of the trial to review interim trial data and safety data. The Trial Statistician generated the summaries of trial results for the IDMC to review, ensuring that the trial team remain blinded to treatment allocation.

MS-STAT2 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). The IDMC will review recruitment against the STOP/GO progression criteria to allow the IDMC to advise on whether the progression criteria has been achieved.

A formal interim analysis will be conducted on an annual basis, presenting safety data and treatment effects on the primary outcome.

At each formal interim analyses, a Kaplan-Meier curve will be presented showing the cumulative incidence of the primary outcome. The effect of treatment on the primary outcome will be presented along with its 95% confidence interval and p-value. Where number of events permits this will be presented as a hazard ratio from a 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. If there are too few events to permit use of survival analysis, Fisher's exact test will be used to compare the proportion of events between the treatment arms.

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.

6.4 Time-Points For Analysis

All final, planned, analyses identified in the protocol and in this SAP will be performed only after the last patient has completed their final follow up. In addition, no database may be locked, random code unblinded, or analyses completed until this SAP has been approved, other than for any specified interim analyses.

6.5 Withdrawals and missing data

The 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 of missing data 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.

6.6 Statistical Software

Data analysis will be performed with Stata® Version 17.0 or later. Other statistical software may also be used where Stata® does not provide the relevant statistical method.

7 EVALUATION OF DEMOGRAPHICS AND BASELINE CHARACTERISTICS

A CONSORT diagram will be used to describe the course of patients through the trial. Baseline characteristics will be summarised by randomised group. For all patient characteristics, continuous variables will be described by the mean and standard deviation. Alternatively, for skewed variables they may be described by the median and inter quartile range (IQR). The range for all continuous variables will also be presented. Categorical variables will be described by frequency and percentages in each category.

7.1 Demographics and Baseline Characteristics

The following characteristics are collected at the screening visit, prior to randomisation:

- Gender
- Height
- Weight
- Dominant hand
- Pulse rate
- Systolic blood pressure
- Diastolic blood pressure
- Ethnicity
- Date of onset of MS symptoms
- Date of MS diagnosis
- Date of secondary progression
- Initial symptoms at onset of MS:
    - vision
    - motor
    - sensory
    - co-ordination
    - bowel/bladder
    - fatigue
    - cognitive
    - encephalopathy
    - other
- Symptoms at onset of progression:
    - vision
    - motor
    - sensory
    - co-ordination
    - bowel/bladder
    - fatigue

    - cognitive
    - encephalopathy
    - other
- Number of relapses within the last 12 months
- Medical history
    - Asthma
    - Depression
    - Anxiety
    - Epilepsy
    - Hypertension
    - Hypothyroidism
    - Hyperlipidaemia
    - Osteoporosis
    - Hysterectomy
    - Type 2 diabetes mellitus
    - Alcohol intake above recommended limits
    - Current/ex smoker
    - Other significant medical conditions or surgical procedures
- Physical examination
    - Clinically significant signs and symptoms
    - Non clinically significant signs and symptoms
- Thyroid function test
    - TSH
    - Free T4
- Haematology tests
    - White blood count
    - Haemoglobin
    - Platelets
- Biochemistry tests
    - ALT/AST
    - Creatine kinase
    - Sodium
    - Potassium
    - Creatinine
    - eGFR
    - HDL
    - LDL
    - Cholesterol
    - Alkaline phosphatase
    - Triglycerides
    - Glucose
- Pregnancy test
- Concomitant medications

At the baseline visit information is collected on the following outcome measures:

- EDSS
- Timed 25 Foot Walk (T25FW)
- 9 Hole Peg Test (9HPT)
- Symbol Digit Modalities Test (SDMT)
- Binocular Sloan Low Contrast Visual Acuity (SLCVA)
- Relapse assessment (number and severity)
- Modified Rankin Scale (mRS)
- California Verbal Learning Test-II (CVLT-II)
- Brief visuospatial memory test- Revised (BVMT-R)
- MS Impact Scale-29 v2 (MSIS-29v2)
- MS Walking Scale-12 v2 (MSWS-12v2)
- Modified Fatigue Index Scale - 21(MFIS-21)
- Chalder Fatigue Questionnaire (CFQ)
- EQ-5D-5L

8 EVALUATION OF TREATMENT COMPLIANCE

8.1 Compliance to Study Drug and Treatment

Compliance will be assessed from the dose each patient is on during the trial and number of days with missed IMP. The dose given to each participant will be assessed from records on the dose prescribed at each visit and changes in doses between visits. Participants will be provided with a drug diary to record their uptake of trial medication between clinic visits. The number of days with missed IMP is then assessed from a self-reported question at each follow-up visit.

Patients will be considered compliant with their randomised intervention on days where they have taken the protocol dose of study IMP or placebo, which is a dose of 80mg/2 tablets after the first month at 40mg/1 tablet. At each visit percent compliance will be calculated as:

$$\% = \frac{days\ compliant}{days\ since\ last\ visit}$$

The days compliant at each visit will be calculated as:

$$days\ compliant = days\ on\ protocol\ dose - \ days\ with\ missed\ IMP$$

A summary measure of compliance will be calculated for each participant using the data recorded:

- date of the 36 month visit in patients who do not progress, die or withdraw from the trial;
- date of progression in those who have confirmed progression;
- date of death (non-MS cause) or withdrawal in patients who die or withdraw from the trial before they have confirmed progression or reach the 36 month visit.

The average compliance will then be calculated over the relevant follow-up period as:

$$\% = \frac{total\ days\ compliant}{total\ days\ follow-up\ from\ randomisation}$$

Patients will be considered to be compliant with their randomised intervention if the summary measure of compliance is over 90%, which means they took the protocol dose on at least 90% of days over the first 36 months of follow-up, or until date of confirmed progression, death or withdrawal if these happened before 36 months.

A secondary measure of compliance will consider both high (80mg) or low (40mg) dose simvastatin. On this measure patients will be considered compliant with their randomised intervention on days where they have taken a dose of at least 40mg/1 tablet. The percent of days with compliance on this measure will be calculated in the same way as above.

9 EVALUATION OF THE IMPACT OF THE COVID-19 PANDEMIC ON STUDY DATA

9.1 Patient characteristics

Baseline patient characteristics will be tabulated by treatment group for those recruited before recruitment was temporarily halted in March 2020 by the COVID-19 pandemic versus those recruited after this point.

9.2 Remote Data Collection

The proportion of study visits attended in person will be tabulated by treatment group for each follow-up time point for study visits occurring:

- Prior to 16th March 2020
- From 16th March 2020 to 19th July 2021
- After 19th July 2021

Baseline characteristics will be tabulated by treatment group and by mode of visit (in-person versus remote) for visits occurring in the three periods identified above.

9.3 Compliance with Treatment

The percent of patients on each IMP dose and compliance with IMP dose in each arm will be tabulated for the treatment groups over each of the three periods given above.

9.4 Patient outcomes

The measured outcomes at each visit will also be tabulated for patients attending in-person visits and those with remote data collection and for the three time periods identified above.

Section 10 below describes a secondary analysis to assess the impact of the COVID-19 pandemic on the primary outcome, confirmed disability progression.

Analysis to assess the impact of the pandemic on secondary outcomes may also be conducted, where it is apparent that the pandemic hampered the usual collection of the outcome data.

10 EVALUATION OF EFFICACY PARAMETERS

10.1 GENERAL PRINCIPLES

Following the ICH Harmonised Guideline on Statistical Principles for Clinical Trials (ICH, 1998; ICH, 2019), an estimand is presented to define the treatment effect of interest for each outcome. Following definition of the estimand, details are given on methods of estimation including handling of missing data.

The estimand includes description of:

- The treatments that will be compared;
- The population of patients;
- The endpoint that is used for the comparison;
- The summary measure that will be used to make the comparison between treatment groups on that endpoint;
- Handling of intercurrent events.

Intercurrent events are events that happen after starting trial treatment that influence either the interpretation of the outcome or mean that the outcome measurement does not exist. An example of an intercurrent event that influences interpretation of the outcome is stopping treatment due to an adverse event, as the outcome measurement would be expected to be changed because of stopping treatment. Death is an example of an intercurrent event that means that the outcome measurement does not exist. Note that withdrawal from the study or missing a visit is not an intercurrent event, instead these are sources of missing data that can be addressed in the analysis.

Different strategies can be taken to addressing intercurrent events, as described in Table 2.

It is not necessary to apply the same strategy to all intercurrent events, instead different strategies may be applied for different types of event.

Table 2: Strategies for handling intercurrent events

Strategy	Description
Treatment Policy	The objective is to compare the outcomes as actually observed, regardless of whether the intercurrent event has happened. It is not possible to implement "treatment policy" strategies where the intercurrent event means the outcome does not exist. For example, if the intercurrent event is discontinuation of treatment due to an adverse event, outcome data after this event is used in the analysis according to the assigned treatment group.
Hypothetical	The objective is to compare the outcomes under a hypothetical scenario where the intercurrent event cannot occur. Therefore, measured values of the endpoint after occurrence of the intercurrent event are not used. Instead, the objective is to estimate the value the outcome would have taken if the intercurrent events had not happened. For example, if the intercurrent event is discontinuation of treatment due to an adverse event, the objective is to compare the treatments in the hypothetical scenario where no patients can discontinue treatment for this reason.
Composite	The intercurrent event is included in the definition of the outcome because provides meaningful information on this outcome. For example, if the intercurrent event is "being unable to walk" this prevents measurement of the timed 25ft walk. Using a composite strategy, patients who experience this intercurrent event are assigned the maximum possible time to complete the test.
While on treatment **/** **While alive**	The objective is to compare the outcomes before the intercurrent event has happened. Values of the outcome are no longer relevant after the intercurrent event occurs. For example, if the intercurrent event is death then the "while alive" strategy aims to compare the outcomes between those patients in each treatment group who are still alive.
Principal stratum	The objective is to compare the outcome in a population who would / would not have the intercurrent event. For example, if the intercurrent event is discontinuation of treatment due to an adverse event, an objective may be to compare the treatments in the principal stratum of patients who would not have experienced the adverse event under either treatment.

10.2 PRIMARY ENDPOINT: PRIMARY ANALYSIS

The primary endpoint is first confirmed disability progression on EDSS. EDSS is assessed up to 54 months after randomisation, which allows progression to be confirmed up to 48 months after randomisation.

10.2.1 Estimand for Primary Analysis

Table 3 defines the estimand of interest for the primary analysis. This analysis aims to estimate the effect of the treatment policy of offering patients with SPMS high dose simvastatin treatment for up to 48 months.

Table 3: Definition of the estimand for the primary analysis of the primary endpoint

Aspect	Definition
Treatment conditions	Intervention - high dose (80mg) simvastatin Usual care – placebo (2 tablets)
Population	Patients with progressive multiple sclerosis aged between 25 and 65 years, with EDSS between 4.0 and 6.5 at time of starting treatment
Endpoint	Confirmed disability progression on the EDSS up to 48 months
Summary measure	Hazard ratio
Handling of intercurrent events	
Death due to MS	Composite – death due to MS counts as confirmed progression
Death due to non-MS causes	While-alive
Non-compliance or treatment discontinuation due to adverse events	Treatment Policy
Non-compliance or treatment discontinuation due to patient/clinician decision	Treatment Policy
Non-compliance or treatment discontinuation due to COVID-19 pandemic (e.g. unable to attend clinic for safety tests)	Treatment Policy
Remote data collection because patient unable to attend for in-person visit	Composite – where available telephone EDSS will be used in place of the planned clinic visit EDSS

10.2.2 Analysis Population

The analysis will include all participants as randomised, irrespective of subsequent compliance with allocated treatment (i.e. including all participants whether or not they took the prescribed study medication).

Patients who die due to MS will be included in the analysis population and death due to MS will be considered a confirmed progression event.

Patients who die from other causes or withdraw from the study for any reason will be included in the analysis and censored at the last visit at which confirmed progression could have occurred. This visit will be the second to last study visit, since a further study visit is required in order to confirm the event.

10.2.3 Analysis model

To estimate the treatment effect hazard ratios and 95% confidence intervals will be calculated using Cox proportional hazards modelling and Kaplan-Meier curves will be produced. The time scale used for survival analysis will be time since randomisation. The model will allow for between centre variability by stratification by centre. 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.

10.2.4 Handling Missing Data

Data will only be used for visits where EDSS was recorded. It is assumed that where there is interval censoring the missing EDSS would not have provided any further information on the timing or occurrence of confirmed progression.

Where an initial progression occurs this will not be considered an event if the patient dose not return for a further study visit to have progression confirmed. This assumes that patients who withdraw or are lost to follow-up without confirmation of the progression did not in fact have confirmed progression.

Censoring patients who withdraw assumes that this censoring process is non-informative and progression rates in those who are censored are the same as those who continue to be followed-up.

10.2.5 COVID-19 pandemic subgroup analysis

To investigate the potential effect of the COVID-19 pandemic on disability progression or on the effects of treatment the follow-up will be split into three periods:

- Prior to 16th March 2020
- From 16th March 2020 to 19th July 2021
- After 19th July 2021

Kaplan-Meier plots will be produced for each period by treatment group, showing cumulative progression from randomisation. These plots will be produced by splitting each participant's follow-up time according to these periods, so the data for some patients will be left as well as right censored. A Cox proportional hazards model will be fitted allowing a different hazard of progression for each time period for each treatment group by including the period as a time-varying covariate and an interaction of this covariate with treatment group. A Wald test will be used to assess whether the progression rate differed between periods and to assess whether there is any evidence that the treatment effect differed between the three time periods.

10.3 PRIMARY ENDPOINT: SENSITIVITY ANALYSIS FOR PROGRESSION EVENTS WHICH ARE NOT CONFIRMED

This analysis will examine whether results are sensitive to the presence of any unconfirmed progressions. The primary endpoint will be disability progression on EDSS, assessed up to 54 months after randomisation. In this analysis progression events will be counted either: where the initial progression is confirmed at least 6 months later or where the patient does not return for any further visits and so confirmation was not possible (i.e. where confirmation of progression is unknown). Progression events will not be counted where the patient returns for a later visit and the initial progression has not been sustained.

10.3.1 Estimand

Table 4 defines the estimand of interest for the primary analysis. This analysis aims to estimate the effect of the treatment policy of offering patients with SPMS high dose simvastatin treatment for up to 54 months.

Table 4: Definition of the estimand for analysis of the primary endpoint to examine sensitivity disability progression events which were not confirmed

Aspect	Definition
Treatment conditions	Intervention - high dose (80mg) simvastatin Usual care – placebo (2 tablets)
Population	Patients with progressive multiple sclerosis aged between 25 and 65 years, with EDSS between 4.0 and 6.5 at time of starting treatment
Endpoint	Disability progression on the EDSS up to 54 months
Summary measure	Hazard ratio
Handling of intercurrent events	
Death due to MS	Composite – death due to MS counts as confirmed progression
Death due to non-MS causes	While-alive
Non-compliance or treatment discontinuation due to adverse events	Treatment Policy
Non-compliance or treatment discontinuation due to patient/clinician decision	Treatment Policy
Non-compliance or treatment discontinuation due to COVID-19 pandemic (e.g. unable to attend clinic for safety tests)	Treatment Policy
Remote data collection because patient unable to attend for in-person visit	Composite – where available telephone EDSS will be used in place of the planned clinic visit EDSS

10.3.2 Analysis Population

The analysis will include all participants as randomised, irrespective of subsequent compliance with allocated treatment (i.e. including all participants whether or not they took the prescribed study medication).

Patients who die due to MS will be included in the analysis population and death due to MS will be considered a confirmed progression event.

Patients who die from other causes or withdraw from the study for any reason will be included in the analysis and censored at the last visit at which progression could have occurred. This visit will be the last study visit they attended.

10.3.3 Analysis model

To estimate the treatment effect hazard ratios and 95% confidence intervals will be calculated using Cox proportional hazards modelling and Kaplan-Meier curves will be produced. The time scale used for survival analysis will be time since randomisation. The model will allow for between centre variability by stratification by centre. 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.

10.3.4 Handling Missing Data

Data will only be used for visits where EDSS was recorded. It is assumed that where there is interval censoring the missing EDSS would not have provided any further information on the timing or occurrence of confirmed progression.

Censoring patients who withdraw assumes that this censoring process is non-informative and progression rates in those who are censored are the same as those who continue to be followed-up.

10.4 PRIMARY ENDPOINT: SENSITIVITY ANALYSIS TO ASSESS TREATMENT EFFECT IN THE ABSENCE OF COVID-19 PANDEMIC CHANGES TO VISIT SCHEDULE

This analysis will compare progression on at 36 months using EDSS collected from in-person visits that happened during time periods when COVID-19 related public health restrictions were not in force. The purpose is to examine the sensitivity of results to any impact the COVID-19 pandemic had on the assessment of confirmed progression, either due to changes in assessment of disability at baseline or during follow-up. This analysis will use data on participants who were randomised before 16th March 2020 and who had their 36 month visit after 19th July 2021, since these participants had the baseline visit before the onset of the pandemic and the 36 month visit after the end of public health restrictions in the UK The analysis will compare progression of EDSS at 36 months and will not make use of the data at interim visits which may have occurred during the pandemic.

10.4.1 Estimand

The estimand of interest is defined in Table 5. This analysis aims to estimate the effect of the treatment policy of offering patients with SPMS high dose simvastatin treatment for 36 months, in the absence the

disruption of the COVID-19 pandemic to the data collection.

10.4.2 Analysis Population

The analysis will include all participants who were randomised before 16th March 2020 and had in-person assessment of EDSS at a 36 month visit that happened after 19th July 2021.

Participants will be included as randomised, irrespective of subsequent compliance with allocated treatment.

Patients who die due to MS will be included in the analysis population and death due to MS will be considered a confirmed progression event.

Patients who die from other causes or withdraw from the study for any reason before 36 months will not be included in the analysis.

Table 5: Definition of the estimand for the sensitivity analysis of the primary endpoint to examine impact of COVID-19 pandemic on the visit schedule

Aspect	Definition
Treatment conditions	Intervention - high dose (80mg) simvastatin Usual care – placebo (2 tablets)
Population	Patients with progressive multiple sclerosis as defined in Table 3 for the primary analysis.
Endpoint	Disability progression on the EDSS at 36 months
Summary measure	Odds ratio
Handling of intercurrent events	
Death due to MS	Composite – death due to MS counts as confirmed progression
Death due to non-MS causes	While-alive
Non-compliance or treatment discontinuation due to adverse events	Treatment Policy
Non-compliance or treatment discontinuation due to patient/clinician decision	Treatment Policy
Non-compliance or treatment discontinuation due to COVID-19 pandemic	Treatment Policy
Remote data collection because patient unable to attend for in-person visit	Hypothetical

10.4.3 Analysis model

To estimate the treatment effect an odds ratio and 95% confidence interval will be calculated using a mixed effects logistic regression model. The model will allow for between centre variability by including a random intercept for centre. The 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.

10.4.4 Handling Missing Data

Data will only be used for visits where in-person EDSS was recorded at the 36 month clinic visit. Where telephone EDSS is available, it will not be used in place of the planned clinic visit EDSS.

This approach assumes that data are missing completely at random – that is the proportion with progression is the same for those who attended the 36 month visit remotely and those who attended the 36 month visit in-person. The plausibility of this assumption will be assessed by comparing patient characteristics between those who attend in-person and remotely. In the event that substantial differences in are found, inverse probability of missing weights (IPW) will be used in the analysis model.

10.5 PRIMARY ENDPOINT: SECONDARY ANALYSIS TO ESTIMATE TREATMENT EFFECT WITH HIGH COMPLIANCE WITH HIGH DOSE TREATMENT

This is a per-protocol analysis that will compare time to first confirmed disability progression on EDSS up to 48 months after randomisation in those who were able to comply with high dose simvastatin treatment.

10.5.1 Estimand

Table 6 defines the estimand of interest for this secondary analysis. This analysis aims to estimate the effect of high dose simvastatin treatment in the patients who had high compliance with randomised treatment for the first 36 months of the study.

10.5.2 Analysis Population

The secondary analysis will include data from participants who completed 36 months of follow-up and complied with high dose protocol treatment (80mg/2 tablets) on at least 90% of days over this period (see section 8.1 for more details).

Patients will be censored if they die from non-MS causes, withdraw from the study for any reason, or at the last visit at which confirmed progression could have occurred as defined for the primary analysis. Death due to MS will be considered a confirmed progression event.

10.5.3 Analysis model

To estimate the treatment the same Cox proportional hazards model will be used as outlined for the primary analysis.

The characteristics of the patients will be compared between those who had high compliance and those who did not. Patterns of non-compliance will be compared between the treatment groups. In the event that substantial differences in non-compliance patterns are found, inverse probability of censoring weights (IPCW) will be used in the analysis model.

10.5.4 Handling Missing data

Data will only be used for visits where EDSS was recorded. This can be either EDSS from an in-person clinic visit or telephone EDSS.

Table 6: Definition of the estimand for the secondary analysis of the primary endpoint to assess treatment effectiveness with high compliance with high dose (80mg) simvastatin

Aspect	Definition
Treatment conditions	Intervention - high dose (80mg) simvastatin Usual care – placebo (2 tablets)
Population	Patients with progressive multiple sclerosis aged between 25 and 65 years, with EDSS between 4.0 and 6.5 at time of starting treatment, who are able to comply with high dose (80mg/2 tablets) treatment.
Endpoint	Confirmed disability progression on the EDSS up to 48 months
Summary measure	Hazard ratio
Handling of intercurrent events	
Death due to MS	Composite – death due to MS counts as confirmed progression
Death due to non-MS causes	While-alive
Non-compliance or treatment discontinuation due to adverse events	Hypothetical – absence of non-compliance
Non-compliance or treatment discontinuation due to patient/clinician decision	Hypothetical – absence of non-compliance
Non-compliance or treatment discontinuation due to COVID-19 pandemic (e.g. unable to attend clinic for safety tests)	Hypothetical – absence of non-compliance
Remote data collection because patient unable to attend for in-person visit	Composite – where available telephone EDSS will be used in place of the planned clinic visit EDSS

10.6 PRIMARY ENDPOINT: SECONDARY ANALYSIS TO ESTIMATE TREATMENT EFFECT WITH HIGH COMPLIANCE WITH LOW OR HIGH DOSE TREATMENT

This is a per-protocol analysis that will compare time to first confirmed disability progression on EDSS up to 48 months after randomisation in those who were able to comply with either high or low dose simvastatin treatment.

10.6.1 Estimand

Table 7 defines the estimand of interest for this secondary analysis. This analysis aims to estimate the effect of high or low dose simvastatin treatment in the patients who had high compliance with randomised treatment for the first 36 months of the study.

10.6.2 Analysis Population

The secondary analysis will include data from participants who completed 36 months of follow-up and complied with either low or high dose protocol treatment (40 or 80mg/1 or 2 tablets) on at least 90% of days over this period (see section 8.1 for more details).

Patients will be censored if they die from non-MS causes, withdraw from the study for any reason, or at the last visit at which confirmed progression could have occurred as defined for the primary analysis. Death due to MS will be considered a confirmed progression event.

Table 7: Definition of the estimand for the secondary analysis of the primary endpoint to assess treatment effectiveness with high compliance with high (80mg) or low (40mg) dose simvastatin

Aspect	Definition
Treatment conditions	Intervention - high dose (80mg) or low dose (40mg) simvastatin Usual care – placebo (2 or 1 tablets)
Population	Patients with progressive multiple sclerosis aged between 25 and 65 years, with EDSS between 4.0 and 6.5 at time of starting treatment, who are able to comply with high or low dose simvastatin treatment (80mg or 40mg).
Endpoint	Confirmed disability progression on the EDSS up to 48 months
Summary measure	Hazard ratio
Handling of intercurrent events	
Death due to MS	Composite – death due to MS counts as confirmed progression
Death due to non-MS causes	While-alive
Non-compliance or treatment discontinuation due to adverse events	Hypothetical – absence of non-compliance
Non-compliance or treatment discontinuation due to patient/clinician decision	Hypothetical – absence of non-compliance
Non-compliance or treatment discontinuation due to COVID-19 pandemic (e.g. unable to attend clinic for safety tests)	Hypothetical – absence of non-compliance
Remote data collection because patient unable to attend for in-person visit	Composite – where available telephone EDSS will be used in place of the planned clinic visit EDSS

10.6.3 Analysis model

To estimate the treatment the same Cox proportional hazards model will be used as outlined for the primary analysis.

The characteristics of the patients will be compared between those who had high compliance and those who did not. Patterns of non-compliance will be compared between the treatment groups. In the event that substantial differences in non-compliance patterns are found, inverse probability of censoring weights (IPCW) will be used in the analysis model.

10.6.4 Handling Missing data

Data will only be used for visits where EDSS was recorded. This can be either EDSS from an in-person clinic visit or telephone EDSS.

10.7 SECONDARY ENDPOINT: MULTICOMPONENT MEASURE OF DISABILITY PROGRESSION

This endpoint is confirmed disability progression on the multi-component measure (EDSS, MSFC 25ft walk, MSFC 9HPT) which will be assessed from the data collected up to 36 months after randomisation.

10.7.1 Estimand

Table 8 defines the estimand of interest.

10.7.2 Analysis Population

The analysis will include all participants as randomised, irrespective of subsequent compliance with allocated treatment (i.e. including all participants whether or not they took the prescribed study medication).

Patients who die due to MS will be included in the analysis population and death due to MS will be considered a confirmed progression event.

Patients who die from other causes or withdraw from the study for any reason before 36 months will not be included in the analysis.

10.7.3 Analysis model

To estimate the treatment effect an odds ratio and 95% confidence interval will be calculated using a mixed effects logistic regression model. The model will allow for between centre variability by including a random intercept for centre. The other variables included in the minimisation process will be included as fixed effects.

10.7.4 Handling Missing Data

Patients who have missing data on the time for the 25ft walk or 9HPT because they could not complete the test due to the severity of their MS will be considered to have progressed on that measure at that visit.

The analysis will not use visits where patients have missing data on the time for the 25ft walk or 9HPT because they did not attend the visit in person, or because the test was not done for operational reasons.

Data will only be used from patients who have data available on confirmed progression on the composite outcome at 36 months.

Table 8: Definition of the estimand for analysis of the multicomponent disability endpoint

Aspect	Definition
Treatment conditions	Intervention - high dose (80mg) simvastatin Usual care – placebo (2 tablets)
Population	Patients with progressive multiple sclerosis as defined in Table 3 for the primary analysis.
Endpoint	Confirmed disability progression on multicomponent measure, defined as confirmed progression on either EDSS, MSFC 25ft walk or MSFC 9HPT up to 36 months.
Summary measure	Odds ratio
Handling of intercurrent events	
Death due to MS	Composite – death due to MS is counted as confirmed progression.
Death due to non-MS causes	While-alive
Unable to complete test due to MS severity	Composite – if unable to complete the MSFC 25ft walk or MSFC 9HPT due to MS this will count as confirmed progression.
Unable to complete test for operational reasons (e.g. equipment not available)	Hypothetical
Unable to complete test due to the COVID-19 pandemic (remote visit)	Hypothetical
Remote data collection because patient unable to attend for in-person visit	Composite – where available telephone EDSS will be used in place of the planned clinic visit EDSS
Non-compliance or treatment discontinuation due to adverse events	Treatment Policy
Non-compliance or treatment discontinuation due to patient/clinician decision	Treatment Policy
Non-compliance or treatment discontinuation due to COVID-19 pandemic	Treatment Policy

10.8 SECONDARY ENDPOINT: INDIVIDUAL COMPONENTS OF DISABILITY PROGRESSION

These endpoints will be confirmed disability progression on the MSFC 25ft walk and confirmed disability progression on MSFC 9HPT which will be assessed from the data collected up to 36 months after randomisation. These outcomes will be analysed using the same approach as for the multi-component disability progression outcome.

10.9 SECONDARY ENDPOINT: MULTIPLE SCLEROSIS FUNCTIONAL COMPOSITE (MSFC)

The MSFC composite Z-score at each visit will be calculated according to the MSFC manual with standardisation to the MS-STAT2 baseline scores (Fischer et al, 2001).

The endpoint of interest will be comparison of the mean score at 36 months.

10.9.1 Estimand

Table 9 defines the estimand of interest. This analysis aims to estimate the effect of the treatment policy of offering patients with SPMS high dose simvastatin treatment for 36 months.

Table 9: Definition of the estimand for comparison of MSFC Z-score between groups

Aspect	Definition
Treatment conditions	Intervention - high dose (80mg) simvastatin Usual care – placebo (2 tablets)
Population	Patients with progressive multiple sclerosis as defined in Table 3 for the primary analysis.
Endpoint	MSFC composite Z-score at 36 months
Summary measure	Difference in means
Handling of intercurrent events	
Death due to MS	While-alive
Death due to non-MS causes	While-alive
Unable to complete test due to MS severity	Composite – if unable to complete the test the patient will be given the maximum allowable time (25ft walk, 9HPT) or lowest possible score (SDMT)
Unable to complete test for operational reasons	Hypothetical
Unable to complete test due to the COVID-19 pandemic (remote visit)	Hypothetical
Non-compliance or treatment discontinuation due to adverse events	Treatment Policy
Non-compliance or treatment discontinuation due to patient/clinician decision	Treatment Policy
Non-compliance or treatment discontinuation due to COVID-19 pandemic	Treatment Policy

10.9.2 Analysis Population

The analysis will include all participants as randomised, irrespective of subsequent compliance with allocated treatment (i.e. including all participants whether or not they took the prescribed study medication).

Patients who die due to MS or die from other causes will be excluded from the analysis.

Patients who withdraw from the study for any reason before 36 months will be included in the analysis, where they have baseline MSFC composite Z-score available.

10.9.3 Analysis model

The difference in mean Z-score at 36 months will be compared between the groups using a linear mixed model, commonly referred to a Mixed Model for Repeated Measures (MMRM). MSFC Z-score at baseline and 36 months will be the outcome variable in the model. Treatment group will be included in the model but at baseline the treatment effects will be constrained to be zero, which is essentially equivalent to allowing adjustment for the baseline MSFC Z-score (Kenward et al., 2010, Liu et al., 2009). An unstructured covariance matrix for the residuals will be used to allow for correlation between repeated measures on an individual. The minimisation variables 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), site [31 sites]], and their interactions with visit, will be included as fixed effects.

The assumptions underlying the model will be assessed and if there is substantial violation of the parametric assumptions, bias corrected and accelerated bootstrap confidence intervals will be used for inference. Bootstrap samples will be taken with clustering on individual and will be stratified by study site and treatment group.

10.9.4 Handling Missing Data

Patients who have missing data on the time for the 25ft walk due to disability will be given a time of 180 seconds, which is the maximum allowable time to complete the walk. Where participants cannot complete the 9HPT due to disability they will be given a time of 300 seconds, which is the maximum allowable time to complete the test. For participants who could not complete the SDMT due to disability a score of 0 will be used.

No imputation will be made for patients who have missing data for other reasons (e.g. lack of equipment). These visits will not be used in the analysis.

10.10 SECONDARY ENDPOINT: MSFC TIMED 25 FOOT WALK

Analysis of T25FW will be based on the inverse (reciprocal) of the mean time (in seconds) of the two trials, as it is expected this will be more normally distributed than walk time or the Z-score for walk time.

The difference in means at 36 months for each component of MSFC will be compared between the group using a mixed effects model as outlined above for the MSFC composite Z-score in section 10.9.

10.11 SECONDARY ENDPOINT: MSFC 9 HOLE PEG TEST (9HPT)

Analysis of 9HPT will be based on the average of: the inverse (reciprocal) of the mean time (in seconds) of the two trials on the right hand; and the inverse of the mean time of the two trials on the left hand.

The difference in means at 36 months for each component of MSFC will be compared between the group using a mixed effects model as outlined above for the MSFC composite Z-score in section 10.9.

10.12 SECONDARY ENDPOINT: SLOAN LOW CONTRAST VISUAL ACUITY (SLCVA)

Analysis of SLCVA will use the number of letters correctly identified (binocular vision) at 3 different contrast levels (100%, 2.5% and 1.25%). Each contrast level will be analysed separately, with the score ranging from 0 to 60. The endpoint of interest will be comparison of the mean score at 36 months.

10.12.1 Estimand

Table 10 defines the estimand of interest, which is the same for each contrast level. This analysis aims to estimate the effect of the treatment policy of offering patients with SPMS high dose simvastatin treatment for 36 months.

Table 10: Definition of the estimand for comparison of SLCVA between groups

Aspect	Definition
Treatment conditions	Intervention - high dose (80mg) simvastatin Usual care – placebo (2 tablets)
Population	Patients with progressive multiple sclerosis as defined in Table 3 for the primary analysis.
Endpoint	Number of letters correctly identified at 36 months
Summary measure	Difference in means
Handling of intercurrent events	
Death due to MS	While-alive
Death due to non-MS causes	While-alive
Unable to complete test due to MS severity	Composite – if unable to complete the test the patient will be given a score of zero
Unable to complete test for operational reasons	Hypothetical
Unable to complete test due to the COVID-19 pandemic (remote visit)	Hypothetical
Non-compliance or treatment discontinuation due to adverse events	Treatment Policy
Non-compliance or treatment discontinuation due to patient/clinician decision	Treatment Policy
Non-compliance or treatment	Treatment Policy

discontinuation due to COVID-19 pandemic	

10.12.2 Analysis Population

The analysis will include all participants as randomised, irrespective of subsequent compliance with allocated treatment (i.e. including all participants whether or not they took the prescribed study medication).

Patients who die due to MS or die from other causes will be excluded from the analysis.

Patients who withdraw from the study for any reason before 36 months will be included in the analysis, where they have baseline SLCVA score available.

10.12.3 Analysis model

The difference in means at 36 months will be compared between the groups using a linear mixed model. The SCLVA score at baseline and 36 months will be the outcome variable in the model. Treatment group will be included in the model but at baseline the treatment effects will be constrained to be zero. An unstructured covariance matrix for the residuals will be used to allow for correlation between repeated measures on an individual. The minimisation variables, and their interactions with visit, will be included as fixed effects.

The assumptions underlying the model will be assessed and if there is substantial violation of the parametric assumptions, bias corrected and accelerated bootstrap confidence intervals will be used for inference. Bootstrap samples will be taken with clustering on individual and will be stratified by study site and treatment group.

10.12.4 Handling Missing Data

For participants who could not complete the SLCVA at a given contrast level due to visual disability a score of 0 will be used.

No imputation will be made for patients who have missing data for other reasons (e.g. lack of equipment). These visits will not be used in the analysis.

10.13 SECONDARY ENDPOINT: MODIFIED RANKIN SCALE (MRS)

This endpoint will be evaluated as progression from baseline to 36 months, with any increase in the ordinal score considered a progression event.

10.13.1 Estimand

Table 11 defines the estimand of interest for the primary analysis. This analysis aims to estimate the effect of the treatment policy of offering patients with SPMS high dose simvastatin treatment for 36 months.

10.13.2 Analysis Population

The analysis will include all participants as randomised, irrespective of subsequent compliance with allocated treatment (i.e. including all participants whether or not they took the prescribed study medication).

Patients who die from any cause will be included in the analysis population and death will be considered a confirmed progression event.

Patients who withdraw from the study for any reason before 36 months will not be included in the analysis.

10.13.3 Analysis model

To estimate the treatment effect an odds ratio and 95% confidence interval will be calculated using a mixed effects logistic regression model. The model will allow for between centre variability by including a random intercept for centre. The other variables included in the minimisation process will be included as fixed effects.

10.13.4 Handling Missing Data

Data will only be where mRS was recorded at both baseline and 36 months.

Table 11: Definition of the estimand for comparison of MRS between groups

Aspect	Definition
Treatment conditions	Intervention - high dose (80mg) simvastatin Usual care – placebo (2 tablets)
Population	Patients with progressive multiple sclerosis as defined in Table 3 for the primary analysis.
Endpoint	Disability progression on the mRS up to 36 months
Summary measure	Odds ratio
Handling of intercurrent events	
Death due to MS	Composite – death due to MS will count as progression
Death due to non-MS causes	Composite - death due to non-MS causes will count as progression
Unable to complete assessment due to the COVID-19 pandemic (remote visit)	Hypothetical
Non-compliance or treatment discontinuation due to adverse events	Treatment Policy
Non-compliance or treatment discontinuation due to patient/clinician decision	Treatment Policy
Non-compliance or treatment discontinuation due to COVID-19 pandemic	Treatment Policy

10.14 SECONDARY ENDPOINT: BRIEF INTERNATIONAL COGNITIVE ASSESSMENT FOR MULTIPLE SCLEROSIS (BICAMS)

Scores on California Verbal Learning Test-II (CVLT-II) Brief visuospatial memory test- Revised (BVMT-R) and Symbol Digit Modalities Test (SDMT) will be each analysed separately. To assess the effects of high dose simvastatin on cognition the raw scores on each of the three BICAMS scales (SDMT, CVLT, BVMT) will be compared between groups. The endpoint of interest will be comparison of the mean score at 36 months.

To describe the cognitive profile of the group at baseline the raw scores will be converted into z-scores using an Irish cohort as reference and following methods given by O'Connell et al (2015) to account for age, sex and education level. We will report the numbers and proportions of patients impaired on each scale (scoring lower than -1.5 on the z-score) and the number impaired on 1, 2 or 3 of the scales.

10.14.1 Estimand

Table 12 defines the estimand of interest for the cognitive outcomes.

Table 12: Definition of the estimand for the analysis of cognitive test scores

Aspect	Definition
Treatment conditions	Intervention - high dose (80mg) simvastatin Usual care – placebo (2 tablets)
Population	Patients with progressive multiple sclerosis as defined in Table 3 for the primary analysis.
Endpoint	Cognitive test score at 36 months
Summary measure	Difference in means
Handling of intercurrent events	
Death from any cause	While-alive
Unable to complete test due to MS severity	Composite – if the participant is unable to complete the test due to severity of MS cognitive symptoms they will be given the lowest possible score for that test.
Unable to complete test for operational reasons	Hypothetical
Unable to complete test due to the COVID-19 pandemic (remote visit)	Hypothetical
Non-compliance or treatment discontinuation due to adverse events	Treatment Policy
Non-compliance or treatment discontinuation due to patient/clinician decision	Treatment Policy

Non-compliance or treatment discontinuation due to COVID-19 pandemic	Treatment Policy

10.14.2 Analysis Population

The analysis will include all participants as randomised, irrespective of subsequent compliance with allocated treatment (i.e. including all participants whether or not they took the prescribed study medication).

Patients who die from any cause will be excluded from the analysis population.

Patients who withdraw from the study for any reason will be included in the analysis if they have data available on the cognitive test at baseline.

10.14.3 Analysis model

For each outcome the difference in mean score at 36 months will be compared between the groups using a linear mixed model. The score at baseline and 36 months will be the outcome variable in the model. Treatment group will be included in the model but at baseline the treatment effects will be constrained to be zero. An unstructured covariance matrix for the residuals will be used to allow for correlation between repeated measures on an individual. Minimisation variables, and their interactions with visit, will be included as fixed effects.

The assumptions underlying the model will be assessed and if there is substantial violation of the parametric assumptions, bias corrected and accelerated bootstrap confidence intervals will be used for inference. Bootstrap samples will be taken with clustering on individual and will be stratified by study site and treatment group.

10.14.4 Handling Missing Data

Patients who are not able to complete a test due to problems with their cognition will be included in the analysis. At the visit(s) where the test was not completed due to cognitive problems the patient will be given a score of 0 on that test, which represents the worst possible score.

Patients will not be included if they have missing data at both baseline and 36 months for reasons other than problems with cognition (e.g. patient did not want to complete test).

10.15 SECONDARY ENDPOINT: RELAPSE ASSESSMENT (NUMBER AND SEVERITY)

The relapse rate up to 36 months will be compared between the treatment groups.

10.15.1 Estimand

Table 13 defines the estimand of interest.

10.15.2 Analysis Population

The analysis will include all participants as randomised, irrespective of subsequent compliance with allocated treatment (i.e. including all participants whether or not they took the prescribed study medication).

Patients who die from any cause or who withdraw from the study will be included in the analysis population and their follow-up time accounted for in the analysis.

10.15.3 Analysis model

A mixed effects negative binomial regression model will be used to compare relapse rate between the treatment groups. The model will allow for between centre variability by including a random intercept for centre. The other variables included in the minimisation process will be included as fixed effects. Follow-up time in years will be included as an offset in the model.

A descriptive listing of severity of relapses will also be provided by treatment group.

10.15.4 Handling Missing Data

This analysis will be based on the number of relapses reported for each patient during the trial. It will be assumed that reporting of relapse is complete.

Table 13: Definition of the estimand for the analysis of relapse rate

Aspect	Definition
Treatment conditions	Intervention - high dose (80mg) simvastatin Usual care – placebo (2 tablets)
Population	Patients with progressive multiple sclerosis as defined in Table 3 for the primary analysis.
Endpoint	Rate of relapse up to 36 months
Summary measure	Incidence rate ratio
Handling of intercurrent events	
Death from any cause	While-alive
Non-compliance or treatment discontinuation due to adverse events	Treatment Policy
Non-compliance or treatment discontinuation due to patient/clinician decision	Treatment Policy
Non-compliance or treatment discontinuation due to COVID-19 pandemic	Treatment Policy

10.15.5 COVID-19 pandemic subgroup analysis

To investigate the potential effect of the COVID-19 pandemic on relapses or on the effects of treatment on relapses the follow-up will be split into three periods:

- Prior to 16th March 2020
- From 16th March 2020 to 19th July 2021
- After 19th July 2021

The relapse rate will be calculated for each period by treatment group by splitting each participants follow-up time according to these periods. A mixed effects negative binomial regression model will be fitted for each time period to model the relapse rate during each time period. As specified in section 10.15.3 these models will allow for between centre variability by including a random intercept for centre. The other variables included in the minimisation process will be included as fixed effects. Follow-up time in years during the relevant timer period will be included as an offset in the model. A Wald test based will be used to will be used to assess whether there is evidence of a difference in relapse rate between the above periods and whether there is any evidence that the treatment effect differed between the three time periods. The variance-covariance matrix for the relevant coefficients for the Wald test will be obtained via bootstrapping. Bootstrap samples will be taken with clustering on individual and will be stratified by study site and treatment group.

10.16 SECONDARY ENDPOINT: MS IMPACT SCALE-29 V2 (MSIS-29V2)

MSIS-29 total scores and the physical and psychological subscores will separately analysed.

10.16.1 Estimand

Table 14 defines the estimand of interest. This analysis aims to estimate the effect of the treatment policy of offering patients with SPMS high dose simvastatin treatment for 36 months.

10.16.2 Analysis Population

The analysis will include all participants as randomised, irrespective of subsequent compliance with allocated treatment (i.e. including all participants whether or not they took the prescribed study medication).

Patients who die due to MS or die from other causes will be excluded from the analysis.

Patients who withdraw from the study for any reason before 36 months will be included in the analysis, where they have data on MSIS available at one or more visits.

10.16.3 Analysis model

The difference in mean score 36 months will be compared between the groups using a linear mixed model. The score at each time point (baseline, 12, 24, 36 months) will be the outcome variable in the model. An interaction between visit and treatment group will allow for estimation the mean difference in score at each visit. At baseline the treatment effects will be constrained to be zero. An unstructured covariance matrix for the residuals will be used to allow for correlation between repeated measures on an individual. The minimisation variables, and their interactions with visit, will be included as fixed effects.

The assumptions underlying the model will be assessed and if there is substantial violation of the parametric assumptions, bias corrected and accelerated bootstrap confidence intervals will be used for inference. Bootstrap samples will be taken with clustering on individual and will be stratified by study site and treatment group.

10.16.4 Handling Missing Data

Patients who have missing data at all visits will be excluded from the analysis.

Table 14: Definition of the estimand for analysis of patient reported outcomes

Aspect	Definition
Treatment conditions	Intervention - high dose (80mg) simvastatin Usual care – placebo (2 tablets)
Population	Patients with progressive multiple sclerosis as defined in Table 3 for the primary analysis.
Endpoint	Score at 36 months
Summary measure	Difference in means
Handling of intercurrent events	
Death due to MS	While-alive
Death due to non-MS causes	While-alive
Unable to complete for operational reasons	Hypothetical
Responses altered due to due to COVID-19 pandemic restrictions (e.g. lockdowns)	Treatment Policy
Non-compliance or treatment discontinuation due to adverse events	Treatment Policy
Non-compliance or treatment discontinuation due to patient/clinician decision	Treatment Policy
Non-compliance or treatment discontinuation due to COVID-19 pandemic	Treatment Policy

10.16.5 COVID-19 pandemic subgroup analysis

To investigate the potential effect of the COVID-19 pandemic on the MSIS-29, study visits will be split according to whether they occurred:

- Prior to 16th March 2020

- Between 16th March 2020 and 2nd August 2021 (19th July 2021 plus two weeks to allow MSIS-29 recall period to be after the end of COVID-19 restrictions)
- After 2nd August 2021

The analysis model specified in 10.16.3 will be extended to include indicator variables for the period when the visit occurred will be included in the model as predictors along with their interaction with treatment group to allow the mean score to differ according to whether the questionnaire asked about MS impact during a period when COVID-19 public health restrictions were in force. Wald tests will be used to assess whether there is evidence of a difference in means between periods and whether there any evidence that the treatment effect differed between the three time periods.

10.17 SECONDARY ENDPOINT: MS WALKING SCALE-12 V2 (MSWS-12V2)

Group means on the MSWS-12v2 will be compared at 36 months using a linear mixed model including all available time points (baseline, 12, 24, 36 months) as outlined above for the MSIS in section 10.16.3. A COVID-19 pandemic subgroup analysis will be conducted as outline above for MSIS in section 10.16.5.

10.18 SECONDARY ENDPOINT: MODIFIED FATIGUE INDEX SCALE - 21(MFIS-21)

Group means on the MFIS-21 will be compared at 36 months using a linear mixed model including all available time points (baseline, 12, 24, 36 months) as outlined above for the MSIS in section 10.16.3. A COVID-19 pandemic subgroup analysis will be conducted as outline above for MSIS in section 10.16.5, but for MSFIS the this subgroup analysis will split visits according to whether they occurred:

- Prior to 16th March 2020
- Between 16th March 2020 and 16th August 2021 (19th July 2021 plus four weeks to allow for MSFIS-21 recall period)
- After 16th August 2021

10.19 SECONDARY ENDPOINT: CHALDER FATIGUE QUESTIONNAIRE (CFQ)

Group means on the CFQ will be compared at 36 months using a linear mixed model including all available time points (baseline, 12, 24, 36 months) as outlined above for the MSIS in section 10.16.3. A COVID-19 pandemic subgroup analysis will be conducted as outline above for MSIS in section 10.16.5, but for CFQ the subgroup analysis will split visits according to whether they occurred:

- Prior to 16th March 2020
- Between 16th March 2020 and 19th August 2021 (19th July 2021 plus one month to allow for CFQ recall period)
- After 19th August 2021

11 SENSITIVITY ANALYSIS TO ASSESS THE IMPACT OF THE COVID-19 PANDEMIC ON PATIENT REPORTED ENDPOINTS

Although patient reported outcomes were measured during the COVID-19 pandemic using remote data collection, public health restrictions such as lockdowns could have influenced the answers patients gave to these questionnaires. Therefore, a secondary sensitivity analysis will be conducted which aims to estimate the effect of treatment on these outcomes during time periods when COVID-

19 related restrictions were not in force. This analysis will use data on participants who were randomised before 16th March 2020 and who had the 36 month visit after 19th July 2021 plus the relevant recall period (e.g. after 2nd August 2021 for the MSIS-29). The analysis will compare outcomes at 36 months adjusting for the baseline score and will not make use of the data at interim visits which may have occurred during the pandemic.

11.1 MS IMPACT SCALE-29 V2 (MSIS-29V2)

MSIS-29 total scores and the physical and psychological subscores will separately analysed.

11.1.1 Estimand

Table 15 defines the estimand of interest. This analysis aims to estimate the effect of the treatment policy of offering patients with SPMS high dose simvastatin treatment for 36 months, in the hypothetical scenario that there were no restrictions to participants' daily activities because of the COVID-19 pandemic.

11.1.2 Analysis Population

The analysis will include all participants who were randomised before 16th March 2020 and who had the 36 month visit after 2nd August 2021.

The analysis will include all participants as randomised, irrespective of subsequent compliance with allocated treatment (i.e. including all participants whether or not they took the prescribed study medication).

Patients who die due to MS or die from other causes will be excluded from the analysis.

Patients who withdraw from the study for any reason before 36 months will be included in the analysis, where they have data on MSIS available at baseline.

Table 15: Definition of the estimand for sensitivity analysis of patient reported outcomes

Aspect	Definition
Treatment conditions	Intervention - high dose (80mg) simvastatin Usual care – placebo (2 tablets)
Population	Patients with progressive multiple sclerosis as defined in Table 3 for the primary analysis.
Endpoint	Score at 36 months
Summary measure	Difference in means
Handling of intercurrent events	
Death due to MS	While-alive
Death due to non-MS causes	While-alive
Unable to complete for operational reasons	Hypothetical
Responses altered due to due to COVID-19 pandemic restrictions (e.g. lockdowns)	Hypothetical

Non-compliance or treatment discontinuation due to adverse events	Treatment Policy
Non-compliance or treatment discontinuation due to patient/clinician decision	Treatment Policy
Non-compliance or treatment discontinuation due to COVID-19 pandemic	Treatment Policy

11.1.3 Analysis model

The difference in mean score 36 months will be compared between the groups using a linear mixed model. The score at baseline and 36 months will be the outcome variable in the model. An interaction between visit and treatment group will allow for estimation the mean difference in score at each visit. At baseline the treatment effects will be constrained to be zero. An unstructured covariance matrix for the residuals will be used to allow for correlation between repeated measures on an individual. The minimisation variables, and their interactions with visit, will be included as fixed effects.

The assumptions underlying the model will be assessed and if there is substantial violation of the parametric assumptions, bias corrected and accelerated bootstrap confidence intervals will be used for inference. Bootstrap samples will be taken with clustering on individual and will be stratified by study site and treatment group.

11.1.4 Handling Missing Data

Patients who have missing data at both baseline and 36 months will be excluded from the analysis.

11.2 MS WALKING SCALE-12 V2 (MSWS-12V2)

Group means on the MSWS-12v2 will be compared at 36 months using a linear mixed model as outlined above for the MSIS in section 11.1. The analysis will include all participants who were randomised before 16th March 2020 and who had the 36 month visit after 2nd August 2021.

11.3 MODIFIED FATIGUE INDEX SCALE - 21(MFIS-21)

Group means on the MFIS-21 will be compared at 36 months using a linear mixed model as outlined above for the MSIS in section 11.1. The analysis will include all participants who were randomised before 16th March 2020 and who had the 36 month visit after 16th August 2021.

11.4 CHALDER FATIGUE QUESTIONNAIRE (CFQ)

Group means on the CFQ will be compared at 36 months using a linear mixed model as outlined above for the MSIS in section 11.1. The analysis will include all participants who were randomised before 16th March 2020 and who had the 36 month visit after 19th August 2021.

12 EVALUATION OF SAFETY PARAMETERS

12.1 Adverse Events

Tables will be produced showing the numbers of the following types of adverse event and numbers and proportions of patients experiencing each type of adverse event by study group:

- Any adverse event
- Serious adverse events (SAEs)
- Serious adverse reactions
- Notifiable adverse events (NAEs)
- Deaths

Tables will be produced to show the number each type of event by system organ class. The number and proportion of deaths in each group will be tabulated according to underlying cause of death (MS/non-MS).

A detailed listing of individual SAEs will be provided, displaying details of the event(s) captured on the SAE form. A detailed listing of the deaths will be provided.

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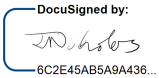
Jennifer Nicholas jennifer.nicholas@lshtm.ac.uk Trial Statistician Security Level: Email, Account Authentication (Optional)	DocuSigned by:  6C2E45AB5A9A436... Signature Adoption: Uploaded Signature Image Using IP Address: 194.80.229.244	Sent: 01 July 2024 | 17:11 Viewed: 02 July 2024 | 12:32 Signed: 02 July 2024 | 12:32
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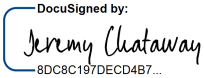
Jeremy Chataway j.chataway@ucl.ac.uk Chief Investigator Security Level: Email, Account Authentication (Optional)	DocuSigned by:  8DC8C197DECD4B7... Signature Adoption: Pre-selected Style Using IP Address: 77.103.46.70	Sent: 01 July 2024 | 17:11 Viewed: 02 July 2024 | 06:40 Signed: 02 July 2024 | 06:40
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