Multiple Sclerosis-Secondary Progressive Multi-Arm Randomisation Trial (MS-SMART): a multiarm phase IIb randomised, double-blind, placebo-controlled clinical trial comparing the efficacy of three neuroprotective drugs in secondary progressive multiple sclerosis

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ABSTRACT

Introduction The major unmet need in multiple sclerosis (MS) is for neuroprotective therapies that can slow (or ideally stop) the rate of disease progression. The UK MS Society Clinical Trials Network (CTN) was initiated in 2007 with the purpose of developing a national, efficient, double-blind, multiarm trial of repurposed drugs. Key underpinning work was commissioned by the CTN to inform the design, outcome selection and drug choice including animal models and a systematic review. This identified seven leading oral agents for repurposing as neuroprotective therapies in secondary progressive MS (SPMS). The purpose of the Multiple Sclerosis-Secondary Progressive Multi-Arm Randomisation Trial (MS-SMART) will be to evaluate the neuroprotective efficacy of three of these drugs, selected with distinct mechanistic actions and previous evidence of likely efficacy, against a common placebo arm. The interventions chosen were: amiloride (acid-sensing ion channel antagonist); fluoxetine (selective serotonin reuptake inhibitor) and riluzole (glutamate antagonist).

Methods and analysis Patients with progressive SPMS will be randomised 1:1:1:1 to amiloride, fluoxetine, riluzole or matched placebo and followed for 96 weeks. The primary outcome will be the percentage brain volumetric brain MRI (PBVC) volume change (PBVC) between baseline and 96 weeks, derived from structural MR brain imaging data using the Structural Image Evaluation, using Normalisation, of Atrophy method. With a sample size of 90 per arm, this will give 90% power to detect a 40% reduction in PBVC in any active arm compared with placebo and 80% power to detect a 35% reduction (analysing by analysis of covariance and with adjustment for multiple comparisons of three 1.67% two-sided tests), giving a 5% overall two-sided significance level. MS-SMART is not powered to detect differences between the three active treatment arms. Allowing for a 20% dropout rate, 110 patients per arm will be randomised. The study will take place at Neuroscience centres in England and Scotland.

Ethics and dissemination MS-SMART was approved by the Scotland A Research Ethics Committee on 13 January 2013 (REC reference: 13/SS/0007). Results of the study will be submitted for publication in a peer-reviewed journal.

Strengths and limitations of this study

► The Multiple Sclerosis -Secondary Progressive Multi-Arm Randomisation Trial (MS-SMART) will be the first multi-arm efficient trial design in progressive multiple sclerosis.
► UK MS society developed the national trial with strong public patient involvement.
► It will test three active repurposed agents with distinct mechanistic profiles based on systematic review.
► The primary outcome in this phase IIb trial will be volumetric brain MRI.
► A definitive disability outcome phase III trial will be needed for any successful candidate drug identified from MS-SMART.
INTRODUCTION

Multiple sclerosis (MS) is a disease of the central nervous system estimated to affect >2.5 million people globally; it is the most common non-traumatic cause of acquired disability for young adults in the industrialised world.1 Most people with MS (PwMS) experience two clinical phases reflecting distinct, but inter-related pathological processes: focal inflammation driving the relapsing-remitting phase (RRMS), whereas neurodegeneration represents the principal substrate of secondary progression (SPMS).2 Conversion to secondary progressive MS occurs at around 2%-5% per annum (typically 10–15 years into the disease trajectory), and is characterised by accumulating and irreversible disability across a range of functions such as walking, balance, vision, cognition, continence and pain control.3 In contrast to the increasing number of effective anti-inflammatory disease-modifying treatments for relapsing-remitting disease, the paucity of therapies for progressive disease represents a major unmet clinical need,5 although since this trial commenced, some success has now been seen for ocrelizumab in primary progressive MS and siponimod in SPMS.6

Within the wider context of issues relevant to all drug development programmes, such as high costs and the prolonged time from target selection to regulatory approval, the failure of therapeutic development for SPMS using conventional pipelines8 has led to interest in novel approaches such as ‘drug rescue’ (evaluating drugs at advanced stage of development but abandoned before approval) and ‘repurposing’ (evaluating drugs already approved for other indications),9 this offers the potential to reduce both the cost and time taken to achieve licensed approval status.10 As development costs are brought within a range acceptable to public and third-sector funders, the opportunity for investigator-led phase II/III research increases.

Delivering a successful repositioned neuroprotective treatment for SPMS nevertheless represents a substantial challenge. The prior failure to develop such therapies likely reflects a combination of factors, which include the limited predictive value of existing animal models.11,12 Although such experimental systems capture aspects of the disease, they fail to replicate the complex and multifaceted pathology that underpins neurodegeneration in SPMS including: microglial activation, chronic oxidative injury, accumulation of mitochondrial damage in axons with imbalance of ionic homeostasis and age-related iron accumulation in the human brain.13 The relative importance of these processes, and the therapeutic value of targeting components in isolation remains unclear.14 Given the highly complex pathology of SPMS, an optimum strategy to select drugs for evaluation in repositioning trials has not yet been established. The UK MS Society Clinical Trials Network was initiated in 2007 with a core tenet to develop trials in progressive MS where success had been lacking. Key underpinning work was commissioned to improve trial design, examine available outcomes (interim and final) and systematically review the animal and human data on possible candidate drugs. Based on recognition of substantial mechanistic overlap between SPMS and other ‘classic’ neurodegenerative disorders such as Alzheimer’s disease,15 we performed a systematic review and meta-analysis of all published clinical and preclinical research investigating putative oral neuroprotective drugs in MS, Alzheimer’s disease, Huntington’s disease, amyotrophic lateral sclerosis and Parkinson’s disease. We identified seven agents as lead candidates for therapeutic evaluation.16

These were ibudilast, riluzole, amiloride, pirfenidone, fluoxetine, oxcarbazepine and the polyunsaturated fatty-acid class (linoleic acid, linoleic acid; omega-3 fatty acid, Max EPA oil). The initial choice was amiloride, riluzole and ibudilast, but due to drug supply issues, ibudilast was substituted with fluoxetine.

Testing neuroprotection in SPMS also presents several major challenges relating to trial design such as subject and disease heterogeneity, and the selection of relevant outcomes and end points.14,17 In particular, poor reliability and responsiveness for benchmark clinical outcomes such as the Expanded Disability Status Scale (EDSS) presents a substantial problem for phase III trials.18 Newer clinical disability scales such as the Multiple Sclerosis Functional Composite (MSFC) offer improved psychometric properties, and have recommended definitions for clinically meaningful change.19 However, the selection of relevant end points to evaluate clinically meaningful neuroprotection remains a matter of ongoing debate, with some advocating ‘hard’ definitions such as the composite ‘dead or dependent’.20 In contrast, MRI measures of brain tissue volume reduction over time (brain atrophy) provide both a biomarker of neurodegeneration and a surrogate outcome for disease progression with feasible sample size requirements to support proof-of-concept evaluation at phase II.21 Neuroprotection in SPMS based on MR brain atrophy measurement has been successfully demonstrated in a recent placebo-controlled randomised controlled trial evaluating high-dose simvastatin (MS-STAT).22 The area has recently been comprehensively reviewed.23

Against this background, we set out to design a phase IIb multiamti randomised placebo-controlled trial (MS-SMART; NCT01910259) that would simultaneously evaluate three repurposed oral neuroprotective agents from our previously identified selection of lead candidates. MS-SMART tests the hypothesis that treatment with amiloride or riluzole or fluoxetine versus placebo reduces the rate of brain atrophy in SPMS. In this article, we describe in detail the trial design, rationale for the drug selection and all pre-specified analyses. The trial has fully recruited and is in follow-up, with the last patient last visit occurring on 4th July 2018. This article refers to the current protocol (V7, date 4 June 2018).

METHODS AND ANALYSIS

Trial objectives

The primary objective of MS-SMART is to establish whether amiloride or fluoxetine, or riluzole can slow the rate of brain volume loss in SPMS over 96 weeks, against placebo, using MRI-derived percentage brain volume change (PBVC). Secondary objectives are to: (i) establish that a multiamti trial strategy is an efficient way of...
screening drugs in SPMS. (ii) Evaluate anti-inflammatory drug activity using the count of new and enlarging T2 lesions. (iii) Examine for evidence of pseudo-atrophy by MRI. (iv) Examine for clinical efficacy as measured by clinician (EDSS, MSFC, symbol digit modalities test [SDMT], Sloan low-contrast visual acuity [SLCVA] and relapse rate) and patient-reported outcomes (multiple sclerosis impact scale version two [MSIS29v2], multiple sclerosis walking scale version two [MSWSv2]), pain (numeric pain rating scale [NPRS], brief pain inventory [BPI], neuropathic pain scale [NPS]) and fatigue (neurological fatigue index [NFI]). (v) Collect basic health economic data based on the EuroQol five dimensions questionnaire (EQ-5D-5L).

Exploratory objectives are to evaluate putative neuroprotection by: (i) proportion of new and enlarging T2 lesions at 24 weeks being persistently T1 hypointense at week 96; (ii) grey matter brain volume change. In certain centres (UCL/Edinburgh), further advanced metrics are measured (not described further here): MR spectroscopy, MR magnetisation transfer ratio, cervical cord imaging, optical coherence tomography and cerebrospinal fluid neurofilament levels.

Overview of design
MS-SMART is a phase IIB multicentre, multiarm, double-blind, randomised placebo-controlled trial that compares three oral repurposed candidate neuroprotective therapies (amiloride 5 mg twice a day, fluoxetine 20 mg twice a day and riluzole 50 mg twice a day) against a shared placebo arm in people with SPMS. The primary end point is brain volume loss over 96 weeks as measured using MRI-derived PBVC. Four hundred and forty participants randomised in a 1:1:1:1 ratio. Participants will be evaluated during nine study visits and a final telephone safety evaluation at week 100 (figure 1).

PARTICIPANTS, INTERVENTIONS AND OUTCOMES
Trial setting
MS-SMART will be conducted across 13 UK hospital research facilities in London, Edinburgh, Liverpool, Sheffield, Brighton, Truro, Oxford, Stoke-on-Trent, Plymouth, Newcastle, Leeds, Nottingham and Glasgow. All imaging acquisition will be performed in the local neuro-imaging facility before being transferred to the central facility (Queen Square MS Centre) for central quality control and blinded analysis.

Eligibility criteria
Inclusion and exclusion criteria for MS-SMART are shown in table 1.

Ascertainment and recruitment
Potential participants will be identified through five routes. (i) Clinics run by principal investigators (PIs) or associated neurologists at participating sites. (ii) Clinics run at other MS centres/neuroscience/hospital centres set up as participant identification centres. (iii) Through existing MS research and other databases such as the Scottish Health Research Register (SHARE, http://www.registerforshare.org) that contain contact details of people who have consented to be contacted directly about relevant research opportunities. (iv) By general practitioners (GPs) at routine appointments. (v) By self-referral from potential participants, in particular using the http://

Figure 1  Multiple Sclerosis-Secondary Progressive Multi-Arm Randomisation Trial participant timeline.


### Table 1  Multiple Sclerosis-Secondary Progressive Multi-Arm Randomisation Trial eligibility criteria (protocol V.7)

#### Inclusion criteria

- Confirmed diagnosis of SPMS. Steady progression rather than relapse must be the major cause of increasing disability in the preceding 2 years. Progression can be evident from either an increase of at least one point in EDSS or clinical documentation of increasing disability in patients notes.
- EDSS 4.0–6.5.
- Aged 25–65 inclusive.
- Women and men with partners of childbearing potential must be using an appropriate method of contraception to avoid any unlikely teratogenic effects of the three drugs from time of consent, to 6 weeks after treatment inclusive.
- Women must have a negative pregnancy test within 7 days prior to the baseline visit unless not of childbearing potential (eg, have undergone a hysterectomy, bilateral tubal ligation or bilateral oophorectomy or they are postmenopausal).
- Willing and able to comply with the trial protocol (eg, can tolerate MRI and fulfils the requirements for MRI, eg, not fitted with pacemakers or permanent hearing aids), ability to understand and complete questionnaires.
- Written informed consent provided.

#### Exclusion criteria

- Pregnancy or breastfeeding patients.
- Baseline MRI scan not of adequate quality for analysis (eg, too much movement artefact).
- Significant organ comorbidity (eg, malignancy or renal or hepatic failure).
- Relapse within 3 months of baseline visit.
- Patients who have been treated with intravenous or oral steroids for an MS relapse/progression within 3 months of baseline visit (these patients can undergo future screening visits once the 3-month window has expired), patients on steroids for another medical condition may enter as long as the steroid prescription will be not for MS (relapse/progression).
- Use of simvastatin at 80 mg dose within 3 months of baseline visit (lower doses of simvastatin and other statins are permissible).
- Commencement of fampridine within 6 months of baseline visit.
- Use of immunosuppressants (eg, azathioprine, methotrexate, ciclosporin) or first-generation disease-modifying treatments (β-interferons, glatiramer) within 6 months of baseline visit.
- Use of fingolimod, fumarate, teriflunomide, laquinimod or other experimental disease-modifying treatment (including research in an investigational medicinal product) within 12 months of baseline visit.
- Use of mitoxantrone, natalizumab, alemtuzumab, daclizumab, if treated within 12 months of baseline visit.
- Primary progressive MS.
- Relapsing-remitting MS.

ALT, Alanine aminotransferase; AST, Aspartate aminotransferase; EDSS, Expanded Disability Status Scale; GT, glutamyl transferase; LFT, liver function test; MS, multiple sclerosis; SPMS, secondary progressive multiple sclerosis; SSRI, selective serotonin-reuptake inhibitor; WBC, white blood cells.

www.ms-smart.org/ website. All such referrals (or patient self-referrals) will require medical history records to confirm that they have MS as per usual clinical practice and any other relevant medical conditions.

Depending on the route of identification several processes to provide information and 'prescreen' for eligibility will be permissible. Candidate participants will be briefed in clinic about the study directly by a member of the clinical team; ‘prescreening’ to ensure that the people with MS will be likely to fulfil the general criteria to enter the trial and candidate participants will be given a patient information leaflet (PIL). Alternatively, candidate participants will receive an initial telephone contact from a member of the research team to explain the trial and ‘prescreen’. Potential participants will then be recontacted by the study team at an interval no less than 24 hours after receiving the PIL to ask if they wish to proceed to screening. If required and following documented permission from the potential participant, their neurologist/GP will also be contacted.
to provide written confirmation of the patient’s medical status with respect to relevant eligibility criteria. This will take place prior to the screening visit in order to avoid unnecessary visits.

The screening visit will involve documentation of written informed consent. Evaluation against trial eligibility criteria will then be performed by individuals who are National Health Service employees (substantive or honorary) and who have access permissions to examine hospital and research databases. Each MS-SMART recruiting site will be required to maintain an anonymised log of all patients who are ineligible for the trial and all eligible patients who will not be randomised because they decline participation. This information will allow generalisation of the trial results in accordance with Consolidated Standards of Reporting Trials (CONSORT) reporting guidelines. Prerandomisation tests to be performed before a participant can enter the study will be detailed. Anonymised information will be collected including: age, sex, date of screening, reason not eligible to participate (if applicable), reason for declining participation despite eligibility (if applicable), any other reason for non-participation (if applicable).

**Details of the intervention**

**Selection of the investigational medicinal products**

Systematic review and meta-analysis as previously described led to our identification of six specific drugs (ibudilast, riluzole, amiloride, pirfenidone, fluoxetine and oxcarbamazepine) and one drug-class (polysaturated fatty-acid dietary supplements) as leading candidates for evaluation as repurposed oral neuroprotective therapies in SPMS. Based on covering several putative mechanisms of action and relative efficacy data, ibudilast, riluzole and amiloride were initially selected. However, drug supply could not be secured for ibudilast and it was therefore replaced by fluoxetine.

**Amiloride**

It is a widely used diuretic and acid-sensing ion channel (ASIC) antagonist, with recently recognised myeloprotective and neuroprotective effects in experimental models of progressive MS. In an open-label single-arm pretest-posttest phase IIA clinical trial, 14 patients with primary progressive MS (PPMS) were observed for 1 year before treatment and after treatment with oral amiloride 5 mg twice a day. A significant reduction was observed in the whole brain atrophy rate compared with pretreatment. Amiloride has been used as a potassium-sparing diuretic since it was first introduced in 1967 and has an extremely good side-effect profile. Although usually well tolerated, minor side effects are reported relatively frequently. Apart from hyperkalaemia, significant adverse reactions have been infrequently reported. Nausea/anorexia, abdominal pain, flatulence and mild skin rash are probably due to amiloride; but other side effects are generally associated with diuresis or with the underlying disease being treated.

**Fluoxetine**

It is an SSRI widely used for depression. Multiple actions have been described of potential relevance to neuroprotection in SPMS such as: stimulating the cAMP-responsive element binding protein; increasing the production of brain-derived neurotrophic factor and the neurotrophic peptide S100beta; enhancing glycogenolysis in astrocytes; blocking voltage-gated calcium and sodium channels and decreasing the conductance of mitochondrial voltage-dependent anion channels. In pilot clinical research, an increase in the cerebral white matter NAA/creatinine ratio has been described suggesting improved axonal energy status. Recently, results from the Fluoxetine in Progressive Multiple Sclerosis (FLUOX-PMS) study (n=137) showed that there was a trend in favour of fluoxetine (p=0.07) on slower progression of disability as measured by 25-foot walk test or 9-Hole Peg Test (9HPT) after 108 weeks. Fluoxetine is usually well tolerated, although minor side effects are reported relatively frequently. The most commonly reported adverse reactions in patients treated with fluoxetine are headache, nausea, insomnia, fatigue and diarrhoea. Patients with a history of suicide-related events, or those exhibiting a significant degree of suicidal ideation prior to commencement of treatment are known to be at greater risk requiring careful monitoring or exclusion from the trial.

**Riluzole**

It is licensed for motor neuron disease/amyotrophic lateral sclerosis and has two modes of action relevant to SPMS: reducing glutamate release and antagonism of voltage-dependent sodium channels. A single phase IIA clinical trial has been performed in progressive MS; a single-arm open-label pretest-posttest design involving 16 participants observed for 1 year before and during treatment with oral riluzole 50 mg twice a day. Beneficial change was seen in the primary outcome of cervical spine cross-sectional area reduction, associated with reduced T1 hypointense lesion accumulation and brain atrophy. Riluzole is generally well tolerated at 100 mg/day, with the most frequent drug-related events being nausea and fatigue. Headache, dizziness, diarrhoea, anorexia and paraesthesiae are also relatively common. Increased liver function tests (LFT) occur in approximately 10% with drug withdrawal being required in approximately 4%.

**Drug supply and overencapsulation**

Amiloride and fluoxetine will be supplied by Actavis UK and riluzole will be supplied by Sanofi Genzyme, with overencapsulation of active or placebo drug in size 00 capsules.

**Labelling, packaging and storage**

Labelling will be blinded in accordance with requirements of EU GMP Annex 13. In order to maintain blindness, bottles will be coded and both shelf life and storage conditions adjusted to maintain blindness. All trial
drugs will be packaged in polyethylene bottles containing the same number of capsules. Trial drug will be stored below 25°C in a dry place and protected from light.

Dispensing, handling and drug accountability

Bottles will be dispensed according to site and study-specific standard operative procedures (SOPs) by the local site pharmacy. A subject-specific accountability log will be kept to record each dose of the trial drug dispensed for each trial participant. All used returned bottles will be kept for potential reconciliation by the sponsor (UCL); they will be discarded by the research staff according to local procedures, on authorisation from the sponsor.

Dosing regimen

Following randomisation at the baseline visit, study drug will be dispensed by the site pharmacy using the following dose regimes: amiloride 5mg once per day for 4 weeks and twice per day thereafter; fluoxetine 20mg once per day for 4 weeks and twice per day thereafter; riluzole 50mg once per day for 4 weeks and twice per day thereafter; placebo one capsule once per day for 4 weeks and twice per day thereafter.

Dose modification and stopping rules

Details on dose modification and stopping rules are reported in figure 2.

Evaluation of adherence to study drug

At each visit participants will bring back the unused study drug and are asked about adherence. Participants will be asked to detail drug adherence over the past 30 days using a diary card to record the number of capsules taken and to indicate any reason for non-adherence.

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**Figure 2**  Dose modification schema. AE, adverse event; PI, principal investigator; pt, patient.
Adherence will be assessed according to the diary card; however, a pill count will also take place. Non-adherence to the protocol study procedures will be documented by the investigator and reported to the sponsor as required. Persistent non-adherence may lead the participant to be withdrawn from the study. Follow-up as per the protocol is attempted for all non-adherent participants.

Secondary outcomes; imaging
Count of new and enlarging T2 lesions has proved sensitive in detecting the efficacy of immunomodulatory drugs to reduce multifocal inflammatory disease activity. Although new and enlarging T2 lesions appear to be less relevant than brain atrophy as a measure of neuroprotection in SPMS, they are included with brain atrophy as a core outcome measure to detect an unanticipated immunomodulatory effect. Rapid resolution of inflammation after treatment initiation can result in an apparent reduction in brain volume; a phenomenon termed pseudoatrophy.

Exploratory outcomes
Two exploratory outcomes will be collected in MS-SMART, reflecting published recommendations following a National MS Society workshop on the measurement of neuroprotection in MS. (i) The proportion of new and enlarging T2 lesions at 24 weeks being persistently T1 hypointense at 96 weeks. Persistently T1 hypointense lesions exhibit greater axonal loss; this measure therefore provides an indication of the extent of axonal loss associated with new inflammatory-demyelinating white matter lesions. (ii) Change in brain grey matter volume. This measure has demonstrated robust correlations with longitudinal change in disability and with cognitive impairment.

Safety and tolerability outcomes
All study visits will capture data on intervening MS relapses and adverse events (AEs). In addition, blood monitoring will be performed to evaluate renal function (serum creatinine, electrolytes, liver function (bilirubin, transaminases and gamma glutamyl transferase [gamma-GT])) and haematological parameters (haemoglobin concentration, white blood cell and platelet counts).

Sample size
A total of 440 patients will be randomised equally (1:1:1:1) between the three active treatments and the placebo. The primary analysis is intention-to-treat on the whole study cohort. Based on two UK phase II trials...
### Table 2  MS-SMART individual visit schedule

| Clinic visit number | 0 | 1 | 2 | 3 | 4 | 5 | 6 | 7 | 8 | MRI visit | 9 | 100 | End of study | Follow-up (Tel.) |
|---------------------|---|---|---|---|---|---|---|---|---|-----------|---|------|-------------|-----------------|
| Visit type          |   | Screening | MRI visit | Baseline | Titration | ±1 week | ±1 week | ±2 week | ±2 week | ±2 week | ±2 week | ±4 days | Unscheduled visit |
| Window              |   | Informed consent | x |   |   |   |   |   |   |   |   |   |   |   |
|                     |   | Inclusion/exclusion criteria review | x |   |   |   |   |   |   |   |   |   |   |   |
|                     |   | Demography | x |   |   |   |   |   |   |   |   |   |   |   |
|                     |   | Review of medical and MS history | x |   |   |   |   |   |   |   |   |   |   |   |
|                     |   | EDSS-review (treating physician) | x |   |   |   |   |   |   |   |   |   |   |   |
|                     |   | Physical examination | x |   |   |   |   |   |   |   |   |   |   |   |
|                     |   | Vital signs | x |   |   |   |   |   |   |   |   |   |   |   |
|                     |   | BDI-II | x |   |   |   |   |   |   |   |   |   |   |   |
|                     |   | Safety bloods | x |   |   |   |   |   |   |   |   |   |   |   |
|                     |   | Compliance assessment | x |   |   |   |   |   |   |   |   |   |   |   |
|                     |   | Relapse assessment (count/grade) | x |   |   |   |   |   |   |   |   |   |   |   |
|                     |   | Record of adverse events | x |   |   |   |   |   |   |   |   |   |   |   |
|                     |   | Concomitant medication | x |   |   |   |   |   |   |   |   |   |   |   |
|                     |   | Randomisation | x |   |   |   |   |   |   |   |   |   |   |   |
|                     |   | Blinding questionnaire | x |   |   |   |   |   |   |   |   |   |   |   |
|                     |   | MRI brain scan | x |   |   |   |   |   |   |   |   |   |   |   |
|                     |   | EDSS—(assessing physician) | x |   |   |   |   |   |   |   |   |   |   |   |
|                     |   | MSFC | x |   |   |   |   |   |   |   |   |   |   |   |
|                     |   | SDMT | x |   |   |   |   |   |   |   |   |   |   |   |
|                     |   | SLCVA | x |   |   |   |   |   |   |   |   |   |   |   |
|                     |   | MSIS29v2 | x |   |   |   |   |   |   |   |   |   |   |   |
|                     |   | MSWSv2 | x |   |   |   |   |   |   |   |   |   |   |   |
|                     |   | NFI | x |   |   |   |   |   |   |   |   |   |   |   |
|                     |   | NFI, NPRS, NPS and BPI | x |   |   |   |   |   |   |   |   |   |   |   |
|                     |   | EQ-5D | x |   |   |   |   |   |   |   |   |   |   |   |

Study-specific activity shown for each study visit, see text for additional details.

BDI-II, Beck Depression Inventory II; BPI, brief pain inventory; EDSS, Expanded Disability Status Scale; EQ-5D, EuroQol five dimensions questionnaire; MSFC, multiple sclerosis functional composite; MS-SMART, Multiple Sclerosis -Secondary Progressive Multi-Arm Randomisation Trial; MSIS29v2, multiple sclerosis impact scale (29 item) version two; MSWSv2, multiple sclerosis walking scale version two; NFI, neurological fatigue index; NPRS, numeric pain rating scale; NPS, neuropathic pain scale; SDMT, symbol digit modalities test; SLCVA, Sloan low-contrast visual acuity.
et al calculations reported by Altmann for measurement about 90 patients/arm completing the study. From the 2 visit, but be off medication. We anticipate therefore a further 10% of the total cohort to come for their year total cohort to drop out of the trial before year 2, and (iii) The drugs supplied from the manufacturers will be repackaged by an organisation independent of the trial and the same organisation supplies pharmacies at participating sites directly with the trial drugs. (iv) Drug supplies to pharmacies will be coded. (v) The randomisation list will be held by the ECTU to ensure that treatment allocation is concealed from the investigator’s team and the participant, while providing provisions for emergency unblinding.

| MRI measurement times | Baseline–96 weeks |
|-----------------------|-------------------|
| Two-sided significance level | 0.0167 | 0.05 |
| Statistical power (%) | 80 | 90 | 80 | 90 |
| Treatment effect: | 123 | 158 | 92 | 123 |
| 30% | 90 | 116 | 68 | 91 |
| 40% | 69 | 89 | 52 | 70 |

Treatment effect will be expressed as relative mean difference in PBVC under treatment. PBVC assessed using the SIENA registration-based method.

MS-SMART, Multiple Sclerosis-Secondary Progressive Multi-Arm Randomisation Trial; PBVC, percentage of brain volume change; SIENA, Structural Image Evaluation, using Normalisation of Atrophy.

and the same organisation supplies pharmacies at participating sites directly with the trial drugs. (iv) Drug supplies to pharmacies will be coded. (v) The randomisation list will be held by the ECTU to ensure that treatment allocation is concealed from the investigator’s team and the participant, while providing provisions for emergency unblinding.

### ASSIGNMENT OF INTERVENTIONS

#### Treatment allocation

Randomisation (1:1:1:1) will be performed by the research nurse via a secure web-based service provided by the Edinburgh Clinical Trials Unit (ECTU). The following minimisation variables will be used: sex, age (<45 years; ≥45 years or more), baseline EDSS (4.0–5.5; 6.0–6.5), trial site. The minimisation algorithm will incorporate a random element to maintain unpredictability of treatment allocation.

#### Blinding

Investigators and participants will be blinded to the treatment allocation. The following measures will be taken to ensure blinding: (i) amiloride, fluoxetine and riluzole are overencapsulated so that they are identical in appearance to one another and to placebo. (ii) The same number of capsules will be prescribed for participants in each arm. (iii) The drugs supplied from the manufacturers will be repackaged by an organisation independent of the trial and the same organisation supplies pharmacies at participating sites directly with the trial drugs. (iv) Drug supplies to pharmacies will be coded. (v) The randomisation list will be held by the ECTU to ensure that treatment allocation is concealed from the investigator’s team and the participant, while providing provisions for emergency unblinding.

### DATA COLLECTION, MANAGEMENT AND ANALYSIS

#### Clinical data collection and management

All clinical data will be collected by staff whose competence to perform their specific role(s) has been recorded in the delegation log and approved by the site PI. Local research staff will enter data onto an electronic case report file (eCRF) via a secure, web-based portal. Access is password protected and limited to nominated staff as recorded on the delegation log. Members of staff will be identifiable by a unique username and password. Site staff will be responsible for recording full and accurate data onto the database. Only anonymised data will be recorded on trial paperwork and the eCRF. Designated staff at ECTU will follow SOPs to obtain missing data and resolve queries with site staff and to ensure data quality and completeness of data across sites. The trial database includes in-built systems to ensure the validity and quality of the data, and to generate queries. Cross-validation is employed and data entry is a single entry.

Trial data will be held on a secure server at ECTU, data will be stored on a secure server according to ECTU standard operating procedures. All transfer of data will be in accordance with the Data Protection Act 1998 and the UCL Information Security Policy and Trust Information Governance Policy.

#### Imaging data acquisition, quality control and image analysis methods

The following MRI sequences will be obtained at all three MR assessment visits for all participants: (i) Sagittal localiser to identify the subcallosal line. (ii) Axial dual echo fast/turbo spin echo proton density (PD)/T2 weighted from foramen magnum to vertex with no gap, in plane resolution 1 mm², slice thickness 3 mm. (iii) Axial fluid attenuated inversion recovery from foramen magnum to vertex with no gap, in plane resolution 1 mm², slice thickness 3 mm. (iv) Axial T1 from foramen magnum to vertex with no gap, in plane resolution 1 mm², slice thickness 3 mm. (v) Sagittal three-dimensional (3D) T1 gradient echo with voxel resolution of 1 mm³. Initial sequence parameters will be proposed (table 4). The core MRI scanning protocol will take 25 min. Final parameters for each site will be agreed between the central MRI facility (Queen Square MS Centre, London) and the local MR team based on provision of a ‘dummy scan’ (healthy volunteer or a person with MS) before trial commencement. Quality control feedback will be generated by review at the central MRI facility soon after scan acquisition and provided to the site.
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PBVC will be quantified using the SIENA method as previously described. Briefly, on receipt of DICOM images to the central MRI facility and after quality control, the T2 lesions will be outlined on PD scans by trained personnel blinded to clinical data using a semi-automatic method (Jim 7 Software, Xinapse Systems, UK). On further MS expert review, T2 lesion masks will be used to fill the 3D T1-weighted images and, from these, brains will be extracted using the geodesic information flows algorithm (TIG, UCL http://cmictig.cs.ucl.ac.uk/niftyweb).46 Finally, the SIENA method will be applied to the 3D T1 image and the segmentation to produce a percentage change in brain volume between baseline and week 96 scans.

| Table 4 | Guide to MS-SMART MRI scan parameters for use as reference in dummy run scan for each site according to scanner model |
|---------|---------------------------------------------------------------------------------------------------------------|
| Scan    | Dual echo PD/T2-weighted FSE/TSE | T2-weighted FLAIR | T1-weighted SE | 3D T1-weighted volumetric MPRAGE/IRFSPGR/TFE |
| Slice orientation | Axial-oblique | Axial-oblique | Axial-oblique | Sagittal-oblique |
| First TE Siemens 1.5 T/3 T | 11/26 ms | 122/100 ms | 126.8 ms | 3.45/4 ms |
| First TE GE 1.5 T/3 T | 21/24 ms | 128/127 ms | 20/20 ms | 5/3 ms |
| First TE Philips 1.5 T/3 T | 16/13 ms | 120/120 ms | 20/10 ms | 4/3.2 ms |
| Second TE Siemens 1.5 T/3 T | 86/97 ms | NA | NA | NA |
| Second TE GE 1.5 T/3 T | 86/85 ms |
| Second TE Philips 1.5 T/3 T | 100/90 ms |
| Siemens 1.5 T/3 T | 2680/2700 ms | 9500/9500 ms | 518/600 ms | 2400/2400 ms |
| GE 1.5 T/3 T | 2900/2600 ms | 10000/9500 ms | 650/700 ms | 13/8 ms |
| Philips 1.5 T/3 T | 3300/2900 ms | 10000/9500 ms | 600/600 ms | 12/6.9 ms |
| Siemens 1.5 T/3 T | NA | 2400/2400 ms | NA | 1000/1000 ms |
| GE 1.5 T/3 T | 2200/2400 ms | 650/450 ms |
| Philips 1.5 T/3 T | 2400/2400 ms | 950/830 ms |
| Siemens 1.5 T/3 T | ≥46 | ≥46 | ≥46 | ≥176 |
| GE 1.5 T/3 T | 3 mm | 3 mm | 3 mm | 1 mm |
| Philips 1.5 T/3 T | 0 mm | 0 mm | 0 mm | 0 mm |
| Siemens 1.5 T/3 T | 7/5 | 19/15 | NA | NA |
| GE 1.5 T/3 T | 10/8 | 19/19 |
| Philips 1.5 T/3 T | 5/6 | 19/19 |
| Siemens 1.5 T/3 T | 25 cmx100% | 25 cmx100% | 25 cmx100% | 25 cmx100% |
| GE 1.5 T/3 T | 256x256 | 256x192 | 256x256 | 256x256 |
| Philips 1.5 T/3 T | 256x256 | 256x256 | 256x256 | 256x256 |
| Siemens 1.5 T/3 T | 0.976 | 0.976 | 0.976 | 0.976 |
| GE 1.5 T/3 T | a/p | a/p | a/p | s/l |
| Philips 1.5 T/3 T | r/l | r/l | r/l | a/p |
| Siemens 1.5 T/3 T | 1 January | 1 January | 1 February | 1 January |
| GE 1.5 T/3 T | 1 January | 1 January | 1 February | 1 January |
| Philips 1.5 T/3 T | 1 January | 1 January | 1 February | 1 January |
| Siemens 1.5 T/3 T | – | – | – | 8° |
| GE 1.5 T/3 T | – | 20° |
| Philips 1.5 T/3 T | – | 8° |

Reference parameters guidance depending on scanner model (ie, Siemens, Philips, GE) and operating field strength (ie, 1.5 T or 3 T). The values listed in bold are mandatory for all of the sites.

a/p, anterior/posterior; FLAIR, fluid attenuated inversion recovery; FSE/TSE, fast/turbo spin echo; IRFSPGR, inversion recovery fast spoiled gradient echo; MPRAGE, magnetisation prepared rapid gradient echo; NA, not applicable; r/l, right/left; SE, spin echo; s/l, superior/inferior; TFE, turbo field echo.
Statistical methods

Descriptive statistics
A CONSORT flow diagram will be reported. Exploratory summary methods will be used to describe baseline characteristics: continuous variables will be summarised using summary statistics (mean, SD, median, IQR, minimum and maximum) by treatment group, and categorical variables will be presented using frequencies and percentages by treatment group. Proportions of patients with missing 96-week MRI data in each treatment group will also be summarised, as will baseline data for patients with missing and non-missing 96-week follow-up data.

Primary MRI outcome measure
A normal linear model will be used to compare each of the three active treatment group arms with placebo, adjusting for baseline normalised brain volume (BNBV) and minimisation variables: age, gender, treatment centre (as a fixed effect) and baseline EDSS. Baseline BNBV will be entered into the model as a continuous variable, as will age and baseline EDSS. Other minimisation variables will be included in the models according to the categories used in the randomisation; if there are fewer than ten patients in any category, categories will be combined where possible. The efficacy measure for each active treatment will be the mean difference in PBVC change versus placebo. All patients for whom baseline and 96-week brain volume data are available will be included in the analysis according to the treatment group to which they were randomised irrespective of which treatment(s) they may have received. Dunnett’s method will be used to adjust for the multiple pairwise comparisons versus a common placebo group. No formal comparisons of the active treatments will be undertaken. The primary analysis will be on complete cases. Three sensitivity analyses, based on pattern mixture modelling, standard multiple imputation and exclusion of extreme outliers on the primary outcome will be used to explore the effect of missing data on the primary outcome analysis.

Counts of new and enlarging T2 lesions
Each active treatment group will be compared with placebo for the number of new and enlarging T2 lesions between the baseline and 96-week MRI. Overdispersed Poisson regression models will be used to estimate a rate ratio for each comparison after adjusting for baseline T2 lesion volume and the minimisation variables: age, gender, treatment centre and baseline EDSS.

Pseudoatrophy
Using the same methods as for the primary MRI outcome analysis, the mean difference in PBVC from baseline to 6 months between the placebo group and each of the active treatment groups will also be assessed. If the reduction in PBVC is significantly greater in any treatment group a secondary analysis will compare PBVC from week 24 to week 96 between that treatment group and the placebo group using normal linear modelling as described for the primary outcome measure.

Clinical secondary outcome measures
If the change over time in continuous outcomes (EDSS, 9HPT, PASAT, MSFC, SDMT, SLCOVA, MSIS29v2, MSWSv2, NFI, NPRS, NPS, BPI and EQ-5D-5L) is found to be reasonably normally distributed, following transformation where necessary, comparison will be made between active treatments and the placebo group using normal linear models as for the primary outcome measure. If normality cannot be assumed, an unadjusted non-parametric Mann-Whitney U test will be used to compare each active treatment to placebo. For NPS, the same method will be used as for the other continuous outcome, but applied to the individual questionnaire items, with the exception of the components of item 8, which will be analysed using logistic regression. Cox proportional hazard models (adjusting for the minimisation variables) will be used for time to first relapse and timed 25 foot walk, with the difference between each active treatment and placebo being expressed in terms of an HR. In exploratory analyses, additional statistical modelling will assess whether composites of imaging and disability measures at baseline can be used to predict temporal evolution of SPMS and response to treatment. The proportion of participants with an increase in EDSS score of at least 1.0 at 96 weeks relative to baseline will be analysed using a multiple logistic regression model adjusting for the minimisation variables.

MONITORING

Data monitoring
An independent Data Monitoring Committee (DMC) will be established to oversee the safety of participants in the trial. The terms of reference of the DMC will be documented in a charter that will be held in the Trial Master File (TMF) at ECTU. Unblinded safety data will be monitored by the DMC to ensure the ongoing safety of patients in the study. Stopping criteria are not prespecified to the DMC and no formal interim analyses will be planned. A Trial Steering Committee (TSC) will be established to oversee the conduct and progress of the trial. The terms of reference of the TSC will be documented in a charter that will be held in the TMF at ECTU.

Harms

Detection, recording and reporting of adverse events
All AEs will be recorded in the medical records from the time a participant signs the consent form to take part in the study until study exit (week 100). Participants will be asked about the occurrence of AEs or serious adverse events (SAEs) at every visit during the study. Open-ended and non-leading verbal questioning of the participant will be used to enquire about AE/SAE occurrence. Participants will also be asked if they have been admitted to hospital, had any accidents, used any...
new medicines or changed concomitant medication regimens. AE data will also be available from information written by the participant on the participant diary, and from laboratory results. Progressive change due to SPMS, in motor, sensory, balance, sphincter (including urinary tract infections), vision, cognitive and fatigue levels will be excluded as AEs/SAEs/Serious Adverse Reactions (SARs) and are not reported as such. In addition, relapses will not be counted as AEs/SAEs/SARs, but will be collated separately.

Reporting to the sponsor will be completed as per the sponsor’s SOP and using the UCL SAE forms (INV/S05). The AE log will be reported to the sponsor at least once per year. All AEs will be reported to the sponsor on a SAE form by the chief investigator (CI) or site PI within 24 hours of them becoming aware of the event. A copy will be also sent in tandem to the ECTU for notification. All Suspected Unexpected Serious Adverse Reactions (SUSARs) will be notified to the sponsor immediately (or at least within 24 hours). The sponsor will notify the main Research Ethics Committee (REC) and Medicines Healthcare products Regulatory Agency (MHRA) of all SUSARs. SUSARs that are fatal or life-threatening will be notified to the MHRA and REC within 7 days after the sponsor has learnt of them. Other SUSARs will be reported to the REC and MHRA within 15 days.

Management of laboratory abnormalities

Clinical biochemistry
If serum potassium is <2.8 or >5.5 mmol/L, or if serum sodium is <125 mmol/L, study drug will be suspended and electrolytes measured at 2–4 weeks. If normalised, treatment will be recommenced. If not normalised, treatment will be suspended for a further 2–4 weeks. If abnormality persists at this stage, treatment will be discontinued. If creatinine >130 µmol/L, confirmatory bloods are performed within a week. If abnormalities persist, study drug will be reduced to ‘half dose’ if taking medication twice a day (ie, ‘full dose’) or stopped if taking ‘half dose’. Repeat measurement will be undertaken at 2–4 weeks. If parameters have normalised, rechallenge will be considered. Derangement of liver function tests where alanine aminotransferase (ALT) or aspartate aminotransferase (AST) or bilirubin or gamma-GT <3 times the upper limit of normal (ULN), commencement, continuation or advancement of placebo/investigational medical product (IMP) will continue as previously planned. If LFT measures are >5 times the ULN, confirmation by repeat measurement will be performed within a week. If abnormalities persist the study drug will be reduced to ‘half dose’ if taking medication twice a day (ie, ‘full dose’) or stopped if taking ‘half dose’. Repeat measurement will be undertaken at 2–4 weeks. If parameters have normalised, rechallenge will be considered. If ALT or AST or bilirubin or gamma-GT >5 times the ULN, study drug will be discontinued.

Clinical haematology
If haemoglobin remains <80 g/L, study drug will be suspended and local protocols should be followed to investigate anaemia. If haemoglobin improves towards baseline at 2–4 weeks, rechallenge will be considered. If haemoglobin remains <80 g/L treatment will be discontinued. If neutrophil count reduces to <1.0×10^9/L or platelet count to <50×10^9/L, study drug will be suspended. If parameters normalised at 2–4 weeks, rechallenge will be considered. Study drug will be discontinued if parameters remain below these levels.

Emergency unblinding procedures
Randomised participants will be given a card to indicate they are on the trial with the emergency contact numbers for medical advice including unblinding. Participants will be instructed to show this card to any healthcare professional involved in their care who will not be involved in the trial. Unblinding may take place in situations where the safe management of the participant’s medical condition necessitates knowledge of the study medication by the person(s) responsible for the participant’s care. Where possible, members of the local research team will remain blinded. If unblinding is required the local PI/other medical staff will use a 24 hours emergency telephone contact as provided on the participant’s card. The person requesting unblinding will provide details including the protocol number and trial name, name of the requester, reason for unblinding, patient name, participant number and timeline to receive the unblinded information. If knowledge of the treatment allocation is required in order to treat the patient, the code break number will be given to the local PI/other medical staff requesting to unblind the patient. The local PI/other medical staff can then use the code break number to reveal the participants treatment allocation. In this way, the treatment will be unblinded at the local site but not to the ECTU member of staff or CIs.

Withdrawal of study participants and early termination of the trial
Trial participants will be free to withdraw from the trial at any point or can be withdrawn by the investigator. If withdrawal occurs, the primary reason for withdrawal will be documented in the participant’s CRF. Trial participant withdrawals will not be replaced. If a participant discontinues study drug, this will not necessarily constitute withdrawal from the trial: in this case, all attempts will be made to follow-up the participant as per protocol and to recommence treatment. The DMC will be able to recommend trial or trial arm suspension/termination, according to the terms of the DMC charter, for example, due to unacceptable AEs.

Auditing
A trial-specific monitoring plan will be established in accordance with the sponsor’s SOPs. An appointed monitor will visit the Investigator site prior to the start of the study and during the course of the study and in accordance with the predefined monitoring plan.
PATIENT PUBLIC INVOLVEMENT

Patient public involvement (PPI) has been a vital part of the evolution of the study, both through the MS CTN, which includes patient representation, and directly through a specifically convened focus group which enabled patients with SPMS to provide constructive feedback on the design of the study. Our PPI representative will be an integral member of the MS-SMART team and will sit on the Study Management Group—ensuring PPI is at the heart of our research and making certain there are meaningful links with and between service providers, users and methodologists. MS-SMART was highlighted in the UK MS Society Patient Conference, MS Life 2012. We identified the training and support needs of PPI members (and researchers in relation to PPI) and provided appropriate support and training. PPI members will be mentored by members of the trial team. The mentorship role will provide research and personal support to PPI members before and after meetings, addressing queries about the research process, language and documentation. We will adhere to INVOLVE guidelines for involving the public in research and reimburse PPI members in accordance with INVOLVE rates. Suggestions from our PPI group were used to inform the design of the research. Specifically: 1) the group emphasised the importance of working with early SPMS patients (EDSS scores <6.5) prior to the ambulatory phase in light that any neuroprotective drug is likely to have most benefit; 2) a multiarm design was preferable to standard single arm versus placebo to ensure that a maximum number of patients would have access to putative neuroprotective repurposed drugs compared with placebo; 3) they considered that the burden of advanced MRI protocol was acceptable to patients in view of the potential advancement that will come from the imaging analysis to the mechanistic elucidation—all their recommendations were taken on board. The scientific approach in MS-SMART was recognised as being completely in tune with what those with SPMS wanted. The results of the study will ultimately be given individually (via email) to those who have taken part.

ETHICS AND DISSEMINATION

Protocol amendments

There have been five substantial protocol amendments and these are listed in Table 5.

Informed consent

All MS-SMART participants will be required to provide written informed consent before any protocol-specific procedures are carried out according to the principle of Good Clinical Practice. The participant will agree to their medical records being inspected by regulatory authorities and representatives of the sponsor(s).

Confidentiality

All laboratory specimens, evaluation forms, reports and other records will be identified in a manner designed to maintain participant confidentiality. All records will be kept in a secure storage area with limited access. Clinical information will not be released without the written permission of the participant. The Investigator and study site staff involved with this study may not disclose or use for any purpose other than performance of the study, any data, record or other unpublished, confidential information disclosed to those individuals for the purpose of the study. Prior written agreement from the sponsor or its designee must be obtained for the disclosure of any said confidential information to other parties. The CRFs will not bear

| Table 5 Protocol amendments |
|-----------------------------|
| Protocol update | Protocol version | Protocol date | Reason for amendment |
| NA | V1 | 1 January 2013 | NA |
| Substantial amendment | V1 | 1 January 2013 | Addition of new sites. |
| Substantial amendment | V2* | 1 December 2013 | See note below. |
| Substantial amendment | V3 | 1 June 2014 | Replacement of the drug ibudilast with fluoxetine. |
| Substantial amendment | V4 | 25 May 2015 | Change to eligibility criteria to exclude patients on high-dose simvastatin. Clarification in patient information sheet about side effects of fluoxetine. |
| Substantial amendment | V5 | 1 November 2016 | Protocol updated to reflect changes to fluoxetine summary of product characteristics. |
| Non-substantial amendment | V6 | 5 October 2017 | To update new trials unit address and telephone numbers. |
| Substantial amendment | V6 | 5 October 2017 | To update change of PI. |
| Non-substantial amendment | V7 | 4 June 2018 | To correct typing error of ClinGov number. |

*Protocol V.2 was submitted for the Clinical Trial Authorisation.

NA, not applicable.
the subject’s name or other personal identifiable data other than the subject’s initials and date of birth.

Access to data
The CIs will have full access to the final data set, following completion of the main trial analysis by study statisticians. Prior to publication of the main findings of MS-SMART, additional plans by the UCL or ECTU trial teams to analyse MS-SMART data must be approved by the CI and trial statistician, with any resulting published outputs, requiring approval from the DMC, TSC and writing committee. Requests for use of MS-SMART data from other collaborators or external parties will require approval from the DMC Chair, TSC Chair and writing committee.

Ancillary and post-trial care
Routine clinical care will continue to be provided by treating neurologists throughout the duration of the trial and following its completion.

Dissemination policy
MS-SMART is listed on three publicly accessible registries: clinicaltrials.gov (NCT01910259); clinicaltrialsregister.eu (2012-005394-31); isrctn.com (ISRCTN28440672).

To maintain the scientific integrity of the study, data will not be released prior to the first publication of the results of the primary end point analysis, either for study publication or oral presentation purposes, without the permission of the DMC and the TSC. The TSC will agree a publication plan and must be consulted prior to release or publication of any study data. All proposed publications and presentations will be discussed with the sponsor, co-CIs and ECTU prior to their release. The clinical trial report will be used for publication and presentation at scientific meetings. Summaries of results will also be made available to investigators for dissemination within their clinics (where appropriate and at their discretion). Credit for the main results will be given to all those who have collaborated in the study, through authorship and by contribution. Uniform requirements for authorship for manuscripts submitted to medical journals will guide authorship decisions (www.icmje.org).

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Acknowledgements
The authors would like to thank Emeritus Professor David Miller for his work in designing the trial and inspiring us. The authors would like to thank the colleagues of the UK Multiple Sclerosis Society for their continued help and support. The authors would like to thank Lorraine Smith from the ECTU and Anne Marie Downey from the UCL Sponsors office. The authors would like to thank all the participants of the MS-SMART trial and all the collaborators involved in the study. Particularly, thanks to Tiggy Beye, Vanessa Bassan, Marius Yaananakas, Almudena Garcia Gomez, Alvin Zapata, Rebecca Samson, Bhavana Solanky, Marcello Moccia and all the Research Nurse teams from the sites. The authors would like to thank the members of the Data Monitoring Committee: Tim Friede (Chair), Michael Hutchinson, Stanley Hawkins; and the members of the Trial Steering Committee: Robert Swingler (Chair), John Thorpe, John O’Brien, Patricia Prestage. The authors would like to thank Allan Walker for designing the trial database. The MS-SMART sites and investigators are: Queen Square Multiple Sclerosis Centre, University College London Hospitals NHS Foundation Trust, London: Jeremy Chatkapy, Claudia Gandini Wheeler-Kingshott, Floriana De Angelis, Domenico Plantone, Anisha Doshi, Nevin John, Thomas Williams, Marie Brasher; NHS Lothian, Anne Rowling Regenerative Neurology Clinic, Royal Infirmary of Edinburgh, Edinburgh: Siddharth Chandran, Peter Connick, Dawn Lyle, James Cameron, Daisy Mollison, Shuna Colville, Baljean Dhillon; ECTU: Christopher J Weir, Richard Parker, Moira Ross, Gina Cranswick; Barts and the London, London: Gavin Giovannoli, Sharmilee Gnanapavan; Imperial College, London: Richard Nicholas; Brighton and Sussex University Hospitals; Waqar Rashid, Julia Aram; Leeds General Infirmary, Leeds: Helen Ford; Southern General Hospital, Glasgow: James Overell; The Walton Centre, Liverpool: Carolyn Young, Heinne Ardt; The Royal Victoria Infirmary, Newcastle: Martin Duddy, Joe Guadagno; Queens Medical Centre, Nottingham: Nikolaos Evangelou; John Radcliffe Hospital, Oxford University Hospitals NHS Trust, Oxford: Matthew Craner, Jacqueline Palace; Derriford Hospital, Plymouth: Jeremy Hobart; Royal Hallamshire Hospital, Sheffield: Basil Sharrack, David Paling; University Hospital of North Staffordshire, Stoke-on-Trent: Clive Hawkins, Seema Karia; Royal Cornwall Hospital, Truro: Brendan McLean. Statistics and Epidemiology, Division of Health Sciences, Warwick Medical School, University of Warwick, Coventry: Nigel Stalliard. Patient Representative: Roger Bastow.

Collaborators
The MS-SMART Collaborators are: Jeremy Chataway, Claudia Gandini Wheeler-Kingshott, Floriana De Angelis, Domenico Plantone, Anisha Doshi, Nevin John, Thomas Williams; Siddharth Chandran, Peter Connick, James Cameron, Daisy Mollison, Baljean Dhillon; Christopher J Weir, Richard Parker; Gavin Giovannoli, Sharmilee Gnanapavan; Richard Nicholas; Waqar Rashid, Julia Aram; Helen Ford; James Overell; Carolyn Young; Martin Duddy, Joe Guadagno; Nikolaos Evangelou; Matthew Craner, Jacqueline Palace; Jeremy Hobart; Basil Sharrack, David Paling; Clive Hawkins, Seema Karia; Brendan McLean.

Contributors
JC, SC, CJ, GG, CAGW-K, SHP, NS, CH, BS, GC, RB, MB researched and wrote the original grant application. All are involved in the set-up and running of the trial. PC, FDA, DP, AD, NJ set-up the trial and are involved in the measurement and quality assurance of the clinical and MRI outcomes. CJW and RAP have written the statistical analysis plan. JS, DMCM, FB, FP SO have set-up and quality assured the MRI acquisition and analysis pipelines. MR and GC are the Edinburgh Clinical Trials Unit (ECTU) managers responsible for the trial.

Funding
MS-SMART is an investigator-led project sponsored by University College London (UCL). This independent research is awarded by the Efficacy and Mechanism Evaluation Programme (EME) and funded by the Medical Research Council (MRC), the UK Multiple Sclerosis Society and the National Multiple Sclerosis Society (USA NMSS) and managed by the National Institute for Health Research (NIHR) on behalf of the MRC-NIHR partnership. Additional support comes from the University of Edinburgh; the National Institute for Health Research University College London Hospitals (NIHR-UCLH) Biomedical Research Centre (BRC) and University College London; NIHR Leeds CRF (DenTRCU). CJW and RAP were supported in this work by NHS Lothian via the Edinburgh Clinical Trials Unit.

Competing interests
PC, FDA, DP, AD, NJ, JS, SHP, CH, CJW, RAP, NS, SC, GC, RB, DMCM, MR declare no conflict of interests with respect to this work. MB has received funding from the UK Multiple Sclerosis Society and NIHR Local Clinical Research Network. FP receives a Guarantors of Brain fellowship. SO receives funding from the EPSRC (EP/T000228/1); the H2020 (665733); and the ARC (MR/J010757/1), the EU FP7 (FP7-ICT-2011-1-260124) and NIHR UCLH BRC (BB. mn.BRC10269). FB serves on the editorial boards of Brain, European Radiology, Journal of Neurology, Neurosurgery & Psychiatry, Neurology, Multiple Sclerosis and...
Neuoradiology, and serves as consultant for Bayer Shering Pharma, Sanofi-Aventis, Biogen-Idec, TEVA Pharmaceuticals, Genzyme, Merck-Serono, Novartis, Roche, Synthion, Jansen Research and Lundbeck. CGKW receives research grants (PI and co-applicant) from Spinal Research, Craig H. Neilson Foundation, EPSRC, Wings for Life, UK MS Society. Horizon 2020, NIHR/MRC. JC has received support from the Efficacy and Mechanism Evaluation Programme and Health Technology Assessment Programme (NIHR); UK Multiple Sclerosis Society and National Multiple Sclerosis Society. In the last 3 years, he has been a local principal investigator for trials in multiple sclerosis funded by: Receptos, Novartis, Roche and Biogen-Ide, and has received an investigator grant from Novartis outside this work. He has taken part in Advisory Boards/consultancy for Roche, Merck, Medday, Biogen and Aiptope. BS has received funding from NIHR and the UK MS Society. Has been a principal investigator for trials in multiple sclerosis funded by: Receptos, Novartis, Biogen, Merck, Genzyme, Roche and Teva. GG is a steering committee member on the cladribum trials for Abbvie, the BG12 and cladribum trials for Biogen-Ide, the fingolimod and siponimod trials for Novartis, the laquinimod trials for Teva and the ocrelizumab trials for Roche. He has also received consultancy fees for advisory board meetings for oral cladribine trials for Merck-Serono, Genzyme-Sanofi and in relation to DSMB activities for Synthon BV, as well as honoraria for speaking at the Physicians’ summit and several medical education meetings. He is also the co-chief editor of Multiple Sclerosis and Related Disorders (Elsevier).

Patient consent Obtained.

Ethics approval MS-SMART was approved by the Scotland A Research Ethics Committee on 13 January 2013 (REC reference: 13/SS/0007).

Provenance and peer review Not commissioned; externally peer reviewed.

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