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OPTIMISE:MS - a pragmatic, prospective observational study to address the need for, and challenges with, real world pharmacovigilance in multiple sclerosis

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OPTIMISE:MS - a pragmatic, prospective observational study to address the need for, and challenges with, real world pharmacovigilance in multiple sclerosis

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Abstract

Introduction: The power of “real world” data to improve our understanding of the clinical aspects of multiple sclerosis (MS) is starting to be realised. Given relatively homogeneous practices in DMT prescription across the UK, driven by national prescribing guidelines, the UK provides an ideal country in which to gather MS outcome data. A rigorously conducted observational study with a focus on pharmacovigilance has the potential to provide important data to inform clinicians and patients whilst testing the reliability of estimates from the pivotal trials when applied to patients in the UK.

Methods and analysis: The primary aim of this study is to characterize the incidence and compare the risk of serious adverse events in people with MS treated with DMTs. The OPTIMISE:MS database enables electronic data capture and secure data transfer. Selected clinical data, clinical histories and patient reported outcomes are collected in a harmonized fashion across sites at the time of routine clinical visits or in direct follow up. To date, 1,615 individuals have baseline data recorded in this study; follow up data is being captured and will be reported in due course.

Ethics and dissemination: This study has ethical review (London City and East; Ref 19/LO/0064). Potential concerns around data storage and sharing are mitigated by the separation of identifiable data from all other clinical data, and limiting access to any identifiable data. The results of this study will be disseminated via publication. Participants provide consent for anonymised data to be shared for further research use, further enhancing the value of the study.

Article summary

- All patients with multiple sclerosis (MS) eligible for disease modifying therapy under the care of participating centres can take part in this study
- The primary aim is to characterise the incidence of serious adverse events in a real world population of patients with MS
- Selected clinical data, recorded during episodes of routine care, are uploaded to a study specific database
- Potential concerns around data storage and sharing are mitigated by the separation of identifiable data from all other clinical data, and limiting access to any identifiable data.
- This study enables future research, as all participants are contacted for future contact about additional research studies

Introduction

Real world data in multiple sclerosis

The power of “real world” data to improve our understanding of the clinical aspects of multiple sclerosis (MS), including the relative risks and benefits of disease modifying treatments, and the potential for these data to impact on the care of people with MS is only just starting to be realised. However, the utility of large datasets is significantly limited by the validity of the data. Concerns regarding data quality and international applicability have limited the translation of findings from large datasets to clinical practice across medicine. A huge number of unanswered questions remain around risk stratification, treatment sequencing, and outcome monitoring, which cannot be answered using a traditional randomised control trial (RCT) design. Furthermore, long term and/or rare outcomes are almost impossible to detect via RCTs. Historically, phase 4 observational studies have been used to study such endpoints. However, these also have limitations due to high drop-out rates and an inherent lack of power to detect rare outcomes, or to evaluate risks associated with prior or subsequent treatment decisions, or comorbid medical conditions.

“Real world data” refers to data gathered in the course of an individual patient’s routine clinical care. The aim is not to discriminate based on age, comorbid conditions, or other such factors that may influence trial eligibility [1]. This data is by its nature highly confounded - which brings significant statistical concerns - but also enables the study of data highly applicable to clinical practice. Such data enables the study of specific areas that cannot be addressed via traditional routes.

Disease-specific registries define participants by disease of interest. Within the MS arena, a number of large real world data initiatives already exist. A number of national registries from European countries, including Sweden, France and Italy have significantly improved our understanding of MS disease trajectories and the influence of treatment on these [16]. One example is MSBase; a collaborative, international disease registry, which captures a range of MS-related data from a large number of countries

[2]. More recently, processes for formal data sharing have started to enable the pooling of data from 5 large registries (Sweden, France, Italy, Denmark, MSBase) [3].

However, to date, harmonised data gathering across the UK has been limited. Rigorous data collection and prospective data entry is time consuming, and frequently does not provide short, or even medium, term benefit to clinicians. Linking data entry to disease modifying therapy (DMT) funding rebates brings a clear risk of biasing data. Whilst many of the concerns regarding missing or incomplete data can be overcome with large numbers of participants [4], in order to overcome reporter bias when examining potentially rare or serious events, data collection and verification needs to be rigorous.

Given the relatively homogeneous practices in DMT prescription across the UK, driven by national prescribing guidelines [5], the UK provides an ideal arena from which to gather MS outcome data.

The need for pharmacovigilance in MS

The therapeutic armoury in MS has increased rapidly, but real-world data concerning safety is limited. The first treatments to be introduced (interferon-beta preparations and glatiramer acetate [Copaxone]) have well-established safety records [6]. Progressive multifocal leukoencephalopathy (PML) risk limits the long-term use of natalizumab in many patients [7]. There are safety signals from clinical trials and early clinical experience suggesting both lymphopaenia [8][9][10] and increased infection rates with newer MS therapies [6-11]. The risks of serious adverse events (SAEs) with individual treatments over a relatively short duration have been reported in clinical trials (Table 1). The rates at which these occur in the real-life treated UK population is, as yet, unknown. The current adverse event reporting system (yellow card system, [11]) has a high risk of missing longer-term rare adverse events; as such there is an urgent need for a formalised reporting system.

As clinical experience with, and the number of patients taking, newer MS treatments increases, concern regarding longer-term effects of treatments and the cumulative risk

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3 associated with treatment switching is increasing (personal communication, MHRA).
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5 Counselling patients regarding switching is limited by information available from clinical
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7 experience, case reports, and occasional small case series.
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11 In a pharmacovigilance study, patients on established first-line treatments provide a
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13 useful reference cohort, as the safety and effectiveness of these medicines are well
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15 understood. They form a readily characterized group; patients tend not to be de-
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17 escalated to first-line injectable therapies outside of specific consideration, such as
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19 those planning pregnancy (observation from personal clinical experiences). While there
20
21 are obvious limitations to indexing outcomes associated with newer treatments to these
22
23 reference populations (e.g., disease and demographic characteristics may be different,
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25 as patients in the reference groups are likely to have lower baseline disease activity
26
27 than those receiving highly active therapies), they provide a pragmatic approach for an
28
29 observational real world study.

30 ***Existing models of disease-specific studies evaluating treatment-associated*** 31 ***events***

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33 National pharmacovigilance is not a novel concept and can contribute to improved
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35 safety for patients. Differences in susceptibilities and pharmacological responses,
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37 diagnostic and prescribing practices, lifestyle and patterns of medicine adherence all
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39 can vary between countries. Both observational registries and prospective cohort
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41 studies are well-established in rheumatology and dermatology and provide a wealth of
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43 data regarding the safety profile of biological agents [12][13][14].
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46 National, automated data capture systems and disease specific registries are
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48 increasing. NHS Digital now curates a number of national data collections [15].
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50 However, MS outcomes are poorly coded in primary care datasets, and individuals with
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52 MS who develop cancer and are entered onto cancer registries do not have detailed
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54 data regarding prior DMT use recorded. It is thus not possible to use existing registries
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56 to study clinical endpoints in MS in detail; however, these registries provide a resource
57
58 to mitigate against loss to follow up via data linkage.

Methods and analysis

Rationale and study design

The OPTIMISE:MS study is a pragmatic, prospective observational cohort study (19/LO/0064). This real world study is planned to run for 7 years in the first instance. It aims to estimate the frequency of serious adverse events with DMT use in routine clinical practice in the UK. All individuals potentially eligible for MS DMT are eligible for this observational study, regardless of any decision regarding DMT use (figure 1). OPTIMISE:MS will recruit people with MS from major MS care clinics across the country.

The primary aim of this study is to characterize the incidence and compare the risk of serious adverse events in people with MS treated with DMTs (comparators will be an untreated cohort, and a cohort treated with first line injectable DMT). A serious adverse event (SAE) in this context is an adverse event resulting in death, requiring in-patient treatment or prolongation of existing in-patient treatment or that results in persistent or significant disability or incapacity. Serious adverse events of particular interest in this study are any infections requiring hospitalisation, any opportunistic infection (i.e. typically associated with immunosuppression), any other serious adverse event believed to be related to treatment (e.g., lymphoma, non-melanoma skin cancer), any MS relapse, and death. Additionally, rates of symptomatic COVID-19, outcomes associated with SARS-COV2 infection and relationship to DMT use and/or immunosuppression will be captured.

Selected clinical data, clinical histories and patient reported outcomes will be collected in a harmonized fashion across sites at the time of routine clinical visits or in direct follow up (for laboratory or paraclinical testing). No additional clinical visits are mandated as part of this pragmatic study. Based on usual (recommended) clinical practice in the UK, we anticipate follow up clinical visits for patients enrolled in this study *at least* on an annual basis. MRI scans and laboratory tests recommended for treatment monitoring will be performed by clinical centres at intervals based on their usual clinical practice and clinical indications in the patients.

Concerns regarding loss to long term follow up can be mitigated to some degree via data linkage with national systems. Following appropriate consent, an individual's NHS number can be used to link individuals via digital.NHS, Hospital Episode Statistics (HES) and the UK Cancer Registry, potentially using HDR-UK infrastructure, to support follow up of serious adverse events.

Data flow and security

The OPTIMISE:MS database (online demo version available via <https://www.optimise-ms.org/demo/>) has been designed to enable electronic data capture and secure data transfer. Data is entered onto site-specific laptops at individual sites, and transferred securely on a regular basis. Every data entry is time stamped according to both date of data entry and date of data collection, to allow for audit and identification of retrospective data entry. Personally identifiable information including NHS number is accessible only to the clinical care team at each site and to those members of the central analysis group responsible for follow up of serious adverse events.

The majority of participant data is stored in a secondary database, in which each subject is pseudonymised and the NHS number and name are not available. This database will be used for analyses performed by the OPTIMISE analytical group and collaborators. A participant data deletion mechanism is incorporated into each form of the database. Data for any subject who withdraws consent and whose data is deleted from the database held at any participating site also will be deleted automatically from the two forms of the database held at the central analysis site.

Patient and public involvement

Patients were involved early in the conception of this study. The study was discussed with patient representatives, who gave feedback around the kind of data that they would be willing to share, and the desired frequency of contact. The main concern of the

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3 patients that we consulted was that their data were to be used for the benefit of people
4 with MS, and not for profit or other third party gain.
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8 ***OPTIMISE database and core dataset*** 9

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11 Whilst software tools for MS patient data entry and curation have been generated
12 before, none are in widespread use. There is no single electronic patient record (EPR)
13 in use across the UK NHS, and utilising individual EPR systems to collect MS-specific
14 data is likely to be both unacceptably time consuming and costly. One major challenge
15 of bespoke MS data collection systems is the need to balance comprehensiveness of
16 data collection with the sustainability of data entry in a busy clinic environment. A further
17 challenge is to ensure compliance with basic requirements for data security and auditing
18 and the ability to remove data if consent is withdrawn.
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27 The OPTIMISE database is used to capture both minimum baseline characteristics and
28 ongoing and follow up data. These include current treatment category, gender,
29 ethnicity, dominant hand, country of origin, primary MS diagnosis, time since diagnosis,
30 age, physical and performance measures (EDSS), relapses within the past 2 years,
31 serious adverse events, malignancies, opportunistic infections, liver function, brain MRI,
32 total white cell and lymphocyte count and anti-JCV antibody status (Table 2).
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39 Participating sites are expected to upload all of the clinical and paraclinical data
40 collected to the central analysis site on a quarterly basis. Visit frequency for patients
41 was determined by usual clinical practice and completeness of data and other quality
42 control assessments are performed on a quarterly basis by the central study team
43 located at Imperial College London. Where data is incomplete in a significant number of
44 records in a single upload, the site is contacted for remedial action to be taken.
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51 ***Statistical analysis*** 52 53 54 55 56 57 58

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3 The statistical analysis will focus on the detection of adverse event signals by identifying
4 specific DMTs and DMT sequences associated with disproportionate numbers of events
5 (relative to the overall study population). A number of disproportionality measures will
6 be applied in parallel to increase sensitivity, including the Reporting Odds Ratio,
7 Empirical Bayes Geometric Mean and Information Component [17] (all originally
8 designed for spontaneous report data, but here adapted to the longitudinal data
9 collected within OPTIMISE:MS), and the incidence rate ratio. Signals will be triggered if
10 the lower one-sided 95% confidence limit for any disproportionality measure exceeds
11 the null value of no association. Two methods will be used to screen out false positive
12 signals. Firstly, a minimum number of events will be imposed in order to eliminate false
13 signals due to random noise when event counts are low. Secondly, a chronological
14 filter based on the LEOPARD methodology will be applied [18]. The LEOPARD filter
15 assesses whether an adverse event occurs more often before or after the prescription
16 of the treatment with which it appears to be associated. This can help to avoid
17 protopathic bias, in which a causal relationship is falsely inferred between an adverse
18 event and the commencement of treatment when in fact both were caused by the
19 underlying progress of disease or other factors.
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34 Poisson (or negative binomial) regression and survival analyses will be carried out to
35 evaluate rates of adverse events, relapse, disability progression, new MRI lesions,
36 mortality, lymphopaenia and liver enzyme elevation in subjects receiving any newer
37 DMT in comparison to those receiving first-line injectable DMTs or no treatment. These
38 analyses will incorporate subject-level covariates to adjust for demographics and
39 disease history.
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46 ***Entry criteria***

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49 All patients with MS as defined by the 2017 McDonald criteria and who are eligible to
50 receive DMT reimbursement from NHS England are eligible for entry into the
51 observational study. This includes patients who are on treatment, as well as those
52 starting, potentially eligible to start but not receiving DMT, or switching DMT. Patients
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3 with either relapsing-remitting or progressive MS who meet these criteria are eligible for
4 inclusion. This allows the inclusion of new groups of patients, such as those with active
5 progressive disease, as new DMTs become available. This study will also enrol children
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7 aged over 11, although children and adolescents who are enrolled should be treated
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9 according to an established protocol within the NHS.
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13 Patients who are not able or not willing to provide informed consent will be excluded
14 from the study. Participants enrolled or planning to be enrolled into a clinical trial with
15 an investigational medical product (IMP) will be excluded for the duration of their
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17 participation in the trial (including any extension study).
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20 **Recruiting during the COVID-19 global pandemic**

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24 Due to the COVID-19 global pandemic and two subsequent lockdowns within the United
25 Kingdom, telephone and video consultations have become the norm for outpatient care,
26 with only emergency appointments taking place. Redeployment of research staff to
27 COVID-19 studies further impacted on recruitment. The lack of face-to-face contact has
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29 prevented direct assessments of EDSS.
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34 Study amendments have been made and approved to accommodate remote enrolment
35 of patients using postal consenting methods. The use of remotely collected EDSS (ref)
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37 has facilitated monitoring of patients at a number of sites.
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41 ***Subjects recruited to date***

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45 Table 3 summarises key baseline attributes of the 1615 subjects recruited as at January
46 2021 according to current DMT class. The low number of individuals with primary and
47 secondary progressive MS (PPMS) is to be expected, given the inclusion criteria of the
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49 study and relatively recent approval of therapies for active progressive MS.
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53 **Ethics and dissemination**

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3 This study has had ethical review via London City and East REC (ref. 19/LO/0064). As
4 this study uses routinely collected medical data as the primary data source, there are
5 minimal burdens on participants.
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10 As this is an observational study, the main risks are of data misuse and subject
11 identification. This risk will be minimized by using double password protected
12 computers, maintaining links between subject identifiers and an anonymized study code
13 separate from the database in a locked compartment in a room with controlled access.
14 Researchers with access to the data will agree not to attempt to identify individual
15 subjects except in the context of direct responsibility for their clinical care. An oversight
16 committee will be put in place to assess study conduct and data security on at least an
17 annual basis, reporting to the study sponsor.
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25 **Conclusions**

26 The OPTIMISE:MS study thus provides a unique opportunity for the UK to rise to the
27 challenge of high quality real world data studies in MS. It sets out to answer a vital
28 research question, with a clearly defined core dataset. By basing the study around a
29 research question that impacts on the overwhelming majority of people with MS, we
30 have enabled the recruitment of a large number of people with MS to this observational
31 study. The use of an adaptable, disease-focussed platform for data entry enables the
32 easy addition of add-on studies, such as those attempting to answer additional research
33 questions, such as those around pregnancy, cognition or pharmacogenomics, subject to
34 additional ethical approvals.
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44 It has become clear that many of the pragmatic questions of importance to people with
45 MS cannot be answered via RCTs, and that real world data has a vital role to play.
46 However, we have a responsibility to ensure that studies using such data do so in a
47 responsible manner, and mitigate against poor data quality as much as possible. This
48 responsibility translates into time and effort spent in data entry, with clear data audit
49 trails and appropriate linkage for audit and verification. Whilst this is a significant
50 undertaking, it is one that is of clear benefit to people with MS - it is only by getting the
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3 systems and studies set up to the highest rigour that we will be able to provide clear
4 answers regarding real life risks and benefits of treatment.
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Table 1: Rates of SAEs in treatment and control groups documented in published clinical trial data. All reported SAE incidences include MS relapses unless otherwise specified.

Abbreviation: PPY, per patient year.

Therapy	Reported rate of SAE in treatment arm	Reported rate of SAE in control arm	Duration of trial (months)
Alemtuzumab <i>Control arm: IFN-β</i>	CAMMS223 [17]: 0.2 PPY	CAMMS223 (IFN- β): 0.3 PPY	36
	CARE-MS I [18]: 0.13 PPY	CARE-MS I (IFN- β): 0.09 PPY	24
	CARE-MS II [19]: 0.17 PPY	CARE-MS II (IFN- β): 0.21 PPY	24
Dimethyl fumarate <i>Control arm: placebo or GA</i>	DEFINE [20]: 18% incidence	DEFINE (placebo): 21% incidence	24
	CONFIRM [21]: 17% incidence	CONFIRM (GA and placebo): 17% (GA); 22% (placebo) incidence	24
Fingolimod <i>Control arm: IFN-β or placebo</i>	TRANSFORMS [22]: 7% incidence excl relapse	TRANSFORMS (IFN- β): 5.8% incidence excl relapse	12
	FREEDOMS I [23]: 10.1% incidence	FREEDOMS I (placebo): 13.4% incidence	24
	FREEDOMS II [24]: 15% incidence	FREEDOMS II (placebo): 13% incidence	24
Natalizumab	AFFIRM [25]: 19% incidence	AFFIRM (placebo): 24% incidence	24
	SENTINEL (+IFN- β) [26]: 18% incidence	SENTINEL (IFN- β): 21% incidence	24
Teriflunomide <i>Control arm: placebo</i>	TEMPO [27]: 14.1% (7mg), 15.9% (14mg) incidence	TEMPO: 12.8% incidence	24
	TOWER [28]: 12% incidence	TOWER: 12% incidence	11
	TOPIC [29]: 9% (7mg), 11% (14mg) incidence	TOPIC: 9%	24
Cladribine Tablets <i>Control arm: placebo</i>	ORACLE [30]: 5% (5.25mg/kg), 11% (3.5mg/kg) incidence	ORACLE (placebo): 10% incidence	22
	CLARITY [31]: 9% (5.25mg/kg), 8.4% (3.5mg/kg) incidence	CLARITY (placebo): 6.4% incidence	22
Ocrelizumab <i>Control arm: placebo</i>	OPERA [32]: 6.9% incidence	OPERA (placebo): 7.8% incidence	6

Table 2: Core baseline characteristic and ongoing / follow data capture for OPTIMISE:MS patient cohort

Core Baseline Characteristics	Ongoing / Follow up data
Physical Measures	Current / Previous DMT treatment
Comorbidities	DMT switch
Performance Measures (EDSS)	Performance Measures (EDSS)
Concomitant medications	Concomitant medications
Relapses within the past 2 years	New medical diagnosis
Serious adverse events, malignancy, opportunistic infections	Serious adverse event, malignancy, opportunistic infection
Previous malignancies or serious infection	Relapses
Current / Previous DMT treatment / DMT switching	New immunosuppressive medication for another indication
Anti-JCV abs status	Anti-JCV abs status
Total white cell and lymphocyte count	Total white cell and lymphocyte count
Liver function	Liver function
Brain MRI	Brain MRI

Table 3: Key baseline attributes of the 1,615 subjects recruited as at January 2021

	All subjects	No DMT	IFN-B/GA	Newer DMTs; no prior DMT	Newer DMTs; escalation
Total n (%)	1615	503 (31%)	157 (10%)	774 (48%)	181 (11%)
F:M (%F)	1140:472 (71%)	351:151 (70%)	128:29 (82%)	525:248 (68%)	136:44 (75%)
Mean age (SD); years	43.5 (12.3)	42.6 (13.4)	48.6 (10.6)	42.8 (11.7)	44.9 (11.9)
Mean time since diagnosis (SD); years					
<5	613 (38%)	243 (48%)	46 (29%)	304 (39%)	20 (11%)
5-9	427 (26%)	121 (24%)	44 (28%)	201 (26%)	61 (34%)
10-14	277 (17%)	64 (13%)	27 (17%)	127 (16%)	59 (33%)
15-19	171 (11%)	40 (8%)	19 (12%)	85 (11%)	27 (15%)
>20	127 (8%)	35 (7%)	21 (13%)	57 (7%)	14 (8%)
Primary MS diagnosis					
RRMS	1528 (95%)	463 (92%)	145 (92%)	743 (96%)	177 (98%)
PPMS	36 (2%)	19 (4%)	1 (1%)	16 (2%)	0 (0%)
SPMS	31 (2%)	14 (3%)	4 (3%)	11 (1%)	2 (1%)

RRMS: Relapsing Remitting MS

PPMS: Primary Progressive MS

SPMS: Secondary Progressive MS

DMT: Disease Modifying Therapy

IFN-B: Interferon beta preparations

GA: Glatiramer acetate

Figure 1: Participant entry criteria flowchart

Author contributions

RD, MC and PMM conceived the study idea

RD drafted the initial study protocol with early and key input from MC and PMM

EW wrote the statistical analysis plan for the study protocol, and provided input into the remainder of the study design

AM, AC, SW, CH, JH, NE, NS, DR, RN, MM, CB, CY and HF reviewed, revised and contributed to the study protocol

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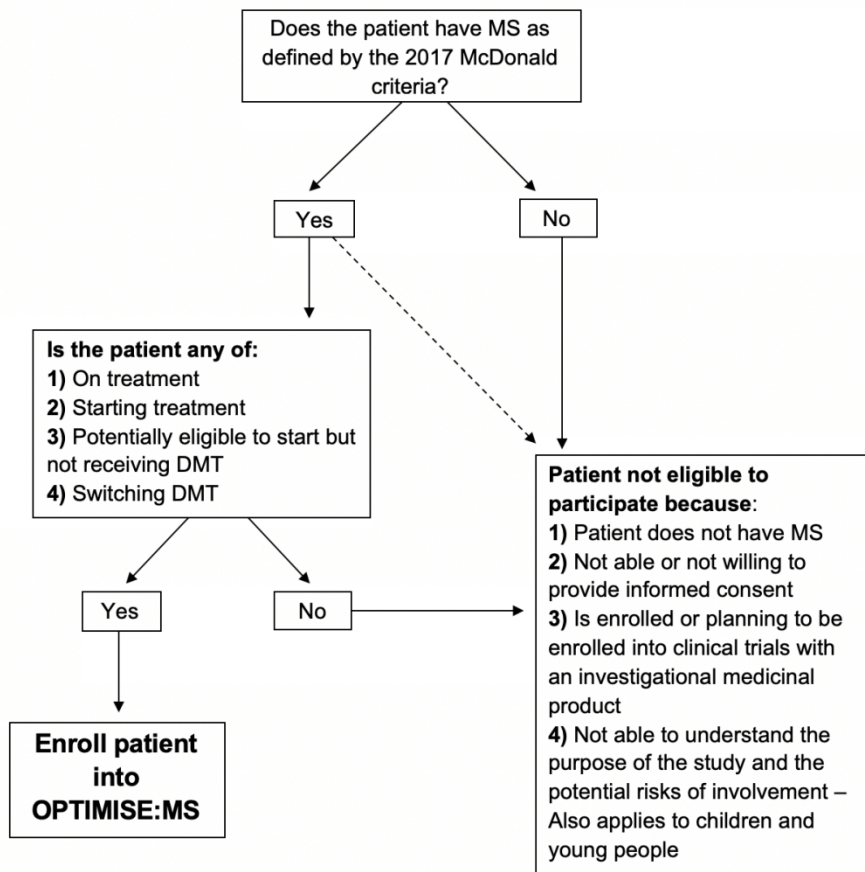
Competing interests

The authors of this protocol have no competing interests with direct relevance to the design of this protocol.

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Participant entry criteria flowchart

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OPTIMISE:MS study protocol. A pragmatic, prospective observational study to address the need for, and challenges with, real world pharmacovigilance in multiple sclerosis

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3 **OPTIMISE:MS study protocol. A pragmatic, prospective observational study to**
4 **address the need for, and challenges with, real world pharmacovigilance in**
5 **multiple sclerosis**
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Abstract

Introduction: The power of “real world” data to improve our understanding of the clinical aspects of multiple sclerosis (MS) is starting to be realised. DMT use across the UK is driven by national prescribing guidelines. As such, the UK provides an ideal country in which to gather MS outcomes data. A rigorously conducted observational study with a focus on pharmacovigilance has the potential to provide important data to inform clinicians and patients whilst testing the reliability of estimates from pivotal trials when applied to patients in the UK.

Methods and analysis: The primary aim of this study is to characterize the incidence and compare the risk of serious adverse events in people with MS treated with DMTs. The OPTIMISE:MS database enables electronic data capture and secure data transfer. Selected clinical data, clinical histories and patient reported outcomes are collected in a harmonized fashion across sites at the time of routine clinical visits. The first patient was recruited to the study on 24 May 2019. As of January 2021, 1,615 individuals have baseline data recorded; follow up data is being captured and will be reported in due course.

Ethics and dissemination: This study has ethical permission (London City and East; Ref 19/LO/0064). Potential concerns around data storage and sharing are mitigated by the separation of identifiable data from all other clinical data, and limiting access to any identifiable data. The results of this study will be disseminated via publication. Participants provide consent for anonymised data to be shared for further research use, further enhancing the value of the study.

Strengths and Limitations

- All patients with multiple sclerosis (MS) eligible for disease modifying therapy under the care of participating centres can take part in this study
- Selected clinical data recorded during episodes of routine care are uploaded to a study specific database, allowing an assessment of data completeness and quality
- Potential concerns around data storage and sharing are mitigated by the separation of identifiable data from all other clinical data, and limiting access to any identifiable data
- Data are representative of patient outcomes in specialist MS centres, where an increasing proportion of MS care is provided; patients at non-specialist centres are not enrolled, so their outcomes will not be captured
- A strength of the study recruitment processes is the consent for contact regarding additional studies; the study database thus provides a rich resource for future research

Introduction

Real world data in multiple sclerosis

The power of “real world” data to improve our understanding of the clinical aspects of multiple sclerosis (MS), including the relative risks and benefits of disease modifying treatments and efficacy in a UK population with MS, and the future impact of these data on the care of people with MS is starting to be realised. However, the utility of large datasets is significantly influenced by the methods used to capture data, as well as the overall validity of these data. Concerns regarding data quality and international applicability have limited the translation of findings from large datasets to clinical practice across medicine. A huge number of unanswered questions remain around risk stratification, treatment sequencing, and outcome monitoring, which cannot be answered using a traditional randomised control trial (RCT) design. Furthermore, long term and/or rare outcomes are almost impossible to detect via RCTs. Historically, phase 4 observational studies have been used to study such endpoints. However, these also have limitations due to high drop-out rates and an inherent lack of power to detect rare outcomes, or to evaluate risks associated with prior or subsequent treatment decisions, or comorbid medical conditions.

“Real world data” refers to data gathered in the course of an individual patient’s routine clinical care. The aim is not to discriminate based on age, comorbid conditions, or other such factors that may influence trial eligibility [1]. This data is by nature highly confounded - which brings significant statistical concerns - but also enables observations relevant to clinical practice. Such data enables the study of specific areas that cannot be addressed via traditional routes.

A number of large real world MS-specific data initiatives already exist. National registries from European countries, including Sweden, France and Italy have significantly improved our understanding of MS disease trajectories and the influence of treatment on these [2]. MSBase is a collaborative, international disease registry, which captures a range of MS-related data from a large number of countries [3]. More

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3 recently, processes for formal data sharing have started to enable the pooling of data
4 from five large registries (Sweden, France, Italy, Denmark, MSBase) [4].
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8 Across the UK, harmonised data gathering has been limited to date. Whilst many
9 databases exist, most lack the granularity needed for the objectives of this study. For
10 example, the database for the Blueteq web-based prior approval system identifies
11 people who are prescribed DMT, but does not capture safety data. Rigorous data
12 collection and prospective data entry is time consuming, and frequently does not
13 provide short, or even medium, term benefit to clinicians. Linking data entry to disease
14 modifying therapy (DMT) funding rebates brings a clear risk of biasing data. Whilst
15 many of the concerns regarding missing or incomplete data can be overcome with large
16 numbers of participants [5], in order to overcome reporter bias when examining
17 potentially rare or serious events, data collection and verification needs to be rigorous.
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27 Given the relatively homogeneous practices in DMT prescription across the UK, driven
28 by national prescribing guidelines [6], the UK provides an ideal arena from which to
29 gather MS outcome data.
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34 ***The need for pharmacovigilance in MS***

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36 The therapeutic armoury in MS has increased rapidly, but real-world data concerning
37 safety is limited. The first treatments to be introduced (interferon-beta preparations and
38 glatiramer acetate [Copaxone]) have well-established safety records [7]. Progressive
39 multifocal leukoencephalopathy (PML) risk limits the long-term use of natalizumab in
40 many patients [8]. There are safety signals from clinical trials and early clinical
41 experience suggesting both lymphopaenia and increased infection rates with newer MS
42 therapies [7-12]. The risks of serious adverse events (SAEs) with individual treatments
43 over a relatively short duration have been reported in clinical trials (Table 1). The rates
44 at which these occur in the real-life treated UK population which includes a population
45 with a wide range of age and co-morbidities, is as yet, unknown. The current adverse
46 event reporting system (yellow card system, [12]) has a high risk of missing longer-term
47 rare adverse events; as such there is an urgent need for a formalised reporting system.
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5 As the number of patients taking newer MS treatments increases, so does our clinical
6 experience. Alongside this, concern regarding longer-term effects of treatments and the
7 cumulative risk associated with treatment switching is increasing (personal
8 communication, MHRA). Counselling patients regarding switching DMT typically uses
9 information available from (often recent) clinical experience, case reports, and
10 occasional small case series.
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17 In a pharmacovigilance study, patients on established first-line treatments provide a
18 useful reference cohort, as the safety and effectiveness of these medicines are well
19 understood. They form a readily characterized group; patients tend not to be de-
20 escalated to first-line injectable therapies outside of specific situations, such as when
21 planning pregnancy or with identification of an active malignancy (observations from
22 authors' clinical experiences). While there are obvious limitations to indexing outcomes
23 associated with newer treatments to these reference populations (e.g., disease and
24 demographic characteristics may be different, as patients in the reference groups are
25 likely to have lower baseline disease activity than those receiving highly active
26 therapies), they provide a pragmatic approach for an observational real-world study.
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36 ***Existing models of disease-specific studies evaluating treatment-associated*** 37 ***events*** 38

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40 National pharmacovigilance is not a novel concept and can contribute to improved
41 safety for patients. Differences in susceptibilities and pharmacological responses,
42 diagnostic and prescribing practices, lifestyle and patterns of medicine adherence all
43 can vary between countries. Both observational registries and prospective cohort
44 studies are well-established in rheumatology and dermatology, where they may be
45 linked to medication funding, and these provide a wealth of data regarding the safety
46 profile of biological agents [13-15] .
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54 National, automated data capture systems, some of which are disease specific, are
55 increasing. NHS Digital now curates a number of national data collections [16].
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3 However, MS outcomes are poorly coded in primary care datasets, and individuals with
4 MS who develop cancer and are entered onto cancer registries do not have detailed
5 data regarding prior DMT use recorded. It is thus not possible to use existing registries
6 to study clinical endpoints in MS in detail; however, these registries provide a resource
7 to mitigate against loss to follow up via data linkage.
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10 **Methods and analysis**

11 **Rationale and study design**

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14 The OPTIMISE:MS study is a pragmatic, prospective observational cohort study
15 (19/LO/0064) planned to run for 7 years in the first instance. It aims to estimate the
16 frequency of serious adverse events with DMT use in routine clinical practice in the UK.
17 All individuals potentially eligible for MS DMT are eligible for this observational study,
18 regardless of any decision regarding DMT use (figure 1). OPTIMISE:MS will recruit
19 people with MS from major MS care clinics across the country.
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28 All participating sites have a site initiation visit prior to approaching any potential
29 participants. Sites receive training in the study aims, and how these will be met using
30 the databases. Database training is provided, with ongoing support from the central
31 team for both technical issues and support for clinical coding or event adjudication.
32 Participating sites are reimbursed for their participation in the study based on numbers
33 recruited and followed up. Set up costs are covered at the time of site initiation, followed
34 by per-participant recruitment costs and subsequent follow up costs. These have been
35 calculated according to the anticipated time for data capture and entry. Patients are not
36 reimbursed for participation in the study, as other than the time taken to consider the
37 study and provide consent, no additional demands are made of them.
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47 The primary aim of this study is to characterize the incidence and compare the risk of
48 serious adverse events in people with MS treated with DMTs (comparators will be an
49 untreated cohort, and a cohort treated with first line injectable DMT). A serious adverse
50 event (SAE) in this context is an adverse event resulting in death, requiring in-patient
51 treatment or prolongation of existing in-patient treatment or that results in persistent or
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3 significant disability or incapacity. Serious adverse events of particular interest in this
4 study are any infections requiring hospitalisation, any opportunistic infection (i.e.
5 typically associated with immunosuppression), any other serious adverse event
6 believed to be related to treatment (e.g., lymphoma, non-melanoma skin cancer), any
7 MS relapse, and death. Additionally, rates of symptomatic COVID-19, outcomes
8 associated with SARS-COV2 infection and relationship to DMT use and/or
9 immunosuppression will be captured. There has been the additional potential to capture
10 data regarding the frequency of asymptomatic COVID-19 infections and responses to
11 vaccination alongside this.
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20 Selected clinical data, clinical histories and patient reported outcomes will be collected
21 in a harmonized fashion across sites at the time of routine clinical visits or in direct
22 follow up (for laboratory or paraclinical testing). No additional clinical visits are
23 mandated as part of this pragmatic study. Based on usual (recommended) clinical
24 practice in the UK, we anticipate follow up clinical visits for patients enrolled in this study
25 *at least* on an annual basis. Current National Institute of Health and Care Excellence
26 (NICE) criteria for the management of MS in the UK along with NHS England DMT
27 financial rebate systems (Bluteq) require at least annual review of all MS patients. The
28 requirement for at least annual review has thus been set in line with minimum standard
29 clinical practice.
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39 MRI scans and laboratory tests recommended for treatment monitoring will be
40 performed by clinical centres at intervals based on their usual clinical practice and
41 clinical indications in the patients. While sites can enter MRI data into the database,
42 there is no mandate for MRI monitoring within the study protocol. Sites are provided
43 with financial support to complete these follow up data in line with the compensation for
44 completing DVLA forms. As part of site support and data queries, the return rate for
45 follow up data and completeness of these data will be audited by the central study team.
46 As all UK patients have a permanent NHS number allocated at birth or migration,
47 participants who move around the country can continue to be monitored.
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Concerns regarding loss to long term follow up can be mitigated to some degree via data linkage with national systems. Following appropriate consent, an individual's NHS number can be used to link individuals via digital.NHS, Hospital Episode Statistics (HES) and the UK Cancer Registry, potentially using HDR-UK infrastructure, to support follow up of serious adverse events.

This study also has the potential for patients to report on the impact of the disease on their daily life via patient reported outcome measures (PROs). However, these would require a separate, patient focussed database portal along with additional consent. This remains an aim for the database. However, given COVID-related delays to initial recruitment and pressure on sites, the current focus is on collecting accurate and complete physician-reported data.

Data flow and security

The OPTIMISE:MS database (online demo version available via <https://www.optimise-ms.org/demo/>) has been designed to enable electronic data capture and secure data transfer. Data is entered onto site-specific laptops at individual sites, and transferred securely on a regular basis. Every data entry is time stamped according to both date of data entry and date of data collection, to allow for audit and identification of retrospective data entry. Personally identifiable information including NHS number is accessible only to the clinical care team at each site and to those members of the central analysis group responsible for follow up of serious adverse events.

The majority of participant data is stored in a secondary database, in which each subject is pseudonymised and the NHS number and name are not available. This database will be used for analyses performed by the OPTIMISE analytical group and collaborators. A participant data deletion mechanism is incorporated into each form of the database. Data for any subject who withdraws consent and whose data is deleted from the database held at any participating site also will be deleted automatically from the two forms of the database held at the central analysis site.

Patient and public involvement

Patients were involved early in the conception of this study. The study was discussed with patient representatives, who gave feedback around the kind of data that they would be willing to share, and the desired frequency of contact. The main concern of the patients that we consulted was that their data were to be used for the benefit of people with MS, and not for profit or other third party gain.

OPTIMISE database and core dataset

Whilst software tools for MS patient data entry and curation have been generated before, none are in widespread use. There is no single electronic patient record (EPR) in use across the UK NHS, and utilising individual EPR systems to collect MS-specific data is likely to be both unacceptably time consuming and costly. One major challenge of bespoke MS data collection systems is the need to balance comprehensiveness of data collection with the sustainability of data entry in a busy clinic environment. A further challenge is to ensure compliance with basic requirements for data security and auditing and the ability to remove data if consent is withdrawn.

The OPTIMISE database is used to capture both minimum baseline characteristics and ongoing and follow up data. These include current treatment category, gender, ethnicity, dominant hand, country of origin, primary MS diagnosis, time since diagnosis, age, physical and performance measures (EDSS), relapses within the past 2 years, serious adverse events, malignancies, opportunistic infections, liver function, brain MRI, total white cell and lymphocyte count and anti-JCV antibody status (Table 2).

Participating sites are expected to upload all of the clinical and paraclinical data collected to the central analysis site on a quarterly basis. Visit frequency for patients was determined by usual clinical practice and completeness of data and other quality control assessments are performed on a quarterly basis by the central study team

located at Imperial College London. Where data is incomplete in a significant number of records in a single upload, the site is contacted for remedial action to be taken. A strength of this study is that data queries regarding missing or implausible data are sent directly to sites, allowing entries to be reconfirmed as required. All changes made in response to these are timestamped and recorded in the database, so that sites with high levels of implausible or missing data can be identified for additional training and support.

Statistical analysis

The statistical analysis will focus on the detection of adverse event signals by identifying specific DMTs and DMT sequences associated with disproportionate numbers of events (relative to the overall study population). A number of disproportionality measures will be applied in parallel to increase sensitivity, including the Reporting Odds Ratio, Empirical Bayes Geometric Mean and Information Component [17] (all originally designed for spontaneous report data, but here adapted to the longitudinal data collected within OPTIMISE:MS), and the incidence rate ratio. Signals will be triggered if the lower one-sided 95% confidence limit for any disproportionality measure exceeds the null value of no association. Two methods will be used to screen out false positive signals. Firstly, a minimum number of events will be imposed in order to eliminate false signals due to random noise when event counts are low. Secondly, a chronological filter based on the LEOPARD methodology will be applied [18]. The LEOPARD filter assesses whether an adverse event occurs more often before or after the prescription of the treatment with which it appears to be associated. This can help to avoid protopathic bias, in which a causal relationship is falsely inferred between an adverse event and the commencement of treatment when in fact both were caused by the underlying progress of disease or other factors.

Poisson (or negative binomial) regression and survival analyses will be carried out to evaluate rates of adverse events, relapse, disability progression, new MRI lesions, mortality, lymphopaenia and liver enzyme elevation in subjects receiving any newer

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3 DMT in comparison to those receiving first-line injectable DMTs or no treatment. These
4 analyses will incorporate subject-level covariates to adjust for demographics and
5 disease history.
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10 Secondary analyses will use additional models to explore the relationships between
11 DMT use and outcomes, including whether effects of DMTs persist after treatment
12 cessation/switch. Several exposure definitions will be applied in parallel. Current
13 exposure models will use the subjects current treatment category at the time of event.
14 Recent exposure models will be dependent on both the current treatment category and,
15 if applicable, the previous treatment category within the preceding six months.
16 Cumulative exposure models will include the total cumulative exposure to each
17 treatment class in patient-months, and time-weighted cumulative exposure models will
18 weight according to both time on treatment and time from exposure to event, with more
19 weight assigned to recent exposures than historic. In these analyses subjects will not be
20 censored at treatment cessation or switch, so each subject can contribute multiple
21 periods of follow up with exposure to different treatment categories.
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32 ***Entry criteria and follow up data***

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36 All patients with MS as defined by the 2017 McDonald criteria and who are eligible to
37 receive DMT reimbursement from NHS England are eligible for entry into the
38 observational study. This includes patients who are on treatment, as well as those
39 starting, potentially eligible to start but not receiving DMT, or switching DMT. Patients
40 with either relapsing-remitting or progressive MS who meet these criteria are eligible for
41 inclusion. This allows the inclusion of new groups of patients, such as those with active
42 progressive disease, as new DMTs become available. This study will also enrol children
43 aged over 11, although children and adolescents who are enrolled should be treated
44 according to an established protocol within the NHS.
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53 Patients who are not able or not willing to provide informed consent will be excluded
54 from the study. Participants enrolled or planning to be enrolled into a clinical trial of an
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3 investigational medical product (IMP) will be excluded for the duration of their
4 participation in the trial (including any extension study).
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8 Enrolling patients via participating major MS centres means that those patients who are
9 treated only general neurology clinics, and/or are not seen in these centres are not
10 included in this study. Centres were selected according to their caseload, with centres
11 able to meet a recruitment target of at least 300 patients selected to take part in the
12 study. Given the infrastructure support required for consent and ongoing data entry, a
13 minimum number of recruits was needed to make the study viable within each centre.
14 An advantage of this approach is that all of the major MS centres selected treat patients
15 with the full range of MS DMTs. However, this approach also introduces a potential
16 source of bias. Patients not seen at MS centres are more likely to be on either no
17 treatment or first line injectable treatments, whereas those treated at MS centres
18 potentially have access to highly active treatment earlier in their disease course.
19 However, early data (table 3) suggests that this strategy has been successful in
20 recruitment patients across a range of DMT.
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32 **Recruiting during the COVID-19 global pandemic**

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36 Due to the COVID-19 global pandemic and two subsequent lockdowns within the United
37 Kingdom, telephone and video consultations became standard for outpatient care, with
38 face to face appointments only taking place sporadically. Redeployment of research
39 staff to COVID-19 studies further impacted on recruitment. The lack of face-to-face
40 contact has prevented direct assessments of EDSS.
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46 Study amendments have been made and approved to accommodate remote enrolment
47 of patients using postal consenting methods. The use of remotely collected EDSS [19]
48 has facilitated monitoring of patients at a number of sites.
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53 ***Subjects recruited to date***

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3 Table 3 summarises key baseline attributes of the 1615 subjects recruited as at January
4 2021 according to current DMT class. The first patient was recruited to this study on 24
5 May 2019. COVID-related delays substantially slowed rates of recruitment in 2020 and
6 through the first half of 2021, from which time improvements have been seen. The low
7 number of individuals with primary and secondary progressive MS (PPMS) is to be
8 expected, given the inclusion criteria of the study and relatively recent approval of
9 therapies for active progressive MS.
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17 **Ethics and dissemination**

18 This study has had ethical review via London City and East REC (ref. 19/LO/0064). As
19 this study uses routinely collected medical data as the primary data source, there are
20 minimal burdens on participants.
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26 As this is an observational study, the main risks are of data misuse and subject
27 identification. This risk will be minimized by using double password protected
28 computers, maintaining links between subject identifiers and an anonymized study code
29 separate from the database in a locked compartment in a room with controlled access.
30 Researchers with access to the data will agree not to attempt to identify individual
31 subjects except in the context of direct responsibility for their clinical care. An oversight
32 committee will be put in place to assess study conduct and data security on at least an
33 annual basis, reporting to the study sponsor.
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41 The OPTIMISE:MS study thus provides a unique opportunity for the UK to rise to the
42 challenge of high quality real world data studies in MS. It sets out to answer a vital
43 research question, with a clearly defined core dataset. The use of an adaptable,
44 disease-focussed platform for data entry enables the easy addition of add-on studies,
45 such as those attempting to answer additional research questions, such as those
46 around pregnancy, cognition or pharmacogenomics, subject to additional ethical
47 approvals. Whilst this study is a significant undertaking, it is one that is of clear benefit
48 to people with MS - it is only by getting the systems and studies set up to the highest
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rigour that we will be able to provide clear answers regarding real life risks and benefits of treatment.

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Table 1: Rates of SAEs in treatment and control groups documented in published clinical trial data. All reported SAE incidences include MS relapses unless otherwise specified.

Abbreviation: PPY, per patient year.

Therapy	Reported rate of SAE in treatment arm	Reported rate of SAE in control arm	Duration of trial (months)
Alemtuzumab <i>Control arm: IFN-β</i>	CAMMS223 [20]: 0.2 PPY	CAMMS223 (IFN- β): 0.3 PPY	36
	CARE-MS I [21]: 0.13 PPY	CARE-MS I (IFN- β): 0.09 PPY	24
	CARE-MS II [22]: 0.17 PPY	CARE-MS II (IFN- β): 0.21 PPY	24
Dimethyl fumarate <i>Control arm: placebo or GA</i>	DEFINE [23]: 18% incidence	DEFINE (placebo): 21% incidence	24
	CONFIRM [24]: 17% incidence	CONFIRM (GA and placebo): 17% (GA); 22% (placebo) incidence	24
Fingolimod <i>Control arm: IFN-β or placebo</i>	TRANSFORMS [25]: 7% incidence excl relapse	TRANSFORMS (IFN- β): 6% incidence excl relapse	12
	FREEDOMS I [26]: 10% incidence	FREEDOMS I (placebo): 13% incidence	24
	FREEDOMS II [27]: 15% incidence	FREEDOMS II (placebo): 13% incidence	24
Natalizumab	AFFIRM [28]: 19% incidence	AFFIRM (placebo): 24% incidence	24
	SENTINEL (+IFN- β) [29]: 18% incidence	SENTINEL (IFN- β): 21% incidence	24
Teriflunomide <i>Control arm: placebo</i>	TEMPO [30]: 14% (7mg), 15.9% (14mg) incidence	TEMPO: 13% incidence	24
	TOWER [31]: 12% incidence	TOWER: 12% incidence	11
	TOPIC [32]: 9% (7mg), 11% (14mg) incidence	TOPIC: 9%	24
Cladribine Tablets <i>Control arm: placebo</i>	ORACLE [33]: 5% (5.25mg/kg), 11% (3.5mg/kg) incidence	ORACLE (placebo): 10% incidence	22
	CLARITY [34]: 9% (5.25mg/kg), 8% (3.5mg/kg) incidence	CLARITY (placebo): 6% incidence	22
Ocrelizumab <i>Control arm: placebo</i>	OPERA [35]: 7% incidence	OPERA (placebo): 8% incidence	6

Fingolimod (paediatric patients) <i>Control arm: IFN-β</i>	PARADIGMS [36]: 17% incidence (including SAE of interest)	PARADIGMS: 7% incidence	24
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Table 2: Core baseline characteristic and ongoing / follow data capture for OPTIMISE:MS patient cohort

Core Baseline Characteristics	Ongoing / Follow up data
Physical Measures	Current / Previous DMT treatment
Comorbidities	DMT switch
Performance Measures (EDSS)	Performance Measures (EDSS)
Concomitant medications	Concomitant medications
Relapses within the past 2 years	New medical diagnosis
Serious adverse events, malignancy, opportunistic infections	Serious adverse event, malignancy, opportunistic infection
Previous malignancies or serious infection	Relapses
Current / Previous DMT treatment / DMT switching	New immunosuppressive medication for another indication
Anti-JCV abs status	Anti-JCV abs status
Total white cell and lymphocyte count	Total white cell and lymphocyte count
Liver function	Liver function
Brain MRI	Brain MRI

Table 3: Key baseline attributes of the 1,615 subjects recruited as at January 2021

	All subjects	No DMT	IFN-B/GA	Newer DMTs; no prior DMT	Newer DMTs; escalation
Total n (%)	1615	503 (31%)	157 (10%)	774 (48%)	181 (11%)
F:M (%F)	1140:472 (71%)	351:151 (70%)	128:29 (82%)	525:248 (68%)	136:44 (75%)
Mean age (SD); years	43.5 (12.3)	42.6 (13.4)	48.6 (10.6)	42.8 (11.7)	44.9 (11.9)
Mean time since diagnosis (SD); years					
<5	613 (38%)	243 (48%)	46 (29%)	304 (39%)	20 (11%)
5-9	427 (26%)	121 (24%)	44 (28%)	201 (26%)	61 (34%)
10-14	277 (17%)	64 (13%)	27 (17%)	127 (16%)	59 (33%)
15-19	171 (11%)	40 (8%)	19 (12%)	85 (11%)	27 (15%)
>20	127 (8%)	35 (7%)	21 (13%)	57 (7%)	14 (8%)
Primary MS diagnosis					
RRMS	1528 (95%)	463 (92%)	145 (92%)	743 (96%)	177 (98%)
PPMS	36 (2%)	19 (4%)	1 (1%)	16 (2%)	0 (0%)
SPMS	31 (2%)	14 (3%)	4 (3%)	11 (1%)	2 (1%)

RRMS: Relapsing Remitting MS

PPMS: Primary Progressive MS

SPMS: Secondary Progressive MS

DMT: Disease Modifying Therapy

IFN-B: Interferon beta preparations

GA: Glatiramer acetate

Figure 1: Participant entry criteria flowchart

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Author contributions

RD, MC and PMM conceived the study idea

RD drafted the initial study protocol with early and key input from MC and PMM

EW wrote the statistical analysis plan for the study protocol, and provided input into the remainder of the study design

AM, AC, SW, CH, JH, NE, NS, DR, RN, MM, CB, CY and HF reviewed, revised and contributed to the study protocol

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Competing interests

The authors of this protocol have no competing interests with direct relevance to the design of this protocol.

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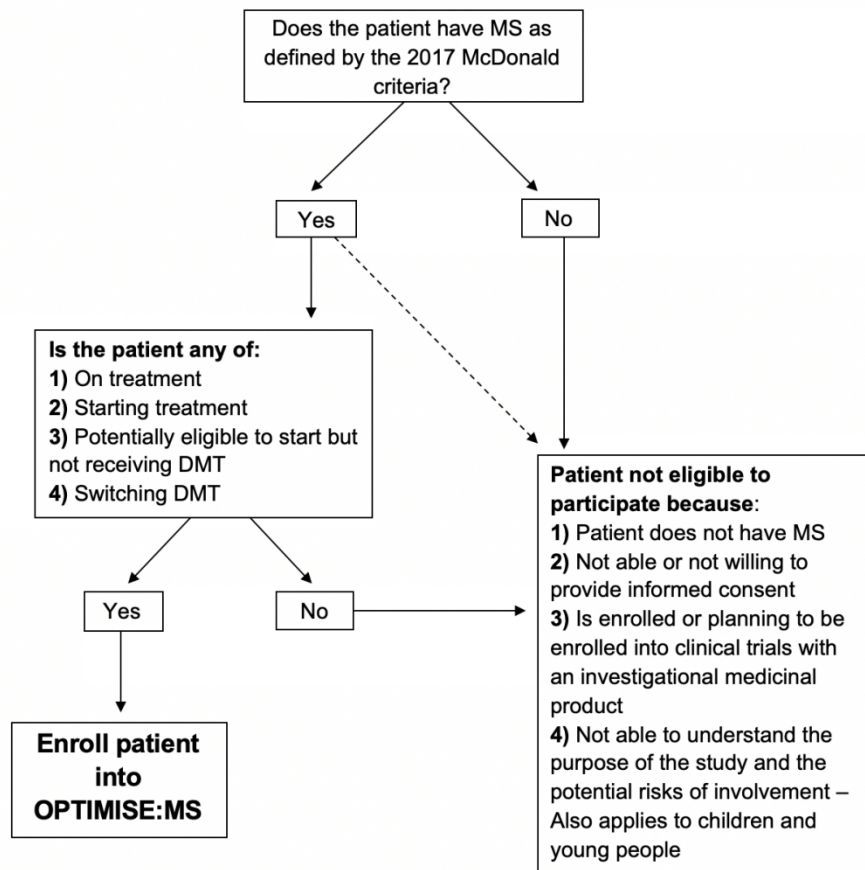
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Participant entry criteria flowchart

BMJ Open

OPTIMISE:MS study protocol. A pragmatic, prospective observational study to address the need for, and challenges with, real world pharmacovigilance in multiple sclerosis

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4 **address the need for, and challenges with, real world pharmacovigilance in**
5 **multiple sclerosis**
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18 Multiple Sclerosis, pharmacovigilance, adverse events, immunosuppression

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Abstract

Introduction: The power of “real world” data to improve our understanding of the clinical aspects of multiple sclerosis (MS) is starting to be realised. DMT use across the UK is driven by national prescribing guidelines. As such, the UK provides an ideal country in which to gather MS outcomes data. A rigorously conducted observational study with a focus on pharmacovigilance has the potential to provide important data to inform clinicians and patients whilst testing the reliability of estimates from pivotal trials when applied to patients in the UK.

Methods and analysis: The primary aim of this study is to characterize the incidence and compare the risk of serious adverse events in people with MS treated with DMTs. The OPTIMISE:MS database enables electronic data capture and secure data transfer. Selected clinical data, clinical histories and patient reported outcomes are collected in a harmonized fashion across sites at the time of routine clinical visits. The first patient was recruited to the study on 24 May 2019. As of January 2021, 1,615 individuals have baseline data recorded; follow up data is being captured and will be reported in due course.

Ethics and dissemination: This study has ethical permission (London City and East; Ref 19/LO/0064). Potential concerns around data storage and sharing are mitigated by the separation of identifiable data from all other clinical data, and limiting access to any identifiable data. The results of this study will be disseminated via publication. Participants provide consent for anonymised data to be shared for further research use, further enhancing the value of the study.

Strengths and Limitations

- All patients with multiple sclerosis (MS) eligible for disease modifying therapy under the care of participating centres can take part in this study
- Selected clinical data recorded during episodes of routine care are uploaded to a study specific database, allowing an assessment of data completeness and quality
- Potential concerns around data storage and sharing are mitigated by the separation of identifiable data from all other clinical data, and limiting access to any identifiable data
- Data are representative of patient outcomes in specialist MS centres, where an increasing proportion of MS care is provided; patients at non-specialist centres are not enrolled, so their outcomes will not be captured
- A strength of the study recruitment processes is the consent for contact regarding additional studies; the study database thus provides a rich resource for future research

Introduction

Real world data in multiple sclerosis

The power of “real world” data to improve our understanding of the clinical aspects of multiple sclerosis (MS), including the relative risks and benefits of disease modifying treatments and efficacy in a UK population with MS, and the future impact of these data on the care of people with MS is starting to be realised. However, the utility of large datasets is significantly influenced by the methods used to capture data, as well as the overall validity of these data. Concerns regarding data quality and international applicability have limited the translation of findings from large datasets to clinical practice across medicine. A huge number of unanswered questions remain around risk stratification, treatment sequencing, and outcome monitoring, which cannot be answered using a traditional randomised control trial (RCT) design. Furthermore, long term and/or rare outcomes are almost impossible to detect via RCTs. Historically, phase 4 observational studies have been used to study such endpoints. However, these also have limitations due to high drop-out rates and an inherent lack of power to detect rare outcomes, or to evaluate risks associated with prior or subsequent treatment decisions, or comorbid medical conditions.

“Real world data” refers to data gathered in the course of an individual patient’s routine clinical care. The aim is not to discriminate based on age, comorbid conditions, or other such factors that may influence trial eligibility [1]. This data is by nature highly confounded - which brings significant statistical concerns - but also enables observations relevant to clinical practice. Such data enables the study of specific areas that cannot be addressed via traditional routes.

A number of large real world MS-specific data initiatives already exist. National registries from European countries, including Sweden, France and Italy have significantly improved our understanding of MS disease trajectories and the influence of treatment on these [2]. MSBase is a collaborative, international disease registry, which captures a range of MS-related data from a large number of countries [3]. More

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3 recently, processes for formal data sharing have started to enable the pooling of data
4 from five large registries (Sweden, France, Italy, Denmark, MSBase) [4].
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8 Across the UK, harmonised data gathering has been limited to date. Whilst many
9 databases exist, most lack the granularity needed for the objectives of this study. For
10 example, the database for the Blueteq web-based prior approval system identifies
11 people who are prescribed DMT, but does not capture safety data. Rigorous data
12 collection and prospective data entry is time consuming, and frequently does not
13 provide short, or even medium, term benefit to clinicians. Linking data entry to disease
14 modifying therapy (DMT) funding rebates brings a clear risk of biasing data. Whilst
15 many of the concerns regarding missing or incomplete data can be overcome with large
16 numbers of participants [5], in order to overcome reporter bias when examining
17 potentially rare or serious events, data collection and verification needs to be rigorous.
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27 Given the relatively homogeneous practices in DMT prescription across the UK, driven
28 by national prescribing guidelines [6], the UK provides an ideal arena from which to
29 gather MS outcome data.
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34 ***The need for pharmacovigilance in MS***

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36 The therapeutic armoury in MS has increased rapidly, but real-world data concerning
37 safety is limited. The first treatments to be introduced (interferon-beta preparations and
38 glatiramer acetate [Copaxone]) have well-established safety records [7]. Progressive
39 multifocal leukoencephalopathy (PML) risk limits the long-term use of natalizumab in
40 many patients [8]. There are safety signals from clinical trials and early clinical
41 experience suggesting both lymphopaenia and increased infection rates with newer MS
42 therapies [7-12]. The risks of serious adverse events (SAEs) with individual treatments
43 over a relatively short duration have been reported in clinical trials (Table 1). The rates
44 at which these occur in the real-life treated UK population which includes a population
45 with a wide range of age and co-morbidities, is as yet, unknown. The current adverse
46 event reporting system (yellow card system, [12]) has a high risk of missing longer-term
47 rare adverse events; as such there is an urgent need for a formalised reporting system.
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3 The yellow card system is voluntary, and medicines that are licensed for less than two
4 years are highlighted. Awareness raising has a substantial impact on both the quantity
5 and quality of reports [13]; highlighting under-reporting and bias in reports.
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10 As the number of patients taking newer MS treatments increases, so does our clinical
11 experience. Alongside this, concern regarding longer-term effects of treatments and the
12 cumulative risk associated with treatment switching is increasing (personal
13 communication, MHRA). Counselling patients regarding switching DMT typically uses
14 information available from (often recent) clinical experience, case reports, and
15 occasional small case series.
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22 In a pharmacovigilance study, patients on established first-line treatments provide a
23 useful reference cohort, as the safety and effectiveness of these medicines are well
24 understood. They form a readily characterized group; patients tend not to be de-
25 escalated to first-line injectable therapies outside of specific situations, such as when
26 planning pregnancy or with identification of an active malignancy (observations from
27 authors' clinical experiences). While there are obvious limitations to indexing outcomes
28 associated with newer treatments to these reference populations (e.g., disease and
29 demographic characteristics may be different, as patients in the reference groups are
30 likely to have lower baseline disease activity than those receiving highly active
31 therapies), they provide a pragmatic approach for an observational real-world study.
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41 ***Existing models of disease-specific studies evaluating treatment-associated*** 42 ***events*** 43 44

45 National pharmacovigilance is not a novel concept and can contribute to improved
46 safety for patients. Differences in susceptibilities and pharmacological responses,
47 diagnostic and prescribing practices, lifestyle and patterns of medicine adherence all
48 can vary between countries. Both observational registries and prospective cohort
49 studies are well-established in rheumatology and dermatology, where they may be
50 linked to medication funding, and these provide a wealth of data regarding the safety
51 profile of biological agents [14-16].
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5 National, automated data capture systems, some of which are disease specific, are
6 increasing. NHS Digital now curates a number of national data collections [17].

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8 However, MS outcomes are poorly coded in primary care datasets, and individuals with
9 MS who develop cancer and are entered onto cancer registries do not have detailed
10 data regarding prior DMT use recorded. It is thus not possible to use existing registries
11 to study clinical endpoints in MS in detail; however, these registries provide a resource
12 to mitigate against loss to follow up via data linkage.
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16 **Methods and analysis**

17 **Rationale and study design**

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19 The OPTIMISE:MS study is a pragmatic, prospective observational cohort study
20 (19/LO/0064) planned to run for 7 years in the first instance, with the potential for longer
21 follow up subject to funding. It aims to estimate the frequency of serious adverse events
22 with DMT use in routine clinical practice in the UK. All individuals potentially eligible for
23 MS DMT are eligible for this observational study, regardless of any decision regarding
24 DMT use (figure 1). OPTIMISE:MS will recruit people with MS from major MS care
25 clinics across the country.
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35 All participating sites have a site initiation visit prior to approaching any potential
36 participants. Sites receive training in the study aims, and how these will be met using
37 the databases. Database training is provided, with ongoing support from the central
38 team for both technical issues and support for clinical coding or event adjudication.
39 Participating sites are reimbursed for their participation in the study based on numbers
40 recruited and followed up. Set up costs are covered at the time of site initiation, followed
41 by per-participant recruitment costs and subsequent follow up costs. These have been
42 calculated according to the anticipated time for data capture and entry. Patients are not
43 reimbursed for participation in the study, as other than the time taken to consider the
44 study and provide consent, no additional demands are made of them.
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3 The primary aim of this study is to characterize the incidence and compare the risk of
4 serious adverse events in people with MS treated with DMTs (comparators will be an
5 untreated cohort, and a cohort treated with first line injectable DMT). A serious adverse
6 event (SAE) in this context is an adverse event resulting in death, requiring in-patient
7 treatment or prolongation of existing in-patient treatment or that results in persistent or
8 significant disability or incapacity. Serious adverse events of particular interest in this
9 study are any infections requiring hospitalisation, any opportunistic infection (i.e.
10 typically associated with immunosuppression), any other serious adverse event
11 believed to be related to treatment (e.g., lymphoma, non-melanoma skin cancer), any
12 MS relapse, and death. Additionally, rates of symptomatic COVID-19, outcomes
13 associated with SARS-COV2 infection and relationship to DMT use and/or
14 immunosuppression will be captured. There has been the additional potential to capture
15 data regarding the frequency of asymptomatic COVID-19 infections and responses to
16 vaccination alongside this.
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29 Selected clinical data, clinical histories and patient reported outcomes will be collected
30 in a harmonized fashion across sites at the time of routine clinical visits or in direct
31 follow up (for laboratory or paraclinical testing). SAEs will be classified according to
32 MedDRA. No additional clinical visits are mandated as part of this pragmatic study.
33 Based on usual (recommended) clinical practice in the UK, we anticipate follow up
34 clinical visits for patients enrolled in this study *at least* on an annual basis. Current
35 National Institute of Health and Care Excellence (NICE) criteria for the management of
36 MS in the UK along with NHS England DMT financial rebate systems (Bluteq) require at
37 least annual review of all MS patients. The requirement for at least annual review has
38 thus been set in line with minimum standard clinical practice.
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48 MRI scans and laboratory tests recommended for treatment monitoring will be
49 performed by clinical centres at intervals based on their usual clinical practice and
50 clinical indications in the patients. While sites can enter MRI data into the database,
51 there is no mandate for MRI monitoring within the study protocol. Sites are provided
52 with financial support to complete these follow up data in line with the compensation for
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3 completing DVLA forms. As part of site support and data queries, the return rate for
4 follow up data and completeness of these data will be audited by the central study team.
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6 As all UK patients have a permanent NHS number allocated at birth or migration,
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8 participants who move around the country can continue to be monitored.
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12 Concerns regarding loss to long term follow up can be mitigated to some degree via
13 data linkage with national systems. Following appropriate consent, an individual's NHS
14 number can be used to link individuals via digital.NHS, Hospital Episode Statistics
15 (HES) and the UK Cancer Registry, potentially using HDR-UK infrastructure, to support
16 follow up of serious adverse events.
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22 This study also has the potential for patients to report on the impact of the disease on
23 their daily life via patient reported outcome measures (PROs). However, these would
24 require a separate, patient focussed database portal along with additional consent. This
25 remains an aim for the database. However, given COVID-related delays to initial
26 recruitment and pressure on sites, the current focus is on collecting accurate and
27 complete physician-reported data.
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33 34 **Data flow and security**

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38 The OPTIMISE:MS database (online demo version available via [https://www.optimise-
40 ms.org/demo/](https://www.optimise-
39 ms.org/demo/)) has been designed to enable electronic data capture and secure data
41 transfer. Data is entered onto site-specific laptops at individual sites, and transferred
42 securely on a regular basis. Every data entry is time stamped according to both date of
43 data entry and date of data collection, to allow for audit and identification of
44 retrospective data entry. Personally identifiable information including NHS number is
45 accessible only to the clinical care team at each site and to those members of the
46 central analysis group responsible for follow up of serious adverse events. Where
47 insufficient data is entered on a participant with an SAE, this will be followed up by the
48 central analysis team as part of quarterly data quality review.
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3 The majority of participant data is stored in a secondary database, in which each
4 subject is pseudonymised and the NHS number and name are not available. This
5 database will be used for analyses performed by the OPTIMISE analytical group and
6 collaborators. A participant data deletion mechanism is incorporated into each form of
7 the database. Data for any subject who withdraws consent and whose data is deleted
8 from the database held at any participating site also will be deleted automatically from
9 the two forms of the database held at the central analysis site.
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16 ***Patient and public involvement***

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18 Patients were involved early in the conception of this study. The study was discussed
19 with patient representatives, who gave feedback around the kind of data that they would
20 be willing to share, and the desired frequency of contact. The main concern of the
21 patients that we consulted was that their data were to be used for the benefit of people
22 with MS, and not for profit or other third party gain.
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30 ***OPTIMISE database and core dataset***

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32 Whilst software tools for MS patient data entry and curation have been generated
33 before, none are in widespread use. There is no single electronic patient record (EPR)
34 in use across the UK NHS, and utilising individual EPR systems to collect MS-specific
35 data is likely to be both unacceptably time consuming and costly. One major challenge
36 of bespoke MS data collection systems is the need to balance comprehensiveness of
37 data collection with the sustainability of data entry in a busy clinic environment. A further
38 challenge is to ensure compliance with basic requirements for data security and auditing
39 and the ability to remove data if consent is withdrawn.
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49 The OPTIMISE database is used to capture both minimum baseline characteristics and
50 ongoing and follow up data. These include current treatment category, gender,
51 ethnicity, dominant hand, country of origin, primary MS diagnosis, time since diagnosis,
52 age, physical and performance measures (EDSS), relapses within the past 2 years,
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serious adverse events, malignancies, opportunistic infections, liver function, brain MRI, total white cell and lymphocyte count (linked to individual level immunosuppression) and anti-JCV antibody status (Table 2).

Participating sites are expected to upload all of the clinical and paraclinical data collected to the central analysis site on a quarterly basis. Quarterly data checks allow sites to focus on ensuring their data is of high quality, and reduces the number of data queries raised to sites. Visit frequency for patients was determined by usual clinical practice and completeness of data and other quality control assessments are performed on a quarterly basis by the central study team located at Imperial College London. Where data is incomplete in a significant number of records in a single upload, the site is contacted for remedial action to be taken. A strength of this study is that data queries regarding missing or implausible data are sent directly to sites, allowing entries to be reconfirmed as required. All changes made in response to these are timestamped and recorded in the database, so that sites with high levels of implausible or missing data can be identified for additional training and support.

Statistical analysis

The statistical analysis will focus on the detection of adverse event signals by identifying specific DMTs and DMT sequences associated with disproportionate numbers of events (relative to the overall study population). With 4000 patients followed up for 5-7 years, this study will generate between 20,000-28,000 patient years of follow up. Site prescribing practices and geographical location will be considered in the analysis, as prescribing is not uniform across the UK, and location may impact on infection risk (rural vs. urban).

A number of disproportionality measures will be applied in parallel to increase sensitivity, including the Reporting Odds Ratio, Empirical Bayes Geometric Mean and Information Component [18] (all originally designed for spontaneous report data, but here adapted to the longitudinal data collected within OPTIMISE:MS), and the incidence

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3 rate ratio. Signals will be triggered if the lower one-sided 95% confidence limit for any
4 disproportionality measure exceeds the null value of no association. Two methods will
5 be used to screen out false positive signals. Firstly, a minimum number of events will
6 be imposed in order to eliminate false signals due to random noise when event counts
7 are low. Secondly, a chronological filter based on the LEOPARD methodology will be
8 applied [19]. The LEOPARD filter assesses whether an adverse event occurs more
9 often before or after the prescription of the treatment with which it appears to be
10 associated. This can help to avoid protopathic bias, in which a causal relationship is
11 falsely inferred between an adverse event and the commencement of treatment when in
12 fact both were caused by the underlying progress of disease or other factors.
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22 Poisson (or negative binomial) regression and survival analyses will be carried out to
23 evaluate rates of adverse events, relapse, disability progression, new MRI lesions,
24 mortality, lymphopaenia and liver enzyme elevation in subjects receiving any newer
25 DMT in comparison to those receiving first-line injectable DMTs or no treatment. These
26 analyses will incorporate subject-level covariates to adjust for demographics and
27 disease history.
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34 Secondary analyses will use additional models to explore the relationships between
35 DMT use and outcomes, including whether effects of DMTs persist after treatment
36 cessation/switch. Several exposure definitions will be applied in parallel. Current
37 exposure models will use the subjects current treatment category at the time of event.
38 Recent exposure models will be dependent on both the current treatment category and,
39 if applicable, the previous treatment category within the preceding six months.
40 Cumulative exposure models will include the total cumulative exposure to each
41 treatment class in patient-months, and time-weighted cumulative exposure models will
42 weight according to both time on treatment and time from exposure to event, with more
43 weight assigned to recent exposures than historic. In these analyses subjects will not be
44 censored at treatment cessation or switch, so each subject can contribute multiple
45 periods of follow up with exposure to different treatment categories.
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Entry criteria and follow up data

All patients with MS as defined by the 2017 McDonald criteria and who are eligible to receive DMT reimbursement from NHS England are eligible for entry into the observational study. This includes patients who are on treatment, as well as those starting, potentially eligible to start but not receiving DMT, or switching DMT. Patients with either relapsing-remitting or progressive MS who meet these criteria are eligible for inclusion. This allows the inclusion of new groups of patients as new DMTs become available. This study will also enrol children aged over 11, although children and adolescents who are enrolled should be treated according to an established protocol within the NHS.

Patients who are not able or not willing to provide informed consent will be excluded from the study. Participants enrolled or planning to be enrolled into a clinical trial of an investigational medical product (IMP) will be excluded for the duration of their participation in the trial (including any extension study).

Enrolling patients via participating major MS centres means that those patients who are treated only general neurology clinics, and/or are not seen in these centres are not included in this study. Centres were selected according to their caseload, with centres able to meet a recruitment target of at least 300 patients selected to take part in the study. Given the infrastructure support required for consent and ongoing data entry, a minimum number of recruits was needed to make the study viable within each centre. An advantage of this approach is that all of the major MS centres selected treat patients with the full range of MS DMTs. However, this approach also introduces a potential source of bias. Patients not seen at MS centres are more likely to be on either no treatment or first line injectable treatments, whereas those treated at MS centres potentially have access to highly active treatment earlier in their disease course. However, early data (table 3) suggests that this strategy has been successful in recruitment patients across a range of DMT.

Recruiting during the COVID-19 global pandemic

Due to the COVID-19 global pandemic and two subsequent lockdowns within the United Kingdom, telephone and video consultations became standard for outpatient care, with face to face appointments only taking place sporadically. Redeployment of research staff to COVID-19 studies further impacted on recruitment. The lack of face-to-face contact has prevented direct assessments of EDSS.

Study amendments have been made and approved to accommodate remote enrolment of patients using postal consenting methods. The use of remotely collected EDSS [20] has facilitated monitoring of patients at a number of sites.

Subjects recruited to date

Table 3 summarises key baseline attributes of the 1615 subjects recruited as at January 2021 according to current DMT class. The first patient was recruited to this study on 24 May 20. COVID-related delays substantially slowed rates of recruitment in 2020 and through the first half of 2021, from which time improvements have been seen. The low number of individuals with primary and secondary progressive MS (PPMS) is to be expected, given the inclusion criteria of the study and relatively recent approval of therapies for active progressive MS.

Ethics and dissemination

This study has had ethical review via London City and East REC (ref. 19/LO/0064). As this study uses routinely collected medical data as the primary data source, there are minimal burdens on participants.

As this is an observational study, the main risks are of data misuse and subject identification. This risk will be minimized by using double password protected computers, maintaining links between subject identifiers and an anonymized study code separate from the database in a locked compartment in a room with controlled access.

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3 Researchers with access to the data will agree not to attempt to identify individual
4 subjects except in the context of direct responsibility for their clinical care. An oversight
5 committee will be put in place to assess study conduct and data security on at least an
6 annual basis, reporting to the study sponsor.
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11 The OPTIMISE:MS study thus provides a unique opportunity for the UK to rise to the
12 challenge of high quality real world data studies in MS. It sets out to answer a vital
13 research question, with a clearly defined core dataset. The use of an adaptable,
14 disease-focussed platform for data entry enables the easy addition of add-on studies,
15 such as those attempting to answer additional research questions, such as those
16 around pregnancy, cognition or pharmacogenomics, subject to additional ethical
17 approvals. Whilst this study is a significant undertaking, it is one that is of clear benefit
18 to people with MS - it is only by getting the systems and studies set up to the highest
19 rigour that we will be able to provide clear answers regarding real life risks and benefits
20 of treatment.
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Table 1: Rates of SAEs in treatment and control groups documented in published clinical trial data. All reported SAE incidences include MS relapses unless otherwise specified.

Abbreviation: PPY, per patient year.

Therapy	Reported rate of SAE in treatment arm	Reported rate of SAE in control arm	Duration of trial (months)
Alemtuzumab <i>Control arm: IFN-β</i>	CAMMS223 [21]: 0.2 PPY	CAMMS223 (IFN- β): 0.3 PPY	36
	CARE-MS I [22]: 0.13 PPY	CARE-MS I (IFN- β): 0.09 PPY	24
	CARE-MS II [23]: 0.17 PPY	CARE-MS II (IFN- β): 0.21 PPY	24
Dimethyl fumarate <i>Control arm: placebo or GA</i>	DEFINE [24]: 18% incidence	DEFINE (placebo): 21% incidence	24
	CONFIRM [25]: 17% incidence	CONFIRM (GA and placebo): 17% (GA); 22% (placebo) incidence	24
Fingolimod <i>Control arm: IFN-β or placebo</i>	TRANSFORMS [26]: 7% incidence excl relapse	TRANSFORMS (IFN- β): 6% incidence excl relapse	12
	FREEDOMS I [27]: 10% incidence	FREEDOMS I (placebo): 13% incidence	24
	FREEDOMS II [28]: 15% incidence	FREEDOMS II (placebo): 13% incidence	24
Natalizumab	AFFIRM [29]: 19% incidence	AFFIRM (placebo): 24% incidence	24
	SENTINEL (+IFN- β) [30]: 18% incidence	SENTINEL (IFN- β): 21% incidence	24
Teriflunomide <i>Control arm: placebo</i>	TEMPO [31]: 14% (7mg), 15.9% (14mg) incidence	TEMPO: 13% incidence	24
	TOWER [32]: 12% incidence	TOWER: 12% incidence	11
	TOPIC [33]: 9% (7mg), 11% (14mg) incidence	TOPIC: 9%	24
Cladribine Tablets <i>Control arm: placebo</i>	ORACLE [34]: 5% (5.25mg/kg), 11% (3.5mg/kg) incidence	ORACLE (placebo): 10% incidence	22
	CLARITY [35]: 9% (5.25mg/kg), 8% (3.5mg/kg) incidence	CLARITY (placebo): 6% incidence	22
Ocrelizumab <i>Control arm: placebo</i>	OPERA [36]: 7% incidence	OPERA (placebo): 8% incidence	6

Fingolimod (paediatric patients) <i>Control arm: IFN-β</i>	PARADIGMS [37]: 17% incidence (including SAE of interest)	PARADIGMS: 7% incidence	24
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Table 2: Core baseline characteristic and ongoing / follow data capture for OPTIMISE:MS patient cohort

Core Baseline Characteristics	Ongoing / Follow up data
Physical Measures	Current / Previous DMT treatment
Comorbidities	DMT switch
Performance Measures (EDSS)	Performance Measures (EDSS)
Concomitant medications	Concomitant medications
Relapses within the past 2 years	New medical diagnosis
Serious adverse events, malignancy, opportunistic infections	Serious adverse event, malignancy, opportunistic infection
Previous malignancies or serious infection	Relapses
Current / Previous DMT treatment / DMT switching	New immunosuppressive medication for another indication
Anti-JCV abs status	Anti-JCV abs status
Total white cell and lymphocyte count	Total white cell and lymphocyte count
Liver function	Liver function
Brain MRI	Brain MRI

Table 3: Key baseline attributes of the 1,615 subjects recruited as at January 2021

	All subjects	No DMT	IFN-B/GA	Newer DMTs; no prior DMT	Newer DMTs; escalation
Total n (%)	1615	503 (31%)	157 (10%)	774 (48%)	181 (11%)
F:M (%F)	1140:472 (71%)	351:151 (70%)	128:29 (82%)	525:248 (68%)	136:44 (75%)
Mean age (SD); years	43.5 (12.3)	42.6 (13.4)	48.6 (10.6)	42.8 (11.7)	44.9 (11.9)
Mean time since diagnosis (SD); years					
<5	613 (38%)	243 (48%)	46 (29%)	304 (39%)	20 (11%)
5-9	427 (26%)	121 (24%)	44 (28%)	201 (26%)	61 (34%)
10-14	277 (17%)	64 (13%)	27 (17%)	127 (16%)	59 (33%)
15-19	171 (11%)	40 (8%)	19 (12%)	85 (11%)	27 (15%)
>20	127 (8%)	35 (7%)	21 (13%)	57 (7%)	14 (8%)
Primary MS diagnosis					
RRMS	1528 (95%)	463 (92%)	145 (92%)	743 (96%)	177 (98%)
PPMS	36 (2%)	19 (4%)	1 (1%)	16 (2%)	0 (0%)
SPMS	31 (2%)	14 (3%)	4 (3%)	11 (1%)	2 (1%)

RRMS: Relapsing Remitting MS

PPMS: Primary Progressive MS

SPMS: Secondary Progressive MS

DMT: Disease Modifying Therapy

IFN-B: Interferon beta preparations

GA: Glatiramer acetate

Figure 1: Participant entry criteria flowchart

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For peer review only

Author contributions

RD, MC and PMM conceived the study idea

RD drafted the initial study protocol with early and key input from MC and PMM

EW wrote the statistical analysis plan for the study protocol, and provided input into the remainder of the study design

AM, AC, SW, CH, JH, NE, NS, DR, RN, MM, CB, CY and HF reviewed, revised and contributed to the study protocol

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Competing interests

The authors of this protocol have no competing interests with direct relevance to the design of this protocol.

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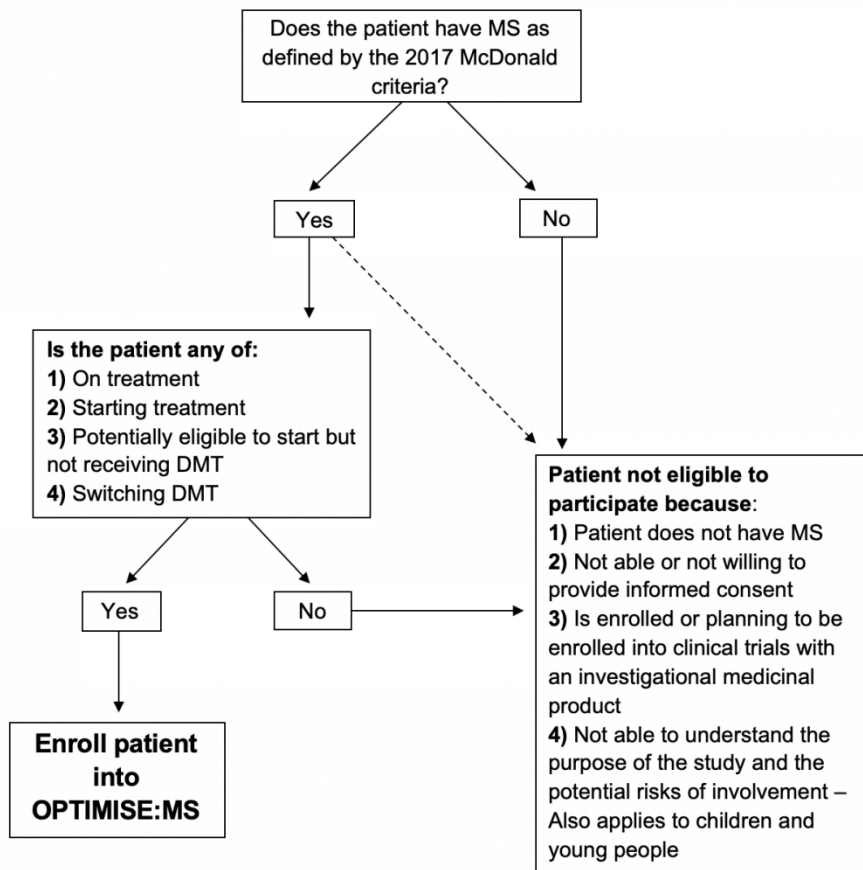
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Participant entry criteria flowchart