MSBASE REGISTRY OBSERVATIONAL STUDY PROTOCOL

MSBase Registry Global Cohort Study of
Multiple Sclerosis and other Neuroimmunological Diseases

This protocol is jointly owned by all MSBase Registry Observational Study Investigators.

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SCHEDULE 2 TO THE MSBASE REGISTRY PARTICIPATION AGREEMENT – UK v3.0 20201221

Abbreviations

DMT	Disease Modifying Treatment
EDSS	Expanded Disability Status Scale
MedDRA	Medical Dictionary for Regulatory Activities
MDS	MSBase Data-entry and Visualisation Software Tool
iMed	MSBase iMed Data-entry and Visualisation Software Tool
MRI	Magnetic Resonance Imaging
MS	Multiple Sclerosis
MG	Myasthenia Gravis
NMO	Neuromyelitis Optica
PwMS	People with Multiple Sclerosis
NIDs	Neroimmunological Diseases
PI	Principal Investigator
I	Investigator
SLG	Scientific Leadership Group
AE	Adverse Event
SAE	Serious Adverse Event
GDPR	General Data Protection Regulation
PIS	Participant Information Sheet
ICF	Informed Consent Form

Definitions

"Centre" means a medical institution, such as a hospital, university or private clinic that has joined the MSBase Registry and holds a unique MSBase Centre Identification Code.

"Principal Investigator" or "PI" means a legally qualified, practicing neurologist at a MS or neurology (NIDs) Centre, who has been given authority from the Centre to transfer pseudonymised data and collaborate in the MSBase Registry Observational Study.

"Investigator" or "I" means a person working for a MSBase centre as part of a healthcare team (e.g. nurses, training doctors, administrative staff, data scientists, research assistants) and have been authorised by the Centre or its PI to join the MSBase Registry and perform tasks as delegated by the Centre or its PI.

"MSBase Members" means any approved member of the MSBase Registry through their Centre, as authorised by MSBase and the Centre at which they work on the MSBase Registry Observational Study.

"Website" means the MSBase Registry Website (www.msbase.org)

"Participation Agreement" means the MSBase Registry Participation Agreement, to which this MSBase Registry Observational Study Protocol is a schedule.

"GDPR" means the Regulation (EU) 2016/679 of the European Parliament and of the Council of 27 April 2016 on the protection of natural persons with regard to the processing of personal data and on the free movement of such data, and repealing Directive 95/46/EC.

"Pseudonymised" means the act of "pseudonymisation" as defined in the GDPR.

Synopsis

MSBase Registry Global Cohort Study of Multiple Sclerosis and other Neuroimmunological Diseases

1. Background

The MSBase Registry Observational Study ("Study") is a longitudinal and observational study of multiple sclerosis (MS) and other neuroimmunological diseases (NIDs), which invites participation from all practicing neurologists, their Centres and healthcare teams, worldwide.

The Study aims to advance Investigator-initiated, multi-centre, multi-national, epidemiological and outcomes research by utilising a uniform, physician-defined minimum dataset and a web-based Research Registry, the MSBase Registry ("Registry") (www.msbase.org) to systematically collect, combine, compare and analyse pseudonymised (codified) demographic and medical data from consented patients with MS and other NIDs such as neuromyelitis optica (NMO), anti-MOG antibody syndromes, and myasthenia gravis (MG).

Participating Centres share pseudonymised datasets to the Registry using either the MSBase Data-entry and Visualisation Software tool (MDS) or the iMed Data-entry and Visualisation Software tool (iMed). Both IT tools are owned, maintained and freely provided by the MSBase Foundation to Member Centres to enable and support the Study. The IT tools are designed with the intention to better support healthcare workers real-time in clinic when treating people with MS (PwMS) or other NIDs and ultimately improve disease management and care. As they are MS and NIDs 'disease-specific' clinical support tools, they have a different purpose to, and should not be confused with standard hospital Electronic Medical Records (EMRs) which typically contain a patient's comprehensive medical chart.

The major challenges for Investigator-initiated research of this nature include the definition of minimum and desirable datasets, identification of collaborators, ongoing communication between study sites, data quality assurance, and all aspects of data management.

The MSBase Foundation is dedicated to providing Investigators with the best possible logistic solution to these challenges at no cost.

2. Rationale

During the past seven years, several clinical trials and cohort studies have shown efficacy of disease-modifying drug therapies (DMTs) in reduction of MS relapses and disability progression.

Similarly, in NMO and anti-MOG antibody disease, small cohort studies have revealed probable DMT effects.

In myasthenia gravis (MG), a mixture of clinical trial and cohort data have revealed DMT effects of several drugs.

In other NIDs definitive evidence for treatment effectiveness evidence is often lacking.

Many areas of uncertainty remain in the management of all these diseases, which can only be answered with prospective cohort studies.

For instance, long-term treatment outcomes are poorly understood, personalised medicine (the right drug for the right patient) is virtually non-existent, and the early and even pre-clinical course of the diseases is uncertain.

The long-term benefit-risk profiles for different therapies and different therapy sequences remain unknown.

The risks versus benefits of drug exposure during early pregnancy, throughout pregnancy and during breast-feeding are virtually unknown, as all studies to date are under-powered.

Disease and treatment outcomes in patients that fall outside the standard trial populations, e.g. children, older patients, and patients with significant comorbid diseases are poorly understood.

Differences in disease outcomes in different ethnic groups or different regions of the world are largely unknown, as individual cohort studies typically do not collect the same outcome data.

Treatment failure is poorly and arbitrarily defined, and the impact of monitoring tests (e.g. serial Magnetic Resonance Imaging [MRI] changes) for prognostication and to guide treatment change are substantially unknown.

For all of the above themes, large, prospectively databased cohorts have major advantages over clinical trials, primarily because the focus is on long-term effectiveness and safety in an entire population rather than short-term outcomes defined in highly selected populations.

Wherever possible, it is important that data collection is embedded into routine standard neurological clinical care.

3. Study aims

The Study aims to assess real-world long-term disease outcomes; in particular, relapse rates and functional/disability change over time. The relationship between demographics, comorbid diseases, relapses, diagnostic and monitoring test results, drug exposures, and outcomes will be assessed using various statistical techniques to minimise indication bias and other biases.

The study also aims to:

- compare disease demographics and outcomes in different countries and regions of the world, and changes in these over time;
- characterise the occurrence of Serious Adverse Events (SAEs) and Adverse Events (AEs) of interest, and their relationship to drug exposure and drug sequencing;
- investigate the relationship between drug exposure in the perinatal period and

serious adverse pregnancy events.

4. Study design

The Study is a prospective, global cohort study that collects observational (non-interventional) data from consented MS and other NIDs patients during routine clinical practice.

5. Eligibility criteria

5.1 Inclusion criteria

All patients with MS or other relevant NIDs, who are attending a Centre, and have provided informed consent at their Centre, are eligible to join the Study.

5.2 Exclusion criteria

Any patient or legal representative who is unable or unwilling to provide a signed patient informed consent form.

6. Informed and explicit patient consent

The Principal Investigator (PI) or an authorised Investigator (I) must provide a Participant Information Sheet (PIS) to all potential participants, explain the Study and provide an opportunity for questions to be asked.

All patients who agree to participate shall be required to sign an Informed Consent Form (ICF) that will sufficiently explain the details of the Study and on agreement of the patient, authorise the release of their pseudonymised (coded) demographic and medical information to the Registry. The consent form must be signed in the patient's treating Centre, in a language fully understood by the patient. A copy must be provided to the patient.

An Institutional Review Board (IRB) or the responsible Ethics Committee (EC) must approve the Study unless it is exempt from approval in the applicable jurisdiction. If no responsible EC, IRB or equivalent legal entity exists, the Centre must still provide a Participant Information Sheet (PIS) and obtain a signed Informed Consent Form (ICF).

A template PIS and ICF (in English) is available on the MSBase Website.

7. Study procedures

The Study procedures are outlined in detail in the MSBase Registry Participation Agreement, to which this Study Protocol is a schedule.

In summary, Investigators use one of the compatible data-entry software tools (MDS or iMed) and agree to collect the defined minimum dataset (Appendix 1) for their patients and to share consented patient records with the Registry at least biannually. In addition to the minimum dataset, Investigators may collect a variety of disease-

specific or other data-fields of interest that exist in the MSBase Data-entry Software and iMed, and can also be collected at the Investigators' discretion. A comprehensive data dictionary for MDS is available in Appendix 2.

Centres, through their PIs, and the MSBase SLG, may propose research analyses and cohort sub-studies of interest to be conducted using the pooled Registry dataset or subsets of the Registry data.

For each analysis and sub-study proposal, the Centre, through its PI always exclusively decide whether to participate and contribute their Centre data for use in the research.

7.1 Investigator-initiated analyses

Centres, through their PIs, and the SLG, can request to receive Registry patient data and perform analyses on the entire Registry dataset or Registry dataset.

The procedures for proposing and conducting scientific analyses are outlined in detail in the MSBase Participation Agreement.

At all times, Centre permission is sought before any of the pseudonymised data is used in any MSBase analyses.

7.2 Investigator-initiated sub-studies

Investigator-initiated prospective sub-studies can be created and managed on the Registry website by PIs. Sub-studies capture specific sub-cohort information (e.g. national, regional, thematic). For any proposed sub-study, each Centre exclusively decides if they wish to participate and share their Centre data. Permission is always sought from the Centre, through its PI, prior to the use of any pseudonymised data in research sub-studies.

Governance and data use frameworks of sub-studies are defined by the sub-study lead PI, and are described in the MSBase Registry Participation Agreement.

7.3 EDSS Quality Assurance

For the purpose of quality assurance, PIs and their healthcare teams who are entering EDSS data into the Registry must be registered MSBase Members and should be accredited with EDSS Competency Certification. Copies of previously achieved EDSS Competency Certificates should be provided to MSBase. Alternatively, MSBase Members can freely sit a competency test online using Neurostatus (www.neurostatus.net) to gain certification (currently Neurostatus).

8. Safety assessments

Safety assessments are not part of the minimum dataset.

SAEs and AEs can be recorded, preferably in MedDRA format if using MDS.

8.1 Pregnancy Outcomes

Pregnancy outcomes are not part of the minimum dataset.

Pregnancy outcomes can be recorded, preferably in EUROCAT format if using MDS.

These may require additional consent in some jurisdictions.

8.2 Serious Adverse Events (SAEs)

SAEs and other serious medical conditions are of special interest to Investigators. An SAE is defined as any untoward medical occurrence that:

- may result in death;
- is life-threatening (i.e. the patient was at risk of death at the time of the event);
- requires inpatient hospitalisation or prolongation of existing hospitalisation;
- results in persistent or significant disability/incapacity;
- is a congenital anomaly/birth defect;
- and/or is another medically important condition (i.e. one which may not be immediately life-threatening or result in death or hospitalisation, but is clearly of major clinical significance.

It may jeopardize the patient or may require intervention to prevent one of the other serious outcomes.

It is the sole responsibility of the participating Centre and its Centre PI to notify their local authorities and/or the manufacturer of a therapeutic agent regarding the occurrence of SAEs, according to applicable regulations in their jurisdiction of practice.

Neither the MSBase Foundation nor the SLG are responsible for reporting any SAEs or AEs to responsible local authorities or the DMT manufacturer.

The Registry can analyse SAE rates over time, in particular to identify associations between SAEs and DMT use.

9. Patient (data subject) reimbursement

There are no subject reimbursements. All diagnostic and treatment related costs are the responsibility of the patient and their individual health insurance.

Appendix 1: MSBase Registry Minimum Dataset

Complete Records fields

Section	Field	Frequency	Definition
Patient Profile	Patient ID	Entry Visit	Patient globally unique ID (system creates)
	Sex	Entry Visit	M / F
	Birth date	Entry Visit	Month and year only
	Date of MS onset	Entry Visit	Date
Visits	Visit Date	Entry & Annual #	Date
	KFS – 8 items	Entry & Annual #	0 to 5 / 0 to 6 / 0 to 12
	EDSS*	Entry & Annual #	0 to 10
Paraclinical tests	Test date	Entry & Annual #	Date
	Test type	Entry & Annual #	MRI, CSF, EP, Biochemistry
Relapses	Relapse Date	Entry & Annual #	Date
	CNS region	Entry & Annual #	Pyramidal, Cerebellum, Brainstem, Sensory functions, Bowel bladder, Visual functions, Neuropsychological functions
	Corticosteroids	Entry & Annual #	Yes, No
Treatments	Treatment ID	Entry & Annual #	Treatment names
	Start date	Entry & Annual #	Date
	End date	Entry & Annual #	Date

Appendix 2: MSBase Data-entry and Visualisation Software Tool (MDS) Data Dictionary

A comprehensive list of fields available in the MDS and the fields uploaded to MSBase are found in the MSBase Data-entry Software (MDS) Data Dictionary (stored online on the MSBase Registry Website, www.msbase.org).