MSBASE/MGBase REGISTRY OBSERVATIONAL STUDY PROTOCOL

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

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

Contact details:

MSBase Foundation Ltd
Managing Director: Professor Helmut Butzkueven
Central Clinical School, Level 6, The Alfred Centre
99 Commercial Rd, Victoria 3004
Australia

Phone: +61 3 9903 8264
Email: info@msbase.org

Contents

Abbreviations

DMT	Disease Modifying Treatment
EDSS	Expanded Disability Status Scale
MGC	Myasthenia Gravis Composite
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 or MGBase Registry and holds a unique MSBase/MGBase 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/MGBase Registry Observational Study.

"Investigator" or "I" means a person working for a MSBase/MGBase 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/MGBase 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.

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

"MGBase Website" means the MGBase Registry Website at www.mgbase.org

"Participation Agreement" means the MSBase and MGBase Registry Participation Agreement, to which this MSBase and MGBase 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/MGBase Registry Global Cohort Study of Multiple Sclerosis and other Neuroimmunological Diseases

1. Background

The MSBase/MGBase Registry Observational Study ("Study") is a longitudinal and observational study of multiple sclerosis (MS), myasthenia gravis (MG) 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 web-based Research Registries, the MSBase and MGBase Registry ("Registry") (www.msbase.org/www.mgbase.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, MG 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 and MGBase Website.

7. Study procedures

The Study procedures are outlined in detail in the MSBase and MGBase 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 and 2) 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 3.

Centres, through their PIs, and the MSBase and MGBase 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 MSBase or MGBase 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 and MGBase Participation Agreement.

At all times, Centre permission is sought before any of the pseudonymised data is used in any MSBase/MGBase 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 MG Rating Scales Quality Assurance

For the purpose of quality assurance, PIs and their healthcare teams who are entering rating scale data into the Registry must be registered MGBase Members and should be familiar with performing the rating scales. If possible, validated or standardised training should be completed.

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 SLGs 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: MGBase Registry Minimum Dataset

MGBase Registry minimum dataset and data entry in to MDS

The table below indicates the minimum dataset recommended for clinicians participating in the MGBase Registry.
Records are considered complete when the fields in **red text** in the table below have been filled.
Fields that are **not** in red text, are all fields that are *recommended* to complete annually, for the purposes of capturing quality data.

Section	Field	Frequency	Definition
Patient profile	Patient ID	Entry visit	Patient globally unique ID
	Last name	Entry visit	
	First name	Entry visit	
	Gender	Entry visit	M / F
	Birth date	Entry visit	Month and year only
MG Diagnosis	Disease category	Entry visit	Disease names
	Date of onset	Entry visit	Date
Visit	**MRS**	Annual #	Value
	MGC	Annual #	Total
	MGC		With scores
	MGFA		Value
	MGFA PIS		Value
	MG-ADL		Total
	MG-ADL		With scores
Paraclinical tests	Test date	If entered	Date
Exacerbation	Date of onset	If entered	Date
	Symptoms	If entered	Symptom names
	Treatment site	If entered	Value
Treatment	Treatment type	If entered	Treatment names
	Start date	If entered	Date
	End date	If entered	Date

Appendix 3: 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/MGBase are found in the MSBase Data-entry Software (MDS) Data Dictionary (stored online on the MSBase/MGBase Registry Website, www.msbase.org; www.mgbase.org).