Qualification opinion briefing book for the Big MS Data network registries on Post Authorization Safety Studies

Patient registry[1] BigMSData Network: Czech Republic MS Registry, Danish MS Registry,

Observatoire Français de la Sclérose En Plaques, Italian MS Registry, Swedish MS Registry and MSBase

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Targeted disease(s): Multiple Sclerosis

Qualification type requested: Qualification Opinion

Context of Use: Performance of PASS. The QO should be applicable both to PASS making use of data from all BMSD registries as well as PASS relying on a sub-set of BMSD registries.

This document is a high-level proposal on content of regulatory submission dossiers for CHMP qualification opinion or qualification advice on patient registries/data sources intended for use in clinical drug development, evaluation and monitoring to support regulatory decision making. It is not binding and sections/subheadings may be added or omitted as appropriate.

This checklist should be read in conjunction with relevant guidelines that can be found on the website of the European Medicines Agency, including e.g. the "EMA Guidance for applicants seeking requesting Scientific Advice and Protocol Assistance", the "Data Quality Framework for EU medicines regulation" and its annex "Data Quality Framework for EU medicines regulation: application to Real-World Data", the guideline on registry-based studies, REQueST Tool and its vision paper (EUnetHTA) etc.

[1] In accordance with the EMA Guideline on registry-based studies, "Patient registry" (referred to as "registry" in the rest of the agenda) is defined as: Organised system that collects uniform data (clinical and other) to identify specified outcomes for a population defined by a particular disease, condition or exposure. The term 'patient' highlights the focus of the registry on health information. It is broadly defined and may include patients with a certain disease, pregnant or lactating women or individuals presenting with another condition such as a birth defect or a molecular or genomic feature.

1. Introduction

Multiple Sclerosis (MS) is a chronic, inflammatory, and demyelinating disease of the central nervous system (CNS) that affects approximately 2.3 million people worldwide. Although there is currently no cure for MS, the development of disease modifying drugs (DMDs) has been very successful in the past 30 years and there is currently a number of different treatment options available for MS patients.

The BigMS Data (BMSD) Network brings together leading MS registries and databases (Figure 1) to allow joint analyses of very large merged or federated sets of structured clinical data.

The BMSD network consist of 6 different MS registries:

The Czech Registry of Patients with MS (ReMuS)

The Danish Multiple Sclerosis Registry (DMSR)

The French Multiple Sclerosis Registry (OFSEP)

The Italian Multiple Sclerosis Register (RISM)

The Swedish Multiple Sclerosis Registry (SMSreg)

The International MSBase Registry (MSBase)

The collection of clinical, treatment and other kind of patient data in the MS registries provides a valuable source of data and has attracted interest from both regulatory and pharmaceutical parties. This kind of real-world data can be used for e.g. effectiveness and safety treatment studies. The current application is focussed on post authorisation safety studies (PASS).

BMSD would benefit from an EMA qualification opinion for PASS as this would provide a comprehensive document to describe the individual registries as well as the BMSD network in support of their suitability to perform PASS.

1.1. Background information on the disease(s) covered by the patient registry

MS treatments have drastically improved in the past 30 years and the development is still ongoing. It is therefore important to be able perform PASS in order to monitor the safety of MS drugs and registries provide a very good source of data for such studies. It is however important to ascertain that data quality and reporting of relevant adverse events are kept at the highest possible level. This application attempts to demonstrate that all six BMSD registries are fit for purpose.

Registries can capture information from multiple practice settings, including non-trial centres and private practices, as well as from nations and regions with different disease modifying treatment (DMT) exposure characteristics and DMT sequencing due to patient and care team preferences, influence of key opinion leaders in particular jurisdictions and differing DMT approval and reimbursement rules.

1.2. High level information on the patient registry

Table 1 shows a brief description of the six BMSD participating registries. More detailed information can be found in under section 2. “Detailed characteristics of the patient registry”. Each BMSD registry has a history and was originally set up to collect

structured clinical information on MS patients to be used for the improvement of health care services and in research. In general, all the registries are based on secondary data. Collection on serious adverse events (SAEs) information is done in accordance with pharmacovigilance rules guidelines (in case of severe or unexpected adverse events). What can be reported as PASS will in principle be based on available registry data and therefore represent secondary use of data.

In addition, for some of the registries, i.e. currently Denmark and Sweden, information on concurrent conditions signifying adverse events can be obtained by linking to comprehensive national patient registries.

Table 1. An overview of the key characteristics of the registries in the BMSD network. The numbers are correct as of June 2024.

Registry	Launch date	Estimated number of patients	Total MS patients on active DMT treatments	Added patients per year	Coverage % *) Number of MS patients in the registry compared to estimated prevalent MS population in the corresponding country	Number of publications
ReMus (Czech Republic)	2013	22.500	17.133	800-1000	70	20
DMSR (Denmark)	1956	34.000	10,340	900	95	190
OFSEP (France)	1980	82.500	37,381	4000-5000	~65	155
RISM (Italy)	2001	93.802 (2025-0430)	51.760	3500-4500	~72	60
SMSreg (Sweden)	2000	24.000	12,684	800	85	300
MSBase (International)	2001	109.000 (82.000 unique pts)	48,808		Variable, depending on the contributing registries	120
BMSD	2014	359.000	167,917	NA	NA	<800

(currently six MS registries)						

1.3. Regulatory status

Currently (2025) all the BMSD registries are participating in ongoing EMA mandated PASS and several of them take part in the same studies. A BMSD core protocol has been developed and describe the principles of how to perform a PASS involving the BMSD registries and is appended to this application. Any specific study would obviously in addition require individual modifications and additions to serve the specific study aims.

Below is a list of ongoing PASS in which the BMSD registries participate:

ReMuS: Lemtrada mortality PASS (EUPAS42543), Lemtrada DUS and safety (EUPAS42540), PML and serious opportunistic infections in Natalizumab patients (EUPAS45445)

DMSR: CLARION (EUPAS24484), MANUSCRIPT (EUPAS28619), Lemtrada mortality PASS
(EUPAS42543), Tysabri PASS (EUPAS45445), VUM PASS (EUPAS1000000285)

OFSEP: CLARION (EUPAS24484), MANUSCRIPT (EUPAS28619), VUM PASS (EUPAS1000000285)

RISM: CLARION (EUPAS24484), MANUSCRIPT (EUPAS28619), Kesimpta PASS (EUPAS104255), Tysabri PASS (EUPAS45445) (ended in 2024)

SMSreg: CLARION (EUPAS24484), MANUSCRIPT (EUPAS28619), Lemtrada mortality PASS (EUPAS42543), Tys PASS (EUPAS45445), VUM PASS (EUPAS1000000285)
MSBase: CLARION (EUPAS24484), MANUSCRIPT(EUPAS28619)

Karolinska Institutet obtained EMA scientific advice on behalf of the network of MS registries, Big MS Data network (BMSD) in 2021 in the context of use of performing registry-based post authorisation safety studies (PASS). The CHMP response to that application was that whereas the BMSD registries deserve support there were two major reasons why formal qualification at that point in time was not given:

1) uncertain extent of safety data collected

and

2) insufficiently described data quality control

BMSD was subsequently issued an EMA letter of support (LoS) describing the methodology under evaluation which also has been published by EMA (January 2022).

In the past years since the LoS, the BMSD registries have been working to improve the descriptions of BMSD especially as regards how safety data is collected by the registries (described as part of a feasibility study) and how data quality is assessed and assured (part of the core protocol). There has been significant further development of the core protocol which in addition to describing reporting of SAEs and data quality controls also

provides more details regarding data management in general (which also includes the recent development of a common data model by BMSD), data analysis and principles applied as regards drug exposure as part of a safety study. The modifications that have been made to the documents submitted as part of the current application have, in our opinion, significantly improved the general quality of the application as well as the general management of the BMSD and studies performed within the network.

1.4. Rationale for seeking advice

The BMSD network hereby requests a qualification opinion (QO) from EMA to conduct post marketing safety studies in the short and long terms (PASS). The QO should be applicable both to PASS making use of data from all member registries of BMSD and also for PASS relying on one or more of the registries. PASS within the BMSD network are typically performed prospectively, although there is often an option to perform retrospective cohort studies on already collected information.

2. Detailed characteristics of the patient registry

2.1. ReMuS:

2.1.1. Origin of the registry:

ReMuS is the first and only nationwide registry for multiple sclerosis (MS) in the Czech Republic, established in May 2013 to consolidate routine clinical information from MS centres into a single, standardised platform.

ReMuS was created thanks to the joint efforts of the professional —specifically the **NLS** (Neuroimmunology and Liquorology Section of the Czech Neurological Society of the Czech Medical Association of J. E. Purkyně, CNS JEP)—and the **IMPULS Endowment Fund**, which originally organised and managed the registry, including raising funds for its administration.

In April 2024, all rights and obligations related to operating the ReMuS Registry were spun off from IMPULS Endowment Fund to **ReMuS Endowment Fund** (ID No. 21453128; Czech legal name: **ReMuS, nadační fond**), which is the owner, operator and data controller.

2.1.2. Purposes:

ReMuS Registry focuses on three basic goals:

1. To map the actual situation of the disease in the Czech Republic,
2. To create a comprehensive picture of effectiveness of the treatment and thus contribute to better planning of healthcare funds,
3. To help with research of multiple sclerosis and the development of new drugs at the national level.

2.1.3. Registry population:

ReMuS is a registry of patients with a suspected or confirmed demyelinating diagnosis and who provide informed consent.

Recent developments allow enrolment of patients with other demyelinating diseases apart from MS, such as NMOSD or Myelin oligodendrocyte glycoprotein antibody-associated disease (MOGAD), The registry was launched in 2013 with 7 sites and currently includes 15 MS centres which are the only facilities nationally authorised to prescribe disease-modifying therapies (DMTs). Current patient counts and coverage statistics are provided in Table 1 (Section 1.2).

2.1.4. Data elements/Metadata list

Data elements:

Please see Minimum ReMuS Registry dataset (Appendix 5 of the Request Tool).

Standard dictionary:

A data dictionary is available (Appendix 6 of the Request Tool) and is aligned with the BMSD Data Dictionary.

Terminology:

From 1 July 2023, MedDRA is used to record SAEs. These legacy records are being progressively mapped to MedDRA based on primary clinical documentation The BMSD dictionary is not yet mapped to a standard such as SNOMED CT.

Lag times:

Data are collected by using iMed software along with routine clinical practice. Twice a year (30 June and 31 December) the centre administrators export their registry data to a centrally secured ReMuS repository.

Further considerations:

The registry has a flexible structure allowing the addition of new data fields when needed (e.g. COVID-19 modules, safety terminology updates). Amendments to the data-collection forms are initiated by the **ReMuS Scientific Lead** or by requests from participating centres or project partners. The proposal is reviewed by the **ReMuS Scientific Board** to assess scientific justification, harmonisation impact and site workload, and, where applicable, the **Managing Board** confirms operational feasibility and budget. Once approved, the change is implemented by the data management and IT support team, validated by test entry, and communicated to all sites through updated guidance and version notes.

Typical timelines: decision within **2–6 weeks** from proposal, implementation and release within an additional **4–8 weeks**, depending on scope.
This process has been applied in previous updates such as the introduction of MedDRA SAE coding (July 2023) and the COVID-19 data module (2020).

Linkage information

Since July, 2023 data linkage has been possible for patients who have provided the updated informed consent. At enrolment, patients may **opt in** to allow linkage of their registry data with relevant external sources *(e.g. Institute of Health Information and Statistics of the Czech Republic, State Institute for Drug Control, Ministry of Labour and Social Affairs of the Czech Republic, Labour Office of the Czech Republic)*. This choice can be changed at any time with prospective effect. Linkage projects are evaluated by the **ReMuS Scientific Board** and, where relevant, by the external data controller.
Linkage to mortality data ("Register of the deceased") has been established at the single site level.

2.1.5. IT infrastructure

Data are collected via the iMed software along with routine clinical practice and stored on local servers at each MS centre. Twice a year centre administrators export their registry data to a secured central ReMuS repository maintained under control of ReMuS Endowment Fund.

An upgraded version of the application, **iMed Web**, is currently in production. It will operate within a **fully secured online environment** and will enable **direct, more efficient data exports** from participating centres to the central ReMuS data repository, reducing administrative workload and improving data timeliness.

2.1.6. Data processing

Roles and responsibilities:

As part of routine clinical care, data are collected through iMed software at all MS centres for patients who: (1) provide informed consent and (2) have a confirmed or suspected diagnosis of MS or another related disease eligible for inclusion. Signing of the informed consent form (ICF) validates use of all collected data within the scope of the consent without need for re-consent for registry-based studies. The BMSD core data set is included in the current ICF. Twice a year, data are compiled centrally by the ReMuS office.

Established processes:

Bi-annual exports (30 June and 31 December) are checked for completeness, consistency, quality, missing visits etc. Query reports with follow-up requests are sent to centres, which then verify their and correct records or provide explanations. This four-cycle QC process is completed within four months after each export. Anonymised data are then released to the data manager for analysis. Raw data are securely backed up and protected against damage or misuse. Annual registry reports have been published on the registry website since 2013.

Degree of automation:

Data entry uses structured drop-down menus and multiple-choice selections; open-text fields are limited. No automatic data transfers to central repository or from external systems are in place. However, ongoing development projects aim to enable direct integration with hospital information systems, including the import of laboratory results,

measurements from diagnostic devices, and other structured clinical data, to further streamline data collection and reduce manual entry.

2.1.7. Quality Management activities

Supportive scientific and technical function:

The **ReMuS Scientific Board** acts as the scientific guarantor for data collection and interpretation. Four key roles support its operations:

a. Data processing & controlling – site support, QC routines and issue queries.

b. Data manager – data wrangling, consistency checks and study preparation.

c. Statistical specialist – co-operates with data manager on registry-based analyses.

d. IT support – maintains operability of data-collection and secure transfer systems.

Following each bi-annual export, data quality is checked for completeness and consistency; queries are sent to centres for correction or confirmation. After validation anonymised data are transferred to the data manager for analysis (typically within four months of export). Raw data are backed up and protected. Annual registry reports are available online..

Data security:

Central ReMuS registry data are stored in a secure EU-based Azure cloud environment operated directly by the ReMuS Endowment Fund. The infrastructure applies GDPR-compliant encryption, access control and audit logging, and all storage and handling conform to current EU data-protection and IT-security standards.

Assurance of qualifications:

Each MS centre is certified highly specialized care centre. Contract is in place with each of the sites. To be included in the registry, the contract stipulates the obligation to designate a hospital representative responsible for data management. These staff are then trained by ReMuS and provided with a ReMuS registry manual. Non-compliant MS centres may be excluded.

Data quality checks:

Automatic checks for completeness and accuracy are defined in ReMuS Sanity Checks. (Appendix 7).

Audits:

IT and data-security audits are conducted regularly. No major issues have been identified. Annual financial and compliance audits are also performed.

2.1.8 Characterisation of the registry data quality

The following processes ensure data quality:

- The iMed software includes built-in checks (e.g. logical date sequences).
- ReMuS runs four-step data-quality process twice a year, involving inspection of each data extraction, error reporting and site query resolution. This process is repeated up to four times every six months.
- If completeness issues are suspected (e.g. pregnancy or relapse records), a benchmarking system is used to identify outlier MS centres.

Each MS site holds a certificate of highly specialized care centre that include obligation to enter patients into ReMuS.

2.1.9 Governance

Governance for collaboration:

- **Publicly available documentation (with website) of key registry characteristics:**

https://www.multiplesclerosis.cz, https://www.remus.ms

The ReMuS registry is based on voluntary provision of informed consent by the patients. Information on registry governance and annual reports is available on the website above. The ReMuS Endowment Fund is listed in the HMA-EMA RWD Catalogue[1] (ID 1000000744).

At present, the registry has contracted **all 15 MS centres** in the Czech Republic, which are the only healthcare facilities, where patients can receive DMTs. Consequently, ReMuS represents vast majority of DMT-treated MS cases in the country (~93% of DMT-treated patients and ~70% of all MS patients, see Table 1 for current patient counts and coverage statistics).

Comprehensive information on registry governance, operational structure, annual reports, and financial transparency is publicly available at:

- General information and annual reports: https://www.multiplesclerosis.cz/en/about-the-registry/
- Funding and financial governance: https://www.multiplesclerosis.cz/en/remus-for-supporters

Governance documents:
https://www.multiplesclerosis.cz/en/basic-documents

- ***Single contact point for information:***

remus@multiplesclerosis.cz

- ***Publicly available policy for collaborations with external organisations:***

[1] *ReMuS, nadacni fond (ReMuS) | HMA-EMA Catalogues of real-world data sources and studies*. (n.d.). https://catalogues.ema.europa.eu/institution/1000000744

The framework for collaboration and data output handling is described by the document *Application for data output / project approval*[2]. Long-term co-operation or study participation is handled within these rules and the ReMuS Scientific Board review process (Annexes 1-6).

- ***Governance structure for decision-making on requests for collaboration:***

Key bodies involved

- **ReMuS Scientific Lead (RSL):** Leads scientific intake and feasibility review; chairs scientific discussions during the request lifecycle.
- **ReMuS Scientific Board:** Operational scientific approval body comprising the **RSL**, **NLS** Committee Members (NLS = *Neuroimmunology and Liquorology Section of the Czech Neurological Society of the Czech Medical Association of J. E. Purkyně*), and **one Leading Clinician per MS centre** (one vote per centre).
- **Managing Board of ReMuS Endowment Fund:** Provides legal/operational consent where applicable; responsible for contracting and regulatory/organisational compliance.
- **Supervisory Board of ReMuS Endowment Fund:** Independent oversight of all ReMuS activities; includes one seat for a **patient representative** (currently a person with MS).

Process and indicative timelines

- **Intake & feasibility:** Administrative staff of ReMuS Endowment Fund and RSL conduct initial review. *(1–2 weeks)*
- **ReMuS Scientific Board e-vote:** consent for any data release *(majority; typically, 7–14 days)*
- **Managing Board of ReMuS Endowment Fund** consent where applicable. *(5–10 days)*
- **Centre-head consents** where required. *(1–2 weeks)*
- **Contract negotiation**: duration varies based on complexity of the project and requesting subject legal and compliance processes. *(typically, 1–4 weeks)*
- **Data preparation, quality checks and delivery:** via internal ReMuS analytics or secure applicant access routes. *(typically, 2–8 weeks)*
- **The Supervisory Board of ReMuS Endowment Fund** oversights all ReMuS activities.

In total, standard data-release requests are typically completed within 8 to 16 weeks from submission to data delivery, depending on project complexity and linkage requirements. Complex requests involving external data linkage or substantial new data collection may require additional time. Requesting subjects are informed of the expected timeline at the feasibility stage.

Decisions on collaborations and data access follow a documented path: intake by the ReMuS Scientific Lead (RSL), scientific approval by the ReMuS Scientific Board (RSL, NLS Committee Members, and one Leading Clinician per MS centre), with the Endowment Fund's Managing Board providing legal/operational consent as applicable.

[2] Available on web page: https://www.multiplesclerosis.cz/en/basic-documents

Oversight is provided by the Supervisory Board, which includes one seat for a patient representative (currently a person with MS).

The "Application for Data Output / Project Approval" defines milestones and indicative durations: submission & admin check (up to 3 days), scientific review by RSL (up to 5 days), budgeting (as needed, up to 14 days), approvals by Scientific Board and Managing Board (up to 10 days), contracting (as needed), and data extraction/processing/delivery (as needed).
In the Briefing Book, the overall end-to-end timing for standard requests is now stated as typically 8–16 weeks from submission to delivery (complex requests may take longer; applicants are informed at feasibility).

Amendments are handled through the same governance bodies as above: RSL intake, Scientific Board evaluation/e-vote, and Managing Board consent if required. Where changes affect the scope or legal basis of processing (e.g., expanding categories of personal data or linkages), the Data Protection Officer and ethics oversight are engaged, aligned with the consent materials (ICF) that define scope, patient rights, and controller/DPO contacts. Implementation occurs within the iMed environment used by ReMuS, with centres exporting to the secured ReMuS repository on the regular cycle; timelines depend on change complexity and deployment scheduling.

The Managing Board of ReMuS Endowment Fund handles legal/operational matters (contracting, regulatory/compliance). Patient representation sits on the Supervisory Board (one seat for a patient representative). (Organisational structure shown in the "Internal & external structure" appendix.)

Patient population covered:

The aim of the ReMuS registry is to cover the majority of the MS patient population in the Czech Republic. All 15 MS centres—the only facilities nationally authorised to prescribe DMTs— contribute data to ReMuS. Current patient counts and coverage statistics are provided in Table 1 (Section 1.2). Approximately 93% of patients treated with DMTs are included in the registry. Ongoing work focuses on capturing patients not regularly treated in MS centres, with estimated current coverage of approximately 70% of all MS patients nationwide.

Data privacy:

Status of implementation of GDPR:
The GDPR is fully implemented and the ReMuS Registry is approved by the Office for Personal Data Protection – highest Czech Republic regulatory body according to GDPR implementation.

Informed consent form and its validity for registry-based studies (or need for re-consent):

Each patient signs an informed consent form allowing use of their data within the defined scope without need for re-consent for registry-based studies. The current ICF includes

the entire BMSD core dataset and an optional checkbox allowing data linkage with other authorised national data sources.

Funding:

Funding sources and impact on short, long-term sustainability and possible conflicts of interest for a specific registry-based study: ReMuS registry costs are divided into core-operational and project-based parts. Core operations are funded through general annual grants, donations, prior savings and accrued interests, all managed by ReMuS Endowment Fund. Project-based costs are carried by the project partner. Due to strict cost management no funding shortage has occurred. Details of funding sources, financial governance and annual reports are publicly available at https://www.multiplesclerosis.cz/en/remus-for-supporters/. Prior to April 2024, registry funding was included in IMPULS Endowment Fund annual reports; the first independent Annual Report (with full financial section) for 2024 will be published by end of 2025.

No personal financial relationships or conflicts of interest exist between registry staff and the fund.

Core operations are funded by general annual grants, donations, prior savings and accrued interest managed by the ReMuS Endowment Fund; project-based costs are covered by the project partner. The funding page and annual reports are publicly available (first independent ReMuS EF annual report for 2024 to be published in 2025).

2.2. DMSR:

2.2.1. Origin of the registry:

The DMSR was formally established in 1956, but prospective data collection had already started in 1948. It started with a nationwide population-based MS prevalence survey by the late Kay Hyllested, who mapped the prevalence of MS in 1949 in all the Danish geographical administrative units for his doctoral thesis. The national prevalence in 1949 was 85/100,000 population. Sources of information were all Danish Hospitals, all general practitioners and the central Disability Insurance Court. By end of 2024 the prevalence was 319/100,000.

Following the introduction of disease-modifying drugs (DMDs) for patients with relapsing-remitting multiple sclerosis (RRMS) in 1996 the Danish Multiple Sclerosis Treatment Register (DMSTR) was established within the framework of Danish Multiple Sclerosis Group (DMSG) as a nationwide scientific database, associated with the Danish Multiple Sclerosis Registry. In 2006, the DMSTR changed from being a research register to a clinical quality database under the auspices of Danish counties and from 2007, Danish Regions. The aim of this database is to monitor indicators of quality of processing immunomodulatory and immunosuppressive therapy of patients with MS with reference to standards given by the DMSG and the Danish Regions (the current administrative units and the owners of the Danish public hospitals). All Danish Quality Databases are operated by the Sundhedsvæsenets Kvalitetsinstitut (The Danish Institute

for Health Quality), https://www.sundk.dk/om-sundhedsvaesenets-kvalitetsinstitut/ (former: Regionernes Kliniske KvalitetudviklingsProgram, https://www.rkkp.dk).

DMSR and DMSTR use the same collection platform, COMPOS, but are otherwise two independent entities. Data registration for the quality database indicators is mandatory in Denmark. This is beneficial for the DMSR as the shared collection platform ensures a high degree of completeness in DMSR as well. However, while DMSR has the right to extract and use all collected data for research, the DMSTR is only allowed to extract data necessary for calculating the quality indicators determined by the steering committee of DMSTR and only after permission from the Danish Health Data Agency.

2.2.2. Purposes:

The purpose of the present collection system is to serve as the common online data collection software for both the DMSR and for the clinical quality database DMSTR. The DMSR serves scientific purpose as it comprises all collected information including treatment with DMT on the entire Danish MS population in the clinics.

2.2.3. Registry population:

DMSR is a registry of patients diagnosed with MS (provided by a neurologist or a department of neurology) with residence in Denmark. Please refer to Appendix 3 "Magyari et al publication" for further information regarding the DMSR characteristics.

The DMSR setting includes 13 Departments of Neurology/MS clinics in public hospitals, where most of the neurological services, diagnostic and clinical management of patients with MS and related disorders are carried out. These are the only units that are authorized to prescribe and dispense disease modifying drugs.

Patients are included if they have a demyelinating condition: MS, radiological isolated syndrome (RIS), and clinical isolated syndrome (CIS). DMSR has extended the target to include the other demyelinating disease, neuromyelitis optica spectrum disorder (NMOSD) and Myelin Oligodendrocyt Glycoprotein Antibody-Associated Disease (MOGAD).

2.2.4. Data elements/Metadata list

Data elements:

The core data set covers:
· Patient characteristics
· Clinical characteristics: onset and diagnosis date and symptom, phenotype, EDSS development
· Tests: MRI, CSF
· Relapses
· Disease modifying treatments
· Adverse Events
· Visits

Please refer to the following appendices for further information on the core data set:
Appendix 3 "Magyari et al publication"

Standard dictionary:

Data dictionary & variable lists are available in Excel format upon request and specified in Appendix 4. The DMSR dictionary is aligned with the BMSD Data Dictionary.

Terminology:

Standards and terminologies are available.
ICD-10 is used for AEs.
Clinicians use the standard current definition for relapse and for EDSS.

Lag times:

Data is collected by using the web-based IT interface COMPOS, provided by OMDA, as part of routine visits.
Data are extracted monthly, and sanity checks of inconsistencies of dates are corrected prior to producing the final data cut of the DMSR. Timelines can vary greatly according to whether linkage to other national registries is required. If no linkage to national registers is required, theoretically, a version of the DMSR can be created daily.

Further considerations:

Capability to amend data elements is possible. Data elements can be added and/or deleted if regarded useful for clinicians as well as researchers and don't compromise existing data. The process of introducing new elements will take a few months from suggestion to decision and implementation depending on the complexity.

Reasons for amendments include suggestions from the clinical staff improving ways of daily data entry; legislation may cause a need for amendments; new research questions arise; new drugs and new guidelines may lead to requests for changes. Depending on the nature of the amendment, decisions are made by the DMSR lead, Data Manager and/or the DMSG. The decision-making is time efficient. Carrying out the amendments may take from a few days to six months, depending on the complexity and availability at the system supplier OMDA. The Data Manager of DMSR facilitates the communication with OMDA.

2.2.5. IT infrastructure

DMSR uses the COMPOS web-based platform provided by OMDA, for data capture, please see https://omda.com/solutions/health-analytics/omda-compos/ which is designed as a decision support tool of value for the clinical situation and provides an overview of the most important information about the patient, including the MS-relevant medical history such as current and previous DMTs, relapses, EDSS, MRI results etc. The data domain used in the clinical routine belongs to the clinical department and new data are every night transferred to the DMSR domain, providing almost real time information.

2.2.6 Data processing

Roles and responsibilities:

Data is recorded on a daily basis into the online platform COMPOS by health care professionals as part of clinical care and transferred automatically to the DMSR data base every morning when an updated DMSR database is created which is then downloaded by DMSR data managers routinely once a month.

Established processes:

All MS treating clinics record data online on all patients with MS related diseases. In Denmark notification is mandatory of all MS patients prescribed disease modifying treatments and DMSR uses this list to ensure that all treated patients are included.

Degree of automation:

Data is collected via the COMPOS software, which is built on structured drop-down menus with very few open text boxes. No data are being automatically transferred to the registry.

2.2.7. Quality Management activities

Supportive scientific and technical functions:

Added patients are double checked by registry staff. There is built-in verification upon data entry and extraction. There is a close collaboration between the DMSR and all MS clinics to include all relevant patients.

Validation studies, comparing registry data with medical records, are performed on a regular basis for patients in DMT, latest in 2019.

The following processes are in place in terms of quality:
· Added patients are double checked by registry staff.
· The data coordinator of the DMSR receives monthly lists of all patients assigned to any of the MS clinics, independent of the notifications by COMPOS, and control of correct case definition has a high priority for the DMSR.
· The clinicians in the DMSG meet regularly and determine indicators and standards for good clinical quality, and recommendations are reported back to clinical personnel in writing for quality improvement and released in public for transparency and accountability.
· The online platform (COMPOS) where health care professional report patient clinical data has many built-in flags and blocks that prevent the imputation of implausible data, especially dates (for example, it is not possible to enter the date of an MS diagnosis before Birth, etc.) as well as built-in imputation features.

The organization Sundhedsvæsenets Kvalitetsinstitut (Danish Institute for Health Quality), https://www.sundk.dk/om-sundhedsvaesenets-kvalitetsinstitut/ (former: Regionernes Kliniske KvalitetudviklingsProgram, https://www.rkkp.dk/) is the responsible party for all Danish clinical quality databases and monitors the quality in health care by quality indicators. It is mandatory for clinics to provide data for these indicators and results (whether standards are met) are available for clinics and hospital

management on a monthly basis on local Management Information Systems. The MIS systems also provide information on which patients do not fulfill the indicator.

An annual report is published for each database - the 2021-2022 report on MS treatment has been added as Appendix 6 "Appendix 6_DMSR_Annual report on MS treatment", Appendix 8 of the Request Tool "SOP for DMSR creation" (including 4 files), and Appendix 9 "DMSR quality statement" for further information.

Data security:

Personal data is being stored and handled in fully secured IT environments according to current standards at Statistics Denmark and the Danish Health Data Authorities.

Assurance of qualifications:

Clinical departments are responsible for the training and qualification of health care professionals entering data in DMSR. Since the COMPOS platform is designed for clinical work and decisions, accuracy of entered data are central to the quality of care.

Data quality checks:

At The Danish Multiple Sclerosis Registry (DMSR) we are continuously working on maintaining and improving high quality data. The quality control and quality assurance start at data entry and continues at data extraction. Please refer to Appendix 9 of the Request Tool, “DMSR Quality Statement” for further details.

Audits:

Auditing procedures include the Danish Institute for Health Quality (body of the regional authorities) performing audits to parts of the DMSR (data included in the DMSTR) at some years intervals. In addition, the registry itself conducts frequent ad hoc quality checks.

2.2.8. Characterisation of the registry data quality

The following processes are in place in terms of ***data verification***:
· Data entry into the DMSR web interface is almost always done by ticking alternatives or boxes to avoid typing errors and variations in spelling.
· DMSR officials perform regular reviews of DMSR data against clinical records
· Quality control is performed ensuring correct format and structure of data, the plausibility and consistency of data within a data set and within longitudinal data of one patient.
· Monthly results are provided for clinical management on key quality indicators.
· The interface of COMPOS is a part of the neurological consultation, therefore there is a good chance that some inconsistencies can be corrected: COMPOS has some built-in features that improve completeness (e.g. some variables must be mandatory imputed by the clinician, such as birth date, etc.), validity (e.g. no dates in the future) of the data. COMPOS also has consistency-check tools of the data (for instance, a feature prevents MS onset date later than MS diagnosis date).

For Quality Check of completeness of certain key variables for specific patient subgroups, COMPOS provides tools that allow clinicians to check completeness of key variables at Clinic, Region or even National level, for specific sex or age groups, etc. The Danish and Swedish COMPOS are not exact the same although they share the same roots. There are differences to accommodate different needs and use in the two countries.

For further information, please refer to Appendix 5 "CRF screenshots" and Table O.1 in Appendix 6: "Annual Report on MS treatment".

The following processes are in place ***to minimize missing data***:
Since the implementation of COMPOS in 2015, missingness and incoherent data has been reduced. As mentioned above this software has an integrated data verification tool to identify missing or incoherent data. Similarly, completeness has increased since the same year.

As an example of statistics for missingness from reports, please refer to Appendix 7 "DQAR CLARION_November 2022". The appendix is the latest (November 2022) Data Quality Assessment Report (DQAR) that is performed yearly on the data provided by MS registries participating in the CLARION PASS (EUPAS24484). Completeness of certain variables identified by the sponsor (MERCK) as constituting a good data quality indicator can be seen in the excel tab called "Completeness". Please note that the completeness of these variables is only valid for the eligible study population in CLARION.

2.2.9. Governance

Governance for collaboration

- **Publicly available documentation (with website) of key registry characteristics:**
  www.DMSR.dk
  DOI: 10.1002/brb3.1921

The Danish Multiple Sclerosis Registry (DMSR) was formally established in 1956, but prospective data collection started already in 1948. It commenced as a nationwide population-based MS prevalence survey and has since continued to register new cases of MS. The DMSR collects data on from the entire country on patients with the demyelinating conditions: MS, radiological isolated syndrome (RIS), and clinical isolated syndrome (CIS). We have extended the target of the DMSR to include the other demyelinating disease, neuromyelitis optica spectrum disorder (NMOSD) as well as Myelin Oligodendrocyt Glycoprotein Antibody-Associated Disease (MOGAD). Data on the population with NMOSD were added retrospectively after a recent nationwide incidence and prevalence survey going back to 2007. Informed consent from the patient is not needed.

Data is entered into the DMSR by clinical staff at the 13 Departments of Neurology/MS clinics in public hospitals (2025) - these are the only units that are authorized to prescribe and dispense disease modifying drugs (https://dmsr.dk/contributing-centers.html)

- **Single contact point for information:**
  scleroseregisteret.rigshospitalet@regionh.dk
  https://dmsr.dk/contact.html

- **Publicly available policy for collaborations with external organizations:**
  https://dmsr.dk/research.html

- **Governance structure for decision-making on requests for collaboration:**
  The Scientific Steering Committee consists of seven neurologists from MS clinics, two patient representatives and one representative from The Danish Multiple Sclerosis Society. http://dmsr.dk/steering-committe.html. The committee meets approximately every 3 months.

An application form can be obtained by request to the DMSR (scleroseregisteret.rigshospitalet@regionh.dk - https://dmsr.dk/contact.html). The application will be processed by the Scientific Steering Committee at its next upcoming meeting - the application needs to be received at least three weeks in advance, the date of the next scheduled meeting can be obtained upon request. If the application is approved by the committee a cooperation agreement is to be signed, an invoice prepared and paid, and additional legal documents prepared and approved before the data transfer can take place. Only variables and data that are necessary for the specific project can be transferred and only to a trusted scientific environment. Data is transferred by sftp-server email. This procedure can take 1-6 months.

If data is to be transferred to a country outside the EU/EØS further legal steps are necessary involving the Data Protection Authority prolonging the time to data delivery with additional months.

Patient population covered

Total number of patients (2025): 34.000. Alive & residing in Denmark (2025): 19.000
New patients per year: 600
Patients lost with reason for exit: 14.000 (Annexes 1-.6).

We estimate that we cover 95 % of all living patients with MS in Denmark

All MS treating clinics record data online on all patients with MS related diseases. Data is recorded by health care professionals (neurologists and nurses).
We have in recent years extended the target of the DMSR to include the other demyelinating disease, neuromyelitis optica spectrum disorder (NMOSD) and Myelin Oligodendrocyt Glycoprotein Antibody-Associated Disease (MOGAD) as mentioned in section 2.2.3.

Data privacy:

• Status of implementation of GDPR: Implemented.

• Informed consent form and its validity for registry-based studies (or need for re-consent):

All patients are informed about their data being recorded. According to the Danish implementation of the General Data Protection Regulation (GDPR), there is no requirement for informed consent from the patient for inclusion in the DMSR, on the explicit condition that data can never be used for any other purpose than pure science and statistics.

Funding:

• Funding sources and impact on short, long-term sustainability and possible conflicts of interest for a specific registry-based study:
The operational costs of the Danish Multiple Sclerosis Registry are funded by The Danish Multiple Sclerosis Society and Copenhagen University Hospital Rigshospitalet. The research activities are funded by grants from public and private foundations, legacies and project collaboration with the pharmaceutical industry.

2.3. OFSEP:

2.3.1. Origin of the registry:

In 1990, Professor Christian Confavreux *(† 2013)* designed a software program called EDMUS (European Database for MUltiple Sclerosis) with European funding. This software enables clinical data from MS patients to be collected and compiled into a database. It is based on a common language that is recognized and accepted for describing the disease.

In France, in 2003, neurologists specializing in MS using the EDMUS software set up a network to exchange their patient follow-up data: a cohort of more than 30,000 patients was thus created. Analysis of the data of these patients led to the publication of a number of articles, improving knowledge of the illness and patient treatment.

2.3.2. Purposes:

OFSEP aims to provide a major epidemiological tool on MS for the scientific community in France and abroad.

2.3.3. Registry population:

OFSEP is a registry of patients diagnosed with MS or a related disease (radiological isolated syndrome (RIS), clinical isolated syndrome (CIS), acute disseminated encephalomyelitis (ADEM), neuromyelitis optica spectrum disorder (NMOSD), myelin oligodendrocyte glycoprotein antibody-associated disease (MOGAD) monitored by an OFSEP-participating neurologist.

2.3.4. Data elements/Metadata list

Data elements:

The core data include the description of the patients, their diseases and their therapeutic care (socio-demographic characteristics, neurological episodes, disability, treatment,

serious adverse events, etc.). See http://www.ofsep.org/fr/FicheMinimaleOFSEP and http://www.ofsep.org/fr/FicheMinimaleOFSEP_EIG for details (in French). MRI (DICOM files) are collected too and biological samples for some patients.

Standard dictionary:

Data dictionary, Minimum dataset and Data description are available. Optional data may be or not present in the EDMUS software/Platform. OFSEP collects Severe Adverse Events (SAEs) only and reports these in MedDRA-codes.

Please refer to the following for the data dictionary: Appendix 10 "Data dictionary"
Please refer to the following for the minimum data set: Appendix 11 "Minimum Dataset" and http://www.ofsep.org/fr/FicheMinimaleOFSEP
Please refer to the following for the data description: Appendix 12 "Data description"

Terminology:

For the description of MS related medical data, international and acknowledged definitions are used (definition of relapses, EDSS score, walking distance, clinical course according to Lublin classification).

MedDRA coding applied for serious adverse events.

Lag times:

Data is collected continuously locally and exported twice annually to the central database

Further considerations:

Changes in the collection of data is possible. As an example, in 2016-17 we implemented a new format for improved systematic collection of serious adverse events, in order to answer requirements of potential PASS studies, but also to improve our knowledge of serious comorbidities.

Each request for a change is carefully evaluated, in terms of scientific relevance (including needs of regulators or pharma) but also impact on the daily activities of neurologists. It has to be kept in mind that neurologists are doing the collection of data on a voluntary basis, and that the time spent is very limited.

Once a proposal of change appears, it is submitted to the OFSEP coordination team (evaluation of relevance, impact, feasibility) then the Scientific Board; if the SB validates the proposal on a scientific point of view, then the Steering Committee finally evaluates for approval. Finally, the OFSEP coordination team modifies the collection materials and guides, and informs the centers. The duration of this process is generally about 6 months.

Linkage information:

We are linking OFSEP data with the SNDS, a French medico-administrative database.

The linkage is scheduled to be performed on an annual basis; the current available (October 2025) covers the period 2009-2023. To be notified that SNDS data are provided with a delay of around 18 months from the real date of the occurrence.

We are carrying out probabilistic linking with a success rate of around 85% (55,000 OFSEP files linked to SNDS files).

The data enriched by the SNDS are consulting, drug dispensing, biological exams, issuance of technical aids, long-term disease, hospitalizations, diagnoses, medical procedures, external consultations, death causes, non-specific MS data including comorbidities, co-prescriptions, recourse to care.

2.3.5. IT infrastructure

Data is collected by using EDMUS software (historical IT for most of the centers) /EDMUS Platform (new IT sytem since 2024 for some centers) (for clinical data) and Shanoir software is used (for DICOM (MRI)) data. Data is recorded daily and exported twice a year to a central registry (June and December).

2.3.6. Data processing

Roles and responsibilities:

All French MS expert centers are providers of data about all patients followed in their centers. See http://www.ofsep.org/en/presentation-en/participating-centers for details.

Established processes:

All the patients sign an informed consent form (or their parents in case of pediatric patients). The form includes information about registry-based studies, therefore there is no need for re-consent.

Degree of automation:

Data is collected using the EDMUS software/Platform, with drop-down menus with few open text boxes. No data are being automatically transferred to the registry.

2.3.7. Quality Management activities

Supportive scientific and technical functions:

Neurologists use the data collected for medical purposes (clinical data entered in EDMUS software/Platform, MRI acquisition protocol optimized for care and research, biological samples collected as part of the care process), it is therefore their interest to ensure the quality and validity of the data collected and entered, which enhances the quality of the database.

The EDMUS software/Platform has an integrated data verification tool to identify missing or incoherent data. If such errors are of a medical nature, a neurologist validates or corrects them.

EDMUS data are collected locally in a stand-alone software. Twice a year, data are extracted, anonymized and sent to the OFSEP coordination team. This aggregation of data constitutes the OFSEP registry.

Every time the national database is updated (twice a year), the OFSEP coordination team is provided with the list of incoherent data entries, which enables processing advice to be proposed to the centers.

The OFSEP coordination team also provides a number of tools to the centers: information documents, data quality indicators and their evolution over time, training sessions and on-site audits (one dedicated CRA with the objective to audit each center once every two years).

Quality procedure implemented for center follow-up and quality checking (POS-COH-03 Suivi d'un centre OFSEP)

Support of the OFSEP coordination team is available for project preparation. It covers evaluation of data availability, methodological and statistical issues, ethical and administrative considerations.

Evaluation of scientific relevance and methodology by the OFSEP scientific board

Quality procedure set up for the management of academic or industrial project (POS-COL.02 gestion des collaborations académiques et industrielles) (Annexes 1-6).

Data security:

Personal data is being stored initially in secure stand-alone servers and, after export to OFSEP, handled in a fully secured IT environment at University Hospital of Lyon (France). Local information of each participating center are sent to OFSEP coordination team by email after encryption (GPG); the OFSEP coordination team is in charge of storing the data in the secure server of the Hospital of Lyon. The export of anonymised data to OFSEP is performed biannually and all procedures are validated by national bodies.

Assurance of qualifications:

To maintain and improve data quality, the OFSEP National Coordination Centre (NCC) provides various tools for the centers:

- training sessions for Clinical Research Assistants and neurologists. These sessions are already organized annually during the Assises de l'OFSEP. They can also be done in web- or telephone conferences with a more limited number of participants.

Two quality procedures implemented (POS-SUP-03 Data Management and POS-SUP-02 Activités statistiques).

Data quality checks:

Two quality procedures that detail all the possible procedures to follow depending on the requirements of each specific study are available for this. With regard to data management, a data management plan is developed that details the data extraction process and how collection of additional data is conducted and the details pertaining to the data cleaning process when inconsistencies are identified. A separate quality

procedure for the statistical analysis detailed each step for the analysis including the development of a statistical analysis plan and the programming stages.

Please refer to the following appendices for further information:
Appendix 13 "POS-SUP-03: Data Management"
Appendix 14 "POS-SUP-03a: Plan de Data Management"
Appendix 15 "POS-SUP-03c: Plan de validation des données"
Appendix 16 "POS-SUP-03d: Formulaire de gel de base"
Appendix 17 "POS-SUP-02: Activités Statistiques"
Appendix 18 "POS-SUP-02c: plan d'analyses statistiques"
Appendix 19 "POS-SUP-02d: Standards internes de programmation".

Audits:

Auditing procedures include on-site audits for all centers, on the basis that data collection required for the participation in the OFSEP registry. The audits are not conducted specifically for safety studies or a project, but rather at the behest of OFSEP coordination team if the previous audit dates back 2 years, if there is a signal about a decrease of organization's quality or of data quality in the center, or to analyze the quality of data compared to other centers, assessing the center´s ability to progress. They are also done to identify risks and implement continuous quality improvement processes, establish actions to maintain the quality of data collection, and define priority actions for database cleaning. Some audits are conducted at the behest of a center if it needs some evaluation and help to improve its organization.
The activities covered in the audit are: patient consent, center organization and data collection circuit, security and confidentiality of database, data verification and review, staff training, utilization of tools dedicated to quality provided by OFSEP (queries, quality indicators...), data monitoring. There is no audit trail in the software, but a list of date of modification and the name of the person who did the change. It is however possible to compare data exported for one patient from one export to the other, every sixth month.

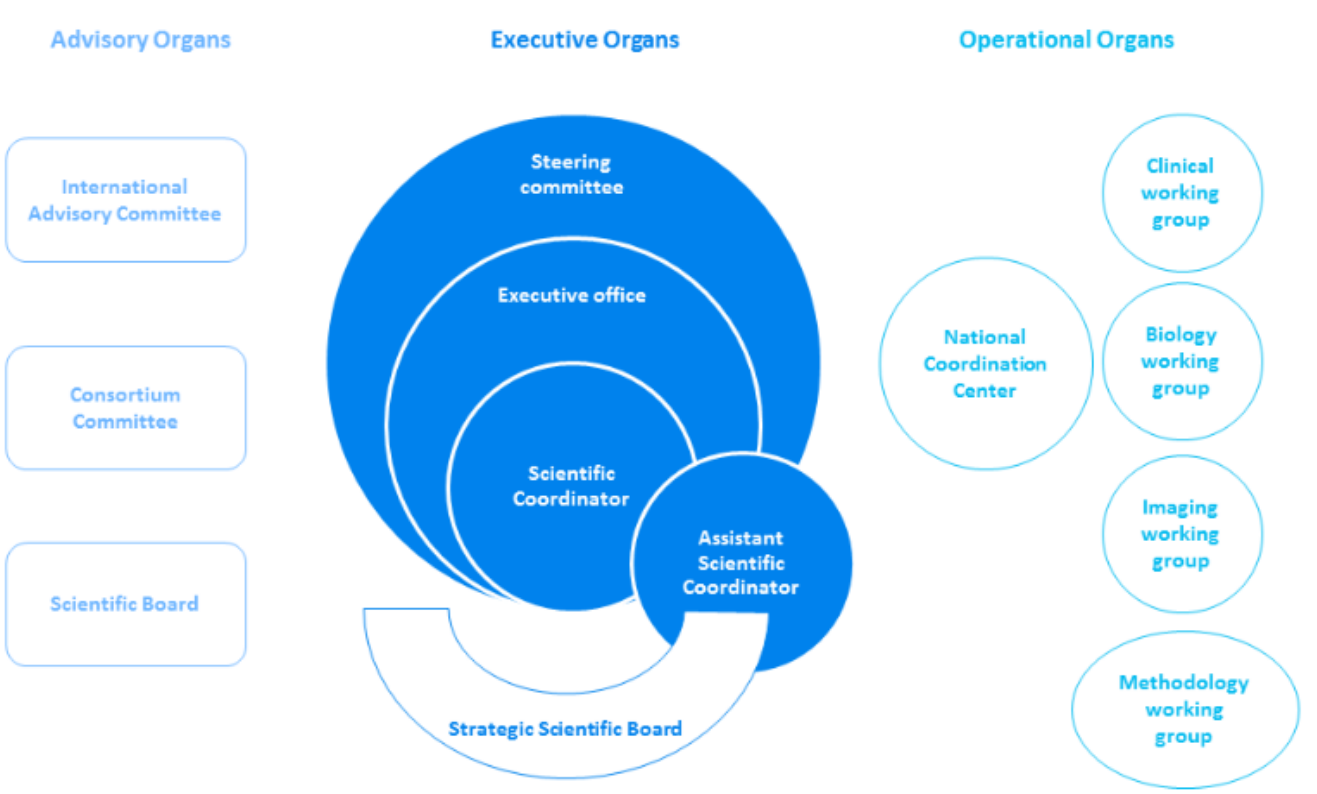
2.3.8. Characterisation of the registry data quality

· The EDMUS software/Platform has an integrated data verification tool to identify missing or incoherent data. If such errors are of a medical nature, a neurologist validates or corrects them.
· EDMUS data are collected locally.
· Data export (extracted and anonymized) to OFSEP is done twice a year and sent to the OFSEP coordination team. This aggregation of data constitutes the OFSEP registry.
· At each database export, the OFSEP coordination team is provided with the list of incoherent data entries, which enables processing advice to be proposed to the centres.
· OFSEP provides other tools to centers to improve data quality such as: information documents, data quality indicators and their evolution over time, training sessions and on· site audits (one dedicated CRA with the objective to audit each centre once every two years).
Please refer to Appendix 8 "POS-COH-01 Gestion de la cohorte" and Appendix 20 "POS-COH03: Suivi d'un centre" for further information on the quality procedure implemented for centre follow-up and quality checking.

The following processes are in place in terms of data verification:
Every time the national database is updated (twice a year), the OFSEP National coordination center is provided with the list of incoherent data entries. Thus, every six months OFSEP coordination team provides a list of incoherent data entries to centers. Centers send their responses and notably if the data are confirmed as true. OFSEP coordination team checks answers and can invalidate the center's validation if answers are problematic. After the new semestrial export, the new list of incoherent data entries includes new incoherences and old ones (invalidate confirmations and data not previously corrected).

2.3.9 Governance

OFSEP - Organization: https://www.ofsep.org/en/presentation-en/organization



The governance of OFSEP has been defined by a Governance Charter since 2012, with the latest update in September 2024.

The ultimate governing body is the Steering Committee.

It has both decision-making and operational responsibilities: it defines the strategic orientations of OFSEP and appoints the people charged with monitoring their implementation. The Steering Committee meets once a month. It may request the opinions of internal experts

(particularly the members of the National Coordination Center) or external experts before coming to a decision.

Missions:

- Routine project management
- Communication and publication of the decisions made and chosen orientations
- Appointment of work group managers
- Appointment of co-chairmen of the Scientific Board
- Coordination with OFSEP's EDMUS centers, BRCs (biological resource centers) and imaging centers
- Distribution of financial resources
- Analysis of recommendations from the Scientific Board and the work groups
- Relations with the health insurance fund, health care authorities and industrial players

The Steering Committee is composed of 15 members (member name as of October 2, 2025):

- the Scientific Coordinator: Pr Sandra VUKUSIC

- the Deputy Scientific Coordinator: Pr Francis GUILLEMIN

- the Co-Chairs of the Scientific Board: Pr Laure MICHEL and Pr Hélène ZEPHIR

- three members representing the Participating Centers: Pr Bruno STANKOFF (Paris, Pitié Salpétrière), Dr Caroline Papeix (Paris, Fondation Rotschild), Pr Jean PELLETIER (Marseille)

- one representative from the National Coordination Center (NCC): Dr Romain Casey (Responsible of the Cohort)

- one representative in their official capacity from each Party to the Mandate, that is, three people: Mrs Lucie BELLON-TABART (EDMUS Fondation), Mrs Delphine Cortial (Hospices Civils de Lyon), Mr Javier OLAIZ (Claude Bernard Lyon1 University)

- the head of each working group in Clinical, Imaging, and Biology, that is, three people: Pr Jérôme DE SEZE, Pr François COTTON, Pr David LAPLAUD

- one patient association representative designated by the Steering Committee upon proposal from the Scientific Coordinator: Mr Bertrand Saudeau (expert patient, caregivers and patients committee)

It should be noted that ethical expertise is present at the Scientific Board level.

Governance for collaboration

• Publicly available documentation (with website) of key registry characteristics:

YES - See web site: http://www.ofsep.org/en/data-access#Documents

• Single contact point for information:

YES - projects@ofsep.org

Publicly available policy for collaborations with external organisations:

YES - The policy and processes are described on the web site:

http://www.ofsep.org/images/ACCES_DONNEES/Plaquette_OFSEP_projects.pdf

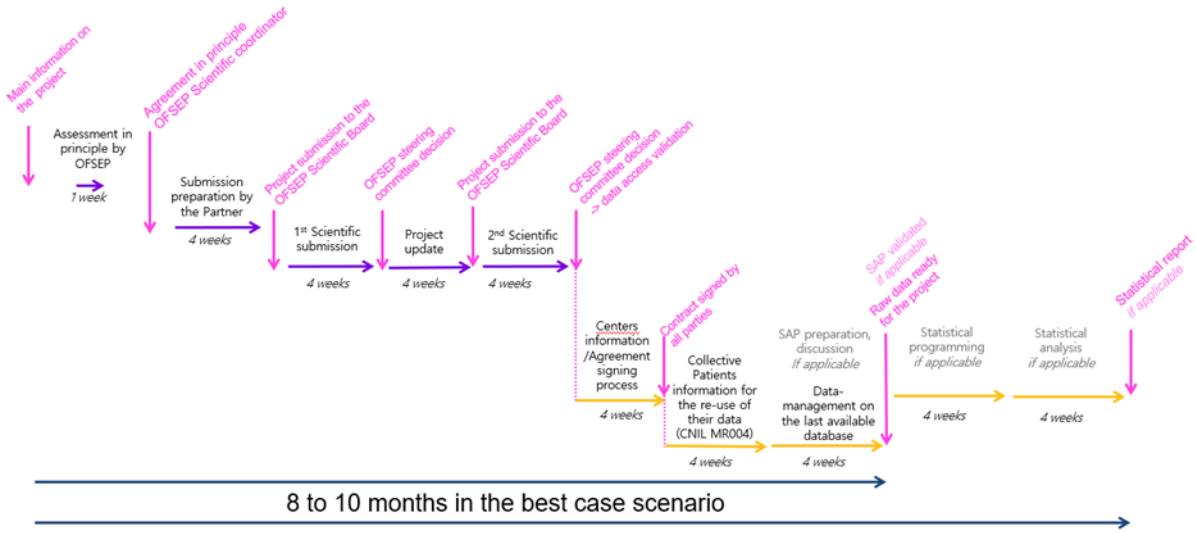
Governance structure for decision-making on requests for collaboration:

The OFSEP Steering Committee validates or invalidates project implementation and access to data within OFSEP on the basis of the opinions given by the Scientific Board (on scientific aspects) and the Coordination Team (on feasibility and availability of data in the registry).

See process at http://www.ofsep.org/en/data-access

Quality procedure (POS-COL-01 Soumission et évaluation d'une demande de collaboration) (Annexes 1-6).

Process for data sharing:



Patient population covered

Number of patients: 83,773 (June 2025) Number of MS patients in France: 120-130,000

Number of new patients entering the registry per year: 4000-5000.

Inclusion and exclusion criteria for participating centres and enrolment of patients:

All MS expert centres participate to OFSEP, as well as other neurological departments from university and general hospitals, and private practice neurologists. In France, as the prescription of disease-modifying drugs is not restricted to MS experts, not all MS patients are followed by participating centres (typically, the most severely disabled patients, to whom DMTs are no longer offered, are rarely seen in MS expert centers).

See http://www.ofsep.org/en/presentation-en/participating-centers for details.

Clarity on patients' inclusion and exclusion criteria:

Any patient with MS or a related disease monitored by an OFSEP-participant neurologist can be included in the OFSEP cohort.

No age exclusion criteria. Specific consents are available for children.

Data privacy:

Status of implementation of GDPR:

OFSEP is compliant to GDPR (information of patients, PIA…); a DPO (Data Protection Officer) has been designated: dpo@fondation-edmus.org

Informed consent form and its validity for registry-based studies (or need for re-consent):

Yes, see http://www.ofsep.org/images/Information_et_Consentement_au_projet_OFSEP.zip (in French).

Funding:

• Funding sources and impact on short, long-term sustainability and possible conflicts of interest for a specific registry-based study. The core operational costs of OFSEP were principally funded by the National French Agency for Research, within the framework of the "France 2030" programme, (contract N°10-COHO-0002 until 31/12/2024) through public funding and SECURE partnership supportive contracts with pharma (contracted for a period of 3 years since 2020 and renewable after each period) through private funding.

2.4. RISM:

2.4.1. Origin of the registry:

The "Italian Multiple Sclerosis and Related Disorders Register" (Registro Italiano Sclerosi
Multipla e Patologie Correlate - RISM) started in 2015, and it is managed and coordinated by

FISM ETS-"Fondazione Italiana Sclerosi Multipla"- and UNIBA -"Dipartimento di Biomedicina Traslazionale e Neuroscienze (DiBraiN), Università di Bari". It is mainly financed by FISM, the foundation of the national charity in Italy on Multiple Sclerosis.

2.4.2. Purposes:

The main objective of RISM is to create an organized multicenter structure to collect data of all MS patients (a near population-level) followed in the larger number of Italian MS centers.

RISM aims to address high-priority areas pertaining to:

- public healthcare area: quality of care, health optimization such as economical optimization, social and welfare information, access to healthcare treatments and healthcare services

- research area: epidemiology, rare MS disease forms such as, primary progressive (PP) MS, pediatric MS as well as early and preclinical/subclinical disease stages represented by clinically isolated syndromes (CIS) and radiologically isolated syndromes (RIS), treatment optimization such as prognostic factors and predictive models of disease course, adherence to treatments, treatment efficacy, and safety (Annexes 1-6).

2.4.3. Registry population:

RISM is a registry of patients diagnosed with MS according to the latest criteria, or present radiologically and clinically isolated syndromes (Radiologically Isolated Syndrome, RIS and Clinically Isolated Syndrome, CIS) suggestive of MS, and MS related conditions, i.e. neuromyelitis optica spectrum disorders (NMOSD) and anti-MOG disease. There are no restrictions and patients without a DMT prescription are collected and regularly visited.

2.4.4. Data elements/Metadata list

Data elements:

The core data set covers:
· Patient characteristics: sex, birth, date of onset, anamnesis
· Disease characteristics: EDSS
· Tests: MRI, CSF, Evoked potentials, laboratory tests
· Relapses
· Treatments: ID, dates
· Adverse events: date, description, outcome, treatment-related. Both AEs and SAEs are captured.

Please refer to the following Request Tool appendices for further information:
Appendix 7.1_RISM_Trojano et al publication
Appendix 7.2_RISM_Mosconi et al publication
Appendix 8_RISM_Data dictionary
Appendices 9.1, 9.2, 9.3, 9.4 for RISM Variable lists
Appendix 10_RISM_Minimum dataset

Appendices 11, 12, 13, 14 for RISM Case Report Forms.
Information is also available at the following links:
https://registroitalianosm.it/en/index.php?page=variablescollected and
https://registroitalianosm.it/dwl/set_minimo_dati_04_04_2016.pdf;

Standard dictionary:

Data dictionary, Variable list, Minimum dataset and Case Report Forms are available.

Please refer to the following for the data dictionary:

Appendix 8_RISM_Data dictionary
Please refer to the following for the minimum data set:
Appendix 10_RISM_Minimum dataset and
https://registroitalianosm.it/en/index.php?page=variablescollected and
https://registroitalianosm.it/dwl/set_minimo_dati_04_04_2016.pdf Please refer to the following for the variables list:
Appendices 9.1, 9.2, 9.3, 9.4 for RISM Variable lists and
https://registroitalianosm.it/en/index.php?page=variablescollected
Please refer to the following for the case report form: Appendices 11, 12, 13, 14 for RISM Case Report Forms.
The following standardized databases are implemented in the Web Application with the aim of harmonization of data collection: FarmaDati, MedDRA, ICD9CM, EUROCAT
Please refer to Appendix 16_RISM_Manual of procedure v5.0_20_06_2025, section 7, for further details.

Terminology:

Standards and terminologies are available.
MedDRA is used for AEs.
ICD9 is used for comorbidities
EUROCAT is used for pregnancy-related issues.

Lag times:

The web-based tool provides real time access to reported data.

Further considerations:

Amendments of data elements are possible by applying a specific request to Ethical committees. The length of the process depends on the type of request and the approval process by the Ethical Committes.

Linkage information:

Currently, linkage is possible with regional information flow of health administrative data (hospital discharges, prescription drugs, ticket exemptions, registration of patients, outpatient visits).

As an example, please refer to this article published in 2022: Ponzio M, Tacchino A, Amicizia D, et al. Prevalence of multiple sclerosis in Liguria region, Italy: an estimate using the capturerecapture method. Neurol Sci. 2022;43(5):3239· 3245. doi: 10.1007/s10072-021-05718-w.

2.4.5. IT infrastructure

Data are collected through a web-based system - the RISM-App - developed ad hoc for the project, and available at **https://registroitalianosm.it/index.php?page=areariservata .** Each center can enter the data after identification through a personalized password (direct login). In the "Italian Multiple Sclerosis and Related Disorders Register", each patient has a unique valid code identifier, obtained through the patient encrypted fiscal code. Each patient is assigned to a center.

2.4.6. Data processing

Roles and responsibilities:

The Technical Methodological and Coordinating Structure (STOC) is the methodological and technical infrastructure that leads the study. Until December 2024, the infrastructure was under the responsibility of the Mario Negri Institute in Milan, from January 2025 is based at FISM. STOC is responsible for the technical-operational coordination of RISM, data analysis, management of the central server that hosts the Web Application (RISM-App) and the aggregated database, reports to the centers, analysis of the quality of data collected, and development of the RISM-App. STOC also guarantees the connectivity with the centers, back-up activities of the data stored on the server, takes appropriate security measures to protect such data, and manages a section in the restricted area of the website, where all the data of the participating centers are stored and periodically updated.
Data is collected by using a web-based tool since 2020. Data are continuously monitored for consistency and quality. Every six months, centers receive a quality report on their data using a benchmark mean value of the entire cohort. The data are now updated in real-time in the website application and a new drug section as part of an Active Pharmacovigilance Plan and a new MRI section have been implemented.

A group of research assistants has been ad hoc trained for the project with the objective to foster the collection of good quality data in the Italian MS centers. Centers are periodically contacted with ad hoc reports with queries on missing data or inconsistencies among the variables collected. Only health care professionals (Neurologists, Child neurologists / Paediatricians, MS nurses) can directly enter data.

Please refer to the following appendices for further information:
Appendix 15_RISM_Register data specifications_june 2025
Appendix 16_RISM_Manual of procedure v5.0_20_06_2025)

Established processes:

All the patients sign an informed consent form (or their parents in case of pediatric patients). The form includes information about registry-based studies, therefore there is no need for re-consent.

Each center has the full responsibility for the data collected. Each operator who wants to make his or her contribution must be part of an Italian center participating in the study. The research assistants interact with the neurologists in charge of the center and enter the data or review the data collected.

Data of the study are available to the participant centers for specific sub-studies. A standardized process to applicate for research study has been developed. Each participating center can propose research studies addressing one of the high priority areas (Research or Public Health areas) of the RISM. All the sub-studies are discussed and evaluated by the Scientific Committee before their acceptance. The submissions of sub-studies to the SC can be made at any time of the year and the process length may vary depending on the assessment of the study and the approval process by the Scientific Committee.

Degree of automation:

Data is collected using a web application software (RISM-App), with drop-down menus with no open text boxes. No data are being automatically transferred to the registry.

2.4.7. Quality Management activities

Supportive and technical functions:

Centers are monthly contacted via e-mail with updates about the progress of the study or the methods of data collection. Annual meetings are scheduled among centers with the aim to present and discuss data collected and quality assessment. Research assistants regularly visit the centers and, on the basis of specific needs related to research studies, carry out formal checks on the data collected. Several quality control tools have been implemented in order to increase the quality and generalizability of data collected:

- A group of research assistants has been ad hoc trained for the project with the objective to foster the collection of good quality data in the Italian MS centers.
- Centers are periodically contacted with ad hoc reports with queries on missing data or inconsistencies among the variables collected.
- A set of seven performance indicators has been identified and adopted with the aim to improve the quality, completeness of the survey, timeliness, generalization, and representativeness of the collected data.

Every six months, each center receives a personalized report with the situation of the center together with data quality indicators.

Please refer to the following Appendices for further information:
Appendix 7.1_RISM_Trojano et al publication
Appendix 7.2_RISM_Mosconi et al publication
Appendix 16_RISM_Manual of procedure v5.0_20_06_2025
Appendix 17.1_RISM_Data quality report_1st file_BA122
Appendix 17.2_RISM_Data quality report_2nd file_BA122

Data security:

Data collected are stored in encrypted form on the dedicated server Microsoft Azure for MySQL located in Northern Italy. Personal and clinical data are encrypted as follows:

- use of the cryptographic module of the sw Database, which requires the identification data to be encrypted with a symmetric key of at least 128 bits, different from that used for the
- encryption of clinical data (also of at least 128 bits). The symmetric keys must be also encrypted, preferably with asymmetric keys of at least 2048 bits;
- commitment of researchers to use equivalent cryptographic algorithms in their studies;
- key management that includes the change of symmetric keys at least every 2 years;
- biennial reviews of cryptographic algorithms based on Ecrypt reports or equivalent.

Assurance of qualifications:

It is in the interest of the neurologists at the participating centers to enter high-quality data. Moreover, activities are in place to monitor the quality of the data entered at the centers, for instance:

- a manual of procedures is available to assure standardized collection of data
- each center is periodically invited to participate to regional or national meetings about the up-todate of the study.
- a group of research assistants has been ad hoc trained for the project with the objective to foster the collection of good quality data in the Italian MS centers and support centers in data entry, which has improved report rates as well as quality.

Please refer to the following Appendix for further information:
Appendix 16_RISM_Manual of procedure v5.0_20_06_2025

Data quality checks:

Data quality is centrally monitored by the STOC. Several quality control tools have been implemented in order to increase the quality and generalizability of data collected. A set of seven performance indicators has been identified and adopted with the aim to improve the quality, completeness of the survey, timeliness, generalization, and representativeness of the collected data. Every six months, each center receives a personalized report with the situation of the center together with data quality indicators.

Audits:

Auditing procedures include periodical contact of the sites with ad hoc reports with queries on missing data or inconsistencies among the variables collected. Until now, this has been done by the team of research assistants of RISM (data entry personnel), for specific research projects. The RISM-App provides an audit trail on data entries, by

tracking dates and the names of persons doing data entries (See Appendix 16_RISM_Manual of procedure v5.0_20_06_2025).

2.4.8. Characterisation of the registry data quality

Centers are periodically contacted (at least every 6 months) with ad hoc reports that include the verification of "not congruent" dates, and queries on missing data or inconsistencies among the variables collected. This is focused on the 7 quality metrics. SAEs are only verified ad hoc, for specific purposes.

The statistics of missingness already included in some PASS reports may be shared as needed. An example of a quality report for the centre of Bari is included in Appendix 17.1_RISM_Data quality report_1st file_BA122 and Appendix 17.2_RISM_Data quality report_2nd file_BA122.

2.4.9. Governance

Governance for collaboration

- Publicly available documentation (with website) of key registry characteristics: Available at https://registroitalianosm.it/en/
- Single contact point for information:

Prof. Maria Trojano – University of Bari Aldo Moro – e-mail address: maria.trojano@uniba.it;

Publicly available policy for collaborations with external organisations
Available at https://registroitalianosm.it/index.php?page=documenti
Governance structure for decision-making on requests for collaboration:
The register is jointly coordinated by the Department of Translational Biomedicine and Neurosciences-DiBraiN, University of Bari and the Italian Multiple Sclerosis Foundation (UNIBA/FISM research Unit).
The governance of RISM includes an Executive Committee (chaired by one representative from FISM and one from University of Bari) with the administrative and organizational role. A Scientific Committee, including clinicians, methodologists, representatives of MS centers, and of the Italian Neurological Society, oversees the scientific initiatives, promotes specific strategic projects, and approves requests of access to centralized data for research projects. Currently, patients are not involved in the governance.
Requests for collaboration should be sent to the single contact point and then discussed by the Scientific Committee of RISM.

Patient population covered:

Total number of patients: The total number of valid cases is 93,802
New patients per year: At least 3.500- 4.500 new patients enter the registry per year.

Data privacy:

The rules of the GDPR have been fully implemented.

Informed consent form and its validity for registry-based studies (or need for re-consent): All the patients sign an informed consent form (or their parents in case of pediatric patients). The form includes information about registry-based studies, therefore there is no need for re-consent.

Funding:

Funding sources and impact on short, long-term sustainability and possible conflicts of interest for a specific registry-based study

The core operational costs of RISM are principally funded by the Italian Multiple Sclerosis Foundation, which leads RISM in collaboration with the University of Bari Aldo Moro. In addition, there is funding for project-based research that is funded by public grants, private foundations, legacies and the pharmaceutical industry.

2.5. SMSreg (Neuroreg):

2.5.1. Origin of the registry:

First launched as the Swedish MS registry in 2001 in a collaboration between university neurology clinics with a joint clinical and scientific interest. From 2011 a sub registry, now one of eleven, of the Swedish Neuro registries national quality registry (www.neuroreg.se).

2.5.2. Purposes:

As SMSreg is a recognized *national quality registry*, data are primarily collected to be used to assure quality of and to improve MS care. A clinical IT data collection platform called COMPOS-DS is designed as a decision support tool which provides direct clinical utility and is used by contributing centers to collect structured clinical data, with the usefulness as the key motivating property for clinicians. From each participating center's database, and for each informed patient, each morning an updated data set is exported to a centralized database domain which constitutes the SMSreg qulity registry. From there data can be exported for secondary use in research projects pending ethics approval.

2.5.3. Registry population:

Data from patients with an MS diagnosis who have been informed and not declined (by the optout principle) of their data exported to the SMSreg database. All neurology clinics caring for MS patients in Sweden contribute data and we estimate a coverage of at least 85 % of the prevalent MS population. We are currently assessing the demographics of MS patients that are not included in SMSreg. Reasons for loss to follow-up from patients in SMSreg are not wanting to remain in the registry, or emigration abroad. The total number of registered cases is currently 23,700 (2025).

2.5.4. Data elements/Metadata list

Data elements:

The core data set covers:
· Patients characteristics: identification with personal number (a unique person identifier, available for all people in Sweden), date of onset and diagnosis
· Tests: MRI, CSF
· Treatments: ID, dates
· MS attacks or relapses
· Symptoms and severity
· Paraclinical tests: MRI
· Pregnancies (mainly obtained through linkage with the National Pregnancy and Delivery registry with the Board of Health and Welfare).
· Adverse events: SAEs and unexpected AEs are captured according to principles of pharmacovigilance. These are part of the core dataset. However, recently we have established a methodology to improve capture of SAEs by linking to the National Patient Registry with the Board of Health and Welfare, and this is from now on the principal SAE identification method for the SMSreg.
· Workability

Please refer to the following appendix for further information on the core data set: Appendix 3 "Hillert et al publication" and Appendix 4 “SMSreg_Variable list”

Standard dictionary:

Data dictionary, Variable list and Case Report Form are available. Core data definitions adhere to internationally established definitions used in clinical trials in MS.

Please refer to the following for the variables list:
https://www.neuroreg.se/en/multipel-skleros/om/
https://www.neuroreg.se/media/dq4pkpje/variabelf%C3%B6rteckning-ms.pdf and Appendix 4 "Variable list"
Please refer to the following for the Case Report Form: Appendix 5 "Form"
Please refer to the following for the Data Dictionary: Appendix 6 "Data dictionary"

Terminology:

Standards and terminologies are available.
MedDRA is used for classification of SAEs.
EDSS, a disability score, is used as a major neurological outcome measure. This adheres to internationally established definitions used in clinical trials on MS.

Lag times:

Data are entered by health care professionals and typically directly in conjunction with a clinical event such as a visit. The SMSreg database is updated every morning and immediately accessible. Information on SAEs and pregnancies obtained by linkage is updated periodically as specified by the respective PASS and display variable lag time depending of the linked data source.

Further considerations:

It is possible to amend variables and the process includes approval by the SMSreg board. As an example, a Covid-19 data collection module was expediently added already in March 2020.

Linkage information

SMSreg data can be linked to national statistical and health care data bases using the unique person identity number. This entails demographics, socioeconomics, co-morbidities including cancers, prescription data, pregnancies and births and a multigenerational database to construct family trees. Linking may take some time and databases have different update frequencies.

2.5.5. IT infrastructure

We use the COMPOS DS web-based platform provided by Omda Inc., for our data capture, please see https://omda.com/solutions/health-analytics/omda-compos/. COMPOS DS is a clinical documentation system and is designed as a decision support tool of value for the clinical situation and provides an overview of the most important information about the patient, including the MSrelevant medical history such as current and previous DMTs, relapses, EDSS, MRI results etc. Originally, COMPOS-DS was considered as the registry platform and was developed in a collaboration between the company and the SMSreg team, but for legal reasons COMPOS-DS has recently been formally separated from the SMSreg itself and is now a clinical documentation system provided by Omda on a contract with each health care provider. From COMPOS-DS, data
from all contributing centers, with the exception of the few patients who have declined participation in the SMSreg registry, are merged in the SMSreg database.

The clinical usefulness of the patient case summary motivates the clinician to assess the COMPOS-DS information at each visit and enter new information, which is done instantly over the web. The data domain used in the clinical routine belongs to the clinical department and for patients who have agreed, new data are transferred every morning to the SMSreg domain, providing close to real-time information to SMSreg. According to national guidelines, visits should be registered at least annually. In addition, patients can report patient reported outcomes (PROMS) using distant secure log-in, which they are encouraged to do before each clinical visit. The PROM data are then reviewed and accepted by the clinician and imported into the clinical server domain and early next morning transferred to SMSreg.

SMSreg data managers have access to an SQL database mirroring the SMSreg domain server from which they may do exports of data for analysis and from which daily back-ups are performed.

2.5.6. Data processing

Roles and responsibilities:

The COMPOS-DS system, SMSreg domain server and SQL database are managed by Omda. Entry into the COMPOS-DS system is performed by health care professionals in neurology departments and as COMPOS-DS is a CE-marked certified medical device,

heads of departments are responsible for the education and training of staff using the software.
SMSreg data managers access the SQL database and export and manage data within a secure IT system at Karolinska Institutet.

Participating health care professionals can access information on patients in their own clinical unit. Only data managers and two registry coordinators have access to all data in the registry.

Established processes:

Patients are informed upon inclusion in SMSreg. Participation in SMSreg is based on "opt-out".

Data for SMSreg is provided by all 60 neurology clinics in Sweden. Contribution of data by neurologists / nurses is voluntary but encouraged by federal authorities, professional organization and heads of departments.

In addition, patients can report patient reported outcomes through the Patient Portal which contains around 20 questionnaire including health related quality of life instruments.

SMSreg officials perform periodic reviews of SMSreg data against clinical records.

Patient level data can be shared with a research party pending ethics board approval. Normally, this will be anonymized, but exceptions are possible if well motivated and IRB approved.

Patients can obtain an excerpt of their registry data from the SMSreg office.

Degree of automation:

Data is collected using COMPOS-DS software, with almost exclusively drop-down menus with only occasional open text boxes. No data are currently being automatically transferred to the registry but efforts to this end are ongoing, starting with the import of laboratory data. For many years, until 2021, test results on antibodies against MS treatments (interferons and natalizumab) were entered automatically into SMSreg.

2.5.7. Quality Management activities

Supportive scientific and technical functions:

The COMPOS-DS is a CE-certified medical device with an detailed quality handbook compiled and regularly updated. For details see https://omda.com/solutions/health-analytics/omda-compos/ .

Data entry into the SMSreg web interface is almost always done by ticking alternatives or boxes with very few open text boxes. Numbers are constrained to reasonable values. A number of variables, typically dates, are connected by logical conditions. Almost 50 such checks and blocks have been implemented to date. See Appendix 10 "SMSreg_QA_QC processes"

Back-ups are made daily and saved for reproducibility and traceability. Systems are in place to verify data upon entry to ensure avoidance of double entries of patients and

errors of dates and numbers. There is an ongoing effort to develop the data verification system further.

The applicant requesting data for research will submit an application and if approved data will be extracted from SMSreg by the data manager and sent to the location indicated in the application.
Data may only be extracted on the basis of research within health care or statistics.

Data security:

Within the COMPOS-DS system, data are handled in a highly professional and secure IT infrastructure provided by Omda Health Analytics. Data access and changes are logged.

Once data have been exported to the academic domain for cleaning, further analysis and distribution, it is handled within the secure IT environment of the Karolinska Institutet which allows sensitive data to be stored. Here, back-ups are made daily and saved for reproducibility and traceability.

Assurance of qualifications:

Data are entered into the COMPOS-DS system as part of clinical care by health care professionals. Heads of departments are responsible for the training of staff according to national and local requirements as the systems serve as decision support tool.

Data quality checks:

Participating centers have access to automated graphic functions on the registry homepage displaying data completeness in relation to coverage of the estimated background population updated in real-time.

Participating centers have access to automated tables, graphs and lists displaying missingness of data to enable completion of data.

When a patient record is opened, a control is run for completeness or key variables and the care giver is notified.

Quality assessments are performed as part of ongoing PASS.

Audits:

The COMPOS-DS is a CE-certified medical device, provided by Omda Health Analytics. with a detailed quality handbook compiled and regularly updated. For details see https://omda.com/solutions/health-analytics/omda-compos/. COMPOS-DS may be subject to audits as a medical device and is currently seeking certification according to the Medical Device Regulation. The current certification is under the MDD regulation.

Auditing procedures have been agreed as part of ongoing PASS.

SMSreg is formally organized under the auspices of the Karolinska University Hospital who has the legal responsibility of how the personal information is being dealt with. Since most clinical units in Sweden belong to the 20 regions outside of the Stockholm region, the Karolinska has no access to primary data from health care documentation. Thus, the Hospital can audit the activities including data storage and handling of the data

until it is formally exported. The Karolinska itself can be audited by the MPA as well as by the NBHW (Annexes 1-6).

The data management has for historical reasons been delegated to the Karolinska Institute (KI), a state university. The activities within KI is subject to internal audits as well as from the national university audit authority UHÄ and occasionally by Riksrevisionsverket.

2.5.8. Characterisation of the registry data quality

The COMPOS-DS system provides a number of automated and interactive tools to assess data completeness/missingness, which can be displayed at a national, regional or local level.

Since data in COMPOS-DS are used in the clinical situation errors are repeatedly assessed by clinicians and therefore prone to get corrected and complemented.

A large validation study of SMSreg data against medical records was published in 2019 (Alping et al, 2019)

A validation study of all MS patients in the county of Värmland confirmed an MS diagnosis in all patients included in the SMSreg (Teljas et al, 2021)

Contributing centers are irregularly monitored by the SMSreg office in order to assess correctness and completeness of registry data against medical records in random samples. In the past decade, not a single patient has been identified with an incorrect MS diagnosis, arguing for a high diagnostic accuracy. We believe the reason is that the COMPOS-DS data are used clinically.

2.5.9. Governance

Governance structure

The SMSreg is a part registry of The Swedish Neuroregister (SNR), a national *quality registry* consisting of 11 part registries covering most diagnostic groups within clinical neurology (with the exemption of stroke), and is thereby subject to the national legislation Patientdatalagen (PDL) (Patient Data Act) in which Chapter 7 specifies that clinical data may be shared between more than one care giver by creating a quality register. There are about 150 such quality registers in Sweden. PDL states that each quality registry is governed by a health care authority which in this case is the board of the Karolinska University Hospital, which is thus responsible for the data protection of clinical information collected in the registry. Karolinska, in turn, has delegated the management of the SNR to a Registry Holder (RH), presently dr Katharina Fink, a neurologist and researcher at Karolinska. According to the guidelines for quality registers, the RH should manage and develop the registry together with a Registry Board (RB), which should represent all parts of Sweden and different health care professions. There are two patient representatives on the RB. According to the by-laws of SNR, each part registry, including SMSreg, has its own part registry chairperson and a part registry board (pRB) representing parts of the country and different professions as well as two patient representatives. Dr Fink is also the chair of the SMSreg pRB.

Governance for adding or changing variables

Changes of content of a part registry, including variables, is proposed to and accepted by the part registry board and subsequently formally accepted by the RH after agreement from the RB. In a highly motivating situation this can be done swiftly, as in the beginning of the COVID-19 pandemic where a COVID-19 module was designed and implemented in less than 2 weeks and data collection enabled already in March 2020.

Governance for collaboration

Researchers can apply for access to SMSreg data by using a formal application procedure after first having obtained an approval from the Swedish Ethical Review Authority. Complete applications are then reviewed by the SMSreg's Research Review Committee which provides a recommendation. Finally, a decision on sharing registry data for research is made by the RH on delegation from the Board of the Karolinska Hospital. Thus, a positive decision can be taken by the RH whereas a negative decision needs to be escalated to the Karolinska Board.

After applying for data access, researchers typically receive a decision within 4-6 weeks and anonymized data is then delivered within a few weeks. In case registry data are to be linked to other data sources such as health data bases with the National Board of Health and Welfare or Statistics Sweden, the turnaround time is prolonged by 2-3 months before a linked anonymized data set can be delivered.

Documentation of governance

- Publicly available documentation (with website) of key registry characteristics: https://www.neuroreg.se/multipel-skleros/

- Single contact point for information: info@neuroreg.se

Publicly available policy for collaborations with external organisations: https://neuroreg.se/forskning/datauttag-for-forskningsandamal/

Patient population covered

We aim to include all patients with an MS diagnosis in Sweden. We have together with the Board of Health and Welfare jointly estimated the coverage of SMSreg to 85 % of prevalent MS patients. Those missing tend to be older and living in distant areas. Efforts are ongoing to increase coverage further. In addition, we have reasons to believe that the prevalence of MS, based on the National Patient Registry (NPR) is overestimated as some patients erroneously get MS diagnoses during the diagnostic work-up, diagnosis that then remain in the NPR. In the Värmland county, 4 % of NPR-defined MS-patients did not have MS according to the current medical records. Thus, the coverage is likely be as high as 90 %.

Data privacy:

Status of implementation of GDPR: Implemented
Informed consent form and its validity for registry-based studies (or need for re-consent): According to Swedish regulations for national quality registers, signed informed consent is not required, whereas patients are to be informed upon inclusion in SMSreg. Participation in SMSreg is based on "opt-out". The responsible clinician is required to certify that information has been given.

Funding:

Funding sources and impact on short, long-term sustainability and possible conflicts of interest for a specific registry-based study:

The SMSreg has been initiated and developed based on almost exclusively public funding through a national quality registry program. In recent years up to 20 % of additional funding has been obtained through fees in commercially sponsored research.

2.6 MSBase:

2.6.1 Origin of the registry:

The MSBase Foundation Ltd is a not-for-profit charitable organisation incorporated as a company in Australia. The Foundation is governed by a Board of Directors who are responsible for the oversight of the charity. The Board also integrates and prioritises the scientific initiatives as determined by the Scientific Leadership Group (SLG).

The Board is led by the Chair, Prof Thomas Leist. A copy of the MSBase Foundation Constitution is available here

In collaboration with participating neurologists, the MSBase Foundation has established a unique, web-based platform, The MSBase Registry, which is dedicated to sharing, tracking and evaluating outcomes data in Multiple Sclerosis and other Central Nervous System demyelinating diseases.

In particular, the MSBase Foundation aims to advance collaborative epidemiological and outcomes research by providing a freely accessible resource to combine, compare and analyse large datasets, for the benefit of people with Multiple Sclerosis.

2.6.2 Purposes:

The MSBase Foundation's mission is to provide collaborative database tools and research support enabling worldwide collaborative outcomes and epidemiologic research for the benefit of people with multiple sclerosis and other neuro-immunological diseases. The registry was launched in 2004

The purpose of the data collection system is to advance Investigator/initiated multi-centre/multinational, epidemiological and outcomes research by utilising a uniform, physician-defined, minimum dataset and a web-based Registry (www.msbase.org) to

systematically collect, combine, compare and analyse highly codified demographic and medical data from consented patients with multiple sclerosis and other neuroimmunological diseases (NIDs) such as neuromyelitis optica (NMO), anti-MOG antibody syndromes, and myasthenia gravis (MG).

2.6.3 Registry population:

MSBase is a registry of patients diagnosed with MS and other neuroimmunological diseases
(NIDs). The global cohort collects observational data from consenting patients during routine clinical practice for as long as the MSBase PI treats the patient and uploads the anonymized data to the registry.

2.6.4 Data elements/Metadata list

Data elements:

The core data set covers:
· Patients characteristics: sex, birth, date of onset
· Disease characteristics: KFS, EDSS
· Tests: MRI, CSF, laboratory tests
· Relapses: Date, CNS region, corticosteroids
· Treatments: ID, dates

Adverse events are not captured at the registry level, this would be driven by a sub-study.

Please refer to the following appendices for further information on the core data set: Appendix 7 "Minimum Dataset"

Standard dictionary:

Please refer to the following for the data dictionary: Appendix 5 "MDS Data Dictionary" and Appendix 6 "iMed Data Dictionary"

Please refer to the following for the minimum data set: Appendix 7 "Minimum Dataset"

Terminology:

MedDRA for classification of Serious Adverse Events (MDS only), EUROCAT used for pregnancy terms and EDSS as major neurological outcome measure.

Further considerations:

Capability to amend data elements is possible but requires approval by the MSBase Board. There is currently no plan to amend the core minimum dataset for people with MS. Recent examples of new data elements have included pregnancy pages (including EUROCAT definitions for adverse outcomes) and specific COVID-19 data collection.

Amendments to the data collection form are received and reviewed by the Executive Management Team for suitability. Minor revisions are approved internally. Significant

changes, such as a complete overhaul of a data entry field, form, or data dictionary, require approval at both the MSBase Board and SLG level. Following approval, the amendments are reviewed for impact and technical feasibility by the Head of Product and the Head of Technology. The data collection form is then adapted and submitted for coding to our IT partner. Minor amendments/changes, from submission to implementation takes approximately 6 weeks to 3 months. Major redevelopments and changes can take 6-12 months to implement.

Linkage information

Currently, linkage is available for national sub-studies performed by investigators, however, there is no data linkage available to administrative or other health databases. As an example, the Australian cervical cancer screening registry has been linked to Australian centres MSBase data.

2.6.5 IT-infrastructure

Data is collected by using two main systems; iMed and the MSBase Data entry Software (MDS), both owned by MSBase. iMed was launched in 2000 and is used by the majority of MSBase centres as a trusted and reliable system for capturing, storing and managing MS patient data. Data can be uploaded to the Registry via manual export, and in recent version, via direct push (sync). MDS was launched in late 2017 and is the new MSBase flagship application for data entry. MDS is substantially similar to iMed but is a modernized data collection tool with more advanced features and functionalities, such as improved data quality through built-in validation checks and built-in MedDRA terminology. Data from consenting patients are uploaded to the Registry using seamless integration via Synchronisation mechanism. It is the choice of the investigator to sync data to the Registry in real time or intermittently. Data is entered by clinicians and neurologists in real time during clinical visits and queries can be reconciled by monthly registry archive and export, after being sent to Principal Investigators.

2.6.6 Data processing

Roles and responsibilities:

Data is collected from patients during routine clinical care and is entered into the chosen data collection software by neurologists and/or members of their health care team. MSBase has members in over 43 countries.

Established processes:

As long as the PIs patients have provided explicit informed consent, all patients with MS or other relevant NIDs can be selected and enrolled to the registry.
We require all participating centers to sign our governance documents including full implementation of GDPR rules and we do explicitly require consent from every data subject.

Degree of automation:

Data quality is also improved by creating a data entry system called ‘data entry wizard’ which sequentially guides the data entry staff to each required visit field. No automated import of data is implemented.

2.6.7 Quality Management activities

Supportive scientific and technical function:

The MSBase SLG sets the scientific direction by developing a strategic plan, which is built with input from MSBase members and Board of Directors. MSBase has an internal Data Manager and an experienced statistician to support scientific collaboration. Technical function is supported by an internal MSBase IT Project Manager and external IT partners Kiandra (Australia based) and ProSynergie (Swiss based).

Data security:

Data is stored and backed up in the the South-Eastern Australian Azure data centre (Azure cloud). This is a SQL database with real-time encryption and decryption, associated backups, and transaction log files at rest enabled. It meets regulatory compliances such as ISO/IEC 27001 & FedRAMP/FISMA, SOC and PCI DSS. Local information of each participating center Individual centre is stored on their hospital network and then the pseudonymised patient data is synced to the MSBase Registry.

Assurance of qualifications:

Data are entered into the iMED and MDS systems as part of clinical care by health care professionals. Heads of departments are responsible for the training of staff according to national and local requirements as the systems serve as decision support tool.

In addition, MSBase requires contributing centers to provide evidence of staff being certified to perform EDSS using the Neurostatus platform, which should be repeated on a 3 yearly basis.

Data quality checks;

In MSBase, quality control checks exist in both MDS and iMed data entry systems as well as extra validation checks built into the registry as part of the ETL process to further sanitise the data. For instance, only valid treatments have been created as options for selection. A separated list of Sanity checks is not available for MSBase; however, MDS and iMed data dictionaries contain all the sanity check information. Please refer to Appendix 5 "MDS data dictionary" and Appendix 6 "iMed data dictionary".

We have a Data Quality Committee dedicated to monitoring and improving data quality within the registry. We have built algorithms for classifying data quality and have implemented a data quality feedback system.

Audits:

In MSBase, the current audit capacity is limited to comparing monthly full data extracts to each other. However, in 2021 MSBase launched an audit trail in it is data entry system

that can be accessed at the centre level. Furthermore, MSBase is comparing core data quality measures such as visit density and visit completeness between centres. Commercial partners can audit relevant MSbase data onsite. The data entry system MDS runs a site-visible audit file. This is not uploaded to MSBase but can be accessed via sites if required by regulatory or other entities. Regarding a data integrity audit at the site level, this is possible but needs to be performed at each site as MSBase only stores de-identified data.

Auditing of the completeness of the minimum dataset is suggested to all member sites but not enforced or audited. r\recoding of safety data includes important negatives recorded at each visit, for example: did the patient have a cancer diagnosed since the last visit, Y/N? These responses are evaluated and audited for classification of data completeness and queried with investigators.

2.6.8. Characterisation of the registry data quality

The following processes are in place in terms of quality:
· MBase has a Data Quality Committee dedicated to monitoring and improving data quality within the registry. The Data Quality Committee meets ad-hoc. Administration performs a quarterly data quality report. Data quality indicators are also available for use by statisticians if they wish to restrict their analyses to centres achieving a pre-specified quality level.
· MSBase has built algorithms for classifying data quality and have implemented a data quality feedback system. Data quality indicators are already used in some analyses as part of data selection.
As an example, please refer to

https://journals.sagepub.com/doi/full/10.1177/1352458516662728?journalCode=msja%E2%80%93+publication+by+Tomas+Kalincik+et+al%2C+%E2%80%98Data+quality+evaluation+for+observational+multiple+sclerosis+registries

2.6.9. Governance

Governance for collaboration

- Publicly available documentation (with website) of key registry characteristics: www.msbase.org – publicly available information regarding the MSBase Scientific Leadership Group (SLG) and Board of Directors, headline statistics, publications list.
https://journals.sagepub.com/doi/10.1177/1352458506070775
MSBase: an international, online registry and platform for collaborative outcomes research in multiple sclerosis

- Single contact point for information: info@msbase.org , Charlotte Sartori/Eloise Hinson.

Publicly available policy for collaborations with external organisations:
Data sharing is handled as part of our standard data requests. Investigators and the MSBase Scientific Leadership Group (SLG) can request data for analyses and this can be

collaborative. A specific policy is not publicly available however the request form is available and can be located on our website: About us > Documents and resources. GDPR data sharing agreements can be executed by the Foundation on behalf of the investigator.

Governance structure for decision-making on requests for collaboration:
The SLG has appointed a Research Committee who are responsible for approving all analyses, including collaborative requests.
The MSBase Registry is owned and operated by the MSBase Foundation, which is a not-for-profit organisation registered in Australia. An appointed Board of Directors governs the MSBase Foundation, responsible for ensuring compliance with legal and regulatory requirements, managing risk, developing strategy, establishing policies, and evaluating performance. The scientific aspects of the MSBase registry are managed by an elected Scientific Leadership Group (SLG), comprising principal investigators, MS specialists, and nurses. There are currently no patients with MS in any of the Governance Groups. The SLG provides scientific assistance to the Foundation with respect to the use and maintenance of the Foundation's web-based Registry platform; makes recommendations to the Foundation with respect to financing of projects that promote the objects of the Foundation; manages the MSBase Registry and acts as custodian of the data in the database. The SLG is a self-constituting entity, subject to the SLG Regulations, Observational Plan and any other requirements of the Foundation.

Governance structure:
Request for data access/collaboration is submitted to the MSBase Operations team who completes an initial feasibility review. The request is then sent to the SLG Research Committee who review the scientific quality of the request. Once approved, all MSBase Principal Investigators (PIs) are contacted for a two week opt out period whereby they can request their data to be excluded from the analysis if they wish. After this time, study collaborators must sign a data use agreement and can be sent the compiled dataset for analysis.

Centre PIs, and the SLG, can request to receive MSBase Registry patient data and perform analyses on the entire Registry dataset or Registry data subsets using a Data Request Form specified by the SLG. Data Request Forms define the aim of the request, provide an analysis plan, state the identity of all proposed data handlers, the data variables required and the Co-authorship Policy. All approved data requests include a guarantee from the Centre that shared data will be destroyed after an appropriate period (typically after a manuscript is published).
Data Request Forms are initially submitted to the MSBase Operations Team for feasibility assessment. If feasible, they are submitted to the SLG for review and approval.
After SLG approval, a permission request is sent, along with the data request and project proposal, to all Centre PIs. Each Centre, through its PI, may opt out of any data request or provide review and comment. The MSBase Statistician will then collate the dataset with the required data variables and exclude data from Centres opting out of the analysis. The statistician then sends the cleaned, encrypted dataset to the requesting Centre PI. Research is conducted by the requesting Centre, in the interest of all involved Centres. This process takes approximately 6 weeks.

Patient population covered

Number of patients: 110,348 from 188 clinics in over 43 countries (Annexes 1-6).
Spain, Australia, Turkey, Ukraine, Iran, United kingdom, Tunisia, Canada, New Zealand, Croatia, Hungary, Slovenia, Kuwait, Italy, Mexico, Colombia, United States, Netherlands, Malta, Lebanon, Greece, Czech Republic, Belgium, Estonia, Egypt, Moldova, United Arab Emirates, Oman, Israel, Saudi Arabia, Latvia, Brazil, Japan, Jordan, India, Argentina, Switzerland, China, Cuba, Germany, Denmark, France, Guatemala, Ireland, Macedonia, Malaysia, Nigeria, Poland, Portugal. Romania, Taiwan, Republic of China

MSBase has members in over 43 countries and in general lacks a meaningful population base. As long as the PIs patients have provided explicit informed consent, all patients with MS or other relevant NIDs can be selected and enrolled to the registry.

Data privacy:

Status of implementation of GDPR:
MSBase has been certified as GDPR compliant and acts as either a data processor or joint controller depending on circumstance.

Refer to attached document: Appendix 3- Introduction to the MSBase governance package. Complete governance documentation can be provided on request.

Informed consent form and its validity for registry-based studies (or need for re-consent): The current MSBase template Participant Information and Consent Form is under review. The revised version can be supplied on request, when available.

PICF allows registry-based studies and external collaborations limited to the approved dataset to proceed without re-consent. If variables outside the approved dataset are required, additional consent must be sought.

Funding:

• Funding sources and impact on short, long-term sustainability and possible conflicts of interest for a specific registry-based study:
The operational costs of MSBase are funded by multiple commercial partners through medium term sponsorship agreements and project collaborations with the pharmaceutical industry. MSBase has been operating for 20 years with proven long-term sustainability through ongoing, long-standing relationships with key pharmaceutical partners. MSBase operations have no personal financial relationships with any commercial sponsor; there are no conflicts of interest for registry-based studies.

2.7 BigMSData Network (BMSD):

2.7.1. Origin of the registry and background:

The Big Multiple Sclerosis Data Network (BMSD) was initiated in 2014 and made possible by an initial grant from Biogen Idec. BMSD consists of the national MS registries of the Czech Republic, Denmark, France, Italy and Sweden as well as the international MSBase.

2.7.2. Purposes:

To propagate MS research and development of MS care.
To benefit patient advocacy and to promote new MS registries.
To actively promote the standardization of definitions and procedures in MS RWE research, including PASS.

2.7.3. Registry population:

BMSD is not a registry itself but builds on data from contributing registries of which most are population based, i.e. national registries, but not necessarily so, i.e. MSBase.

2.7.4. Data elements/Metadata list

Data elements:

BMSD has adopted a common variable list, as part of its common data model. Please see the CMDM document for further information.

Standard dictionary:

BMSD has adopted a common dictionary, as part of its common data model. Please see the CMDM document for further information and information for each registry above.

Terminology:

The BMSD common data model uses MedDRA coding for adverse events. However, as explained in the Feasibility Study, the Swedish and Danish registries obtain their AE information from linkage with their respective national patient registries which code in ICD-10. Therefore, ICD-10 codes are translated into MedDRA coding applying the OHDSI methodology.

Lag times:

BMSD is not a database in itself, but builds on a collaboration and co-ordinated analysis of participating MS registries.

Further considerations:

BMSD can agree on the inclusion of new variables to be collected by the respective registries, changes that subsequently need to be adopted by the respective registry governance rules.
Examples for this is the inclusion of adverse event questions where the four categories

"malignancies", "non-melanoma skin cancers", "treatment related infections" and "other adverse events" were included in the data collection forms of all BMSD registries in 2017 after a joint initiative.

2.7.5 IT infrastructure

BMSD relies on the respective IT infrastructures of contributing registries.

In most studies so far, projects have applied meta-analyses where no actual patient level data has been shared. In a set of three completed studies, BMSD registries *were* able to share actual patient level data which was merged into a single data set. In these projects, the Italian and Swedish registries and MSBase respectively managed data in their respective IT domains.

Presently we are in the process of establishing a federated approach which will allow us to jointly run statistical analyses such as logistic regression, propensity score matching and weighing and Cox regression in a federated learning fashion without sharing actual data. Early results of a logistic regression analysis have shown that this is technically possible and we have recently been able to calculate propensity score weights across four different registries in a federated learning fashion using iterated calculations of beta estimates Next, we will expand the development of regression models for comparison of treatment arms, and aim for first results before the end of the year. Thus, the need of a centralized IT structure is diminished.

2.7.6. Data processing

Roles and responsibilities:

When there is an interest from industry or regulatory parties to perform PASS analyses based on combined patient level data sets from different registries, this will need to be agreed by the governance of BMSD as well as of the involved individual registries.

So far, each new PASS has defined its own common data model (CDM) adapted to the specific needs of that project. However, ROCHE's ongoing PASS "MANUSCRIPT" based its CDM on the BMSD Core PASS protocol.

Recently, BMSD has developed a CDM including a joint data dictionary to facilitate joint analysis and to set a standard for future BMSD collaborations. Scripts are in place to convert data sets from each of the six registries into the BMSD CDM. The script provides a report on the success of conversion and a validation analysis of data completeness and consistency. The CDM will be the subject of a coming publication. A document describing the BMSD CDM is appended to this application.

Thus, the BMSD will greatly facilitate joint analysis of data, whether a meta-analytical or a federated approach will be taken. For each study, a co-ordinating center/MAH/CRO will develop and distribute a statistical analysis plan and typically common scripts to be run on data sets converted into the BMSD CDM. Results are then compiled by the co-ordinating center/MAH/CRO.

Accordingly BMSD aims to influence the PASS process into a more standardized manner which will simplify for the registries, MHAs and regulators. A first example is that Roche included the BMSD Core Protocol on as a reference for the design of the

ongoing European PASS on Ocrelizumab named MANUSCRIPT (BA39730, EUPAS28619).

The status of MAH in ongoing and future PASS is regulated as contractually agreed for the individual study and registry. The conditions applied for an MAH to fulfill pharmacovigilance requirements for collection and reporting of safety events will be specified in the respective agreements.

It is important to note that a BMSD PASS is not intended to replace routine reporting of unexpected or serious adverse events to national MPAs, given that MS Registries are always voluntary for patients as well as for clinicians and cannot guarantee a full coverage of the target patient population.

Established processes:

The current order as how to manage requests for safety studies is that the MAH approaches individual registries and the requests for a federated analysis of a datasets will be handled by the BMSD coordinating center and agreed by the BMSD Scientific Steering Committee. All registries decide individually whether to participate in a specific PASS. BMSD is prepared to take full responsibility for orchestrating a PASS or can collaborate with an MHA/CRO for the coordination. Aggregated results will be shared with the sponsor and regulatory organizations as agreed.

Degree of automation:

Not relevant as BMSD is not a database.

2.7.7. Quality Management activities

Supportive scientific and technical functions:

As described above, the development of a the BMSD Core PASS Protocol, the BMSD CDM and the federated analysis procedures being developed will constitute the basis for a standardized methodology for PASS in MS.

BMSD meetings regularly address analytical methods and the BMSD statistical analysis committee is consulted in matters related to statistical analysis. This committee includes statisticians from each of the participating MS registries, The statistical analysis committee has recurrent virtual meetings and has organized workshops in Bari in 2019 and 2023 with a third workshop planned for September 2025.

Data security:

Not relevant as BMSD is not a database.

Assurance of qualifications:

Qualification of staff for data entry is not a responsibility of BMSD but is encouraged.

Data quality checks:

As described elsewhere, the BMSD CDM package of scripts provide not only data sets for coordinated or joint analysis but also a quality assurance in terms of data compatibility, consistency and completeness. The experience so far is that local registry data formats can readily be converted into the BMSD CDM and that data density is excellent in patient groups representative of those potentially included in a PASS (see BMSD Core protocol).

Data quality determinants, dimensions and measures are discussed in the core protocol.

Audits:

Access to information on registry data for the purpose of audits has been regulated as part of PASS agreements already in place and such agreements will likely also in the future best be regulated at a local level with the individual registries. The details of agreed audit conditions in existing PASS typically will involve study quality supervision including compliance with protective measures, security of computers, servers and other IT equipment and adherence with applicable data protection laws. Further information on quality control per registry is presented in annexes 1-6 as part of the "EMA Appendix 2 Checklist". It is relevant to note that neither BMSD nor the respective registries have the option of source document (i.e. medical records) verification as such documents are not available to the registries. Importantly, still crude registry data are available for audit.

2.7.8 Characterisation of the registry data quality

We have applied the BMSD CDM and performed a quality check on a presumed patient population representative of those potentially eligible for PASS. The results are shown in Table 2 below and indicate the high level of information on some key variables.

Table 2. Patients seen & treated during the past 36 months as of December, 2024

	SMSreg	DMSR	ReMuS	OFSEP	RISM	MSBase
N	11176	10903	17093	25597	34232	40790
Female %	69.1 %	68.8 %	70.5 %	72.2 %	66.9 %	71.0 %
Mean age (SD)	46.7 (11.8)	47.9 (11.8)	45.5 (11.2)	46.6 (12.1)	47.3 (12.35)	46.0 (12.2)
Documented age	99.9 %	100.0 %	100.0 %	100.0 %	100 %	100.0 %
Documented sex	100.0 %	100.0 %	100.0 %	100.0 %	100 %	100.0 %
Documented MS onset date	98.0 %	100.0 %	100.0 %	100.0 %	98.3 %	98.5%
Documented diagnosis date	97.8 %	99.2 %	84.1 %	83.2 %	96.3 %	77.0%
Documented MS course	99.7 %	100.0 %	98.8 %	100 %	95.3 %	96.1 %
Ever recorded relapses	60.1 %	77.8 %	98.6 %	100 %	79.2 %	80.8 %
>= one MRI	93.3 %	99.5 %	75.1 %	97.5 %	93.1 %	87.2 %
>= two MRI	88.9 %	97.3 %	68.0 %	95.7 %	90.9 %	75.7 %
>= one EDSS	94.9 %	99.9 %	100.0 %	100.0 %	100 %	98.9 %

2.7.9. Governance

Governance for collaboration

• Publicly available documentation (with website) of key registry characteristics:

https://bigmsdata.org/

• Single contact point for information:

https://bigmsdata.org/contact/

Publicly available policy for collaborations with external organisations:
https://bigmsdata.org/

Governance structure for decision-making on requests for collaboration:
https://bigmsdata.org/

Patient population covered

The total number of multiple sclerosis (MS) patients in BMSD amounts to over 350,000 of which around 140,000 can be regarded as relevant for inclusion in safety studies in being actively followed and currently on treatment (see the table above).

Data privacy:

Not relevant as BMSD is not a database and does not itself deal with private information.

Funding:

BMSD receives support from sponsoring pharma for coordination costs which includes keeping an office with project management, support for annual meetings and periodic workshops. Each scientific study on BMSD data requires independent funding.

3 Use of registry data to support regulatory assessment and regulatory decision making

3.1 Follow-up of previous advice

Karolinska Institutet requested in 2021 a Qualification Advice for performing registry-based post authorisation safety studies (PASS) for the Big MS Data network (BMSD) including its six participating MS registries. In May 2021, the SAWP agreed on the advice to be given to the Applicant and in the same month the CHMP adopted the advice to be given to the Applicant.

We now believe that the advice has been followed in all relevant aspects and that our application dossier includes all necessary data to allow the EMA to make a renewed

assessment. We refer in parts to the appended documents including an updated **Request Tool** document, an updated **Core Protocol for PASS**, a document describing results of a **Safety Feasibility Study** showing the ability of all registries to collect safety information and a report on our now completed **Common Data Model (CDM).**

In brief, the main points remaining to be shown according to the issued letter of support were:

1) A completed CDM, and an adoption of data quality assessment routines.
2) A formal feasibility study to show fitness-for-purpose and a comparison of SAE frequencies between registries.
3) A report of overall numbers on the actual recording of patient characteristics (aside from SAEs)

As a response to this advice, we would like to state the following:

1. CDM and data quality assessment:

   The BMSD has adopted a common data model. The CDM builds on a common dictionary containing all data items deemed necessary for a PASS. The CDM contains scripts for the translation from each of the registry data formats into the CDM also providing a report of the success of translation. The appendix shows successful translation from all formats with a 100 % success rate of translation. The CDM package also contains a data validation script to be applied on translated data sets resulting in a detailed report on data accuracy and completeness.

2. Feasibility study:

   Since 2021, all BMSD registries have been participating in formal PASS projects of which all have already submitted interim reports to the EMA (The MANUSCRIPT study on Ocrevus, ROCHE and the CLARION study on Mavenclad, Merck).

   As shown in the Feasibility Study appendix, we have compared the incidence rates of classes of SAEs, most importantly infections and malignancies, between the five registries participating in the MANUSCRIPT PASS (Denmark, France, Italy, MSBase and Sweden) and found comparable frequencies of SAEs. In addition, we have used a data set originating from a Sanofi PASS on Lemtrada to compare SAEs between the Czech, Danish and Swedish registries and again found similar levels of SAE incidence.

3. Data density and representativity:

   Together with the high population coverage of the BMSD registries (see the Request Tool and 7.2.1) (less relevant for MSBase) with a comparison of similar high data density for the patients population within each registry relevant for PASS (see Core Protocol, table 3), we believe that we present a strong argument for the BMSD registries to be fit for purpose.

A further aspect of our application in 2021 was the possibility of including new registries in the BMSD. We have now adopted the principle that candidate registries to join BMSD

are required to be capable of converting data into the CDM format and show a validation report at the same level as the existing BMSD registries. In order to show themselves fit-for purpose in the context of a PASS, a comparison of SAE incidences would also be required. It can be noted that the Finnish and German MS registries are independently contributing to ongoing PASS and to submitted interim analyses and should be good candidates. A development of scripts for translation into BMSD CDM is ongoing. We do not however include the Finnish and German MS registries in the current application.

3.2 Relevance and representativeness of data

The BMSD registries are well established MS registries with excellent collections of secondary data on MS patients including clinical and treatment data, together contributing data to over 500 scientific publications. Five are national registries in the Czech Republic, Denmark, France, Italy and Sweden as well as the international MSBase. The coverage of the national registries is generally good (Chapter 1.2, table 1 and the RT document) and the ability to collect data is also fit for purpose as demonstrated in Chapter 2.2 as well as in the appended RT document.

The feasibility study supports that the BMSD registries are all well suited to perform safety studies as they collect clinical and treatment data as well as adverse events (AEs). AEs are either collected by the registries and/or as in some countries (Denmark and Sweden), linkages to national patient registries are already being executed to identify SAEs in the context of ongoing PASS. For details, please see Feasibility Study document.

3.3 Actual ability to collect and report data

All the BMSD registries are also currently participating in various PASS as described in Chapter 1.3 “Regulatory status”. At the time of our previous EMA application, most of the PASS were relatively newly started and the reported results were quite limited. These PASS have since 2021 progressed significantly and much data have satisfactorily been delivered from these studies in interim reports.

Further characteristics on the content of the individual BMSD registries have been described in Chapter 2 above and in the RT document. In addition, we have developed the BMSD PASS core protocol significantly since the previous application and there are now more details on data management and analysis, quality standards as well as details how to define drug exposures in safety studies.

One major improvement on since 2021 has been the advancement of the BMSD common data model (CDM). This has been developed and coordinated primarily by the Czech team and provides a common data dictionary, scripts for conversion into the CDM format and validation and a set of rules how to manage datasets from different sources and create a common framework of transformed and harmonised data. For further details, see the CDM document.

As mentioned previously one of the major concerns from the assessment of the previous application involved data completeness and criteria for data quality for the BMSD collaborations. This has now been further described and detailed in the appended Core Protocol. Furthermore, the R-scripts from the CDM has been successfully run in all the BMSD registries. The testing of the CDM in the registry data was further specified to describe a registry population that would be typical in a PASS (regarding variables such

as age, treatments, disability level, visits to clinics etc) and the results of this is shown as part of the document also describing the CDM.

3.4 Feasibility study

The other principal concern from the evaluation of the 2021 application focussed on the ability of the registries to report SAEs. The BMSD were advised that a PASS feasibility study to demonstrate the registries fit for purpose would be helpful. Especially data availability including confounding and modifying variables as well as quality and completeness of data were requested with an emphasis on providing some assurance on SAE collection by the registries. However, after careful consideration it did not prove practical to perform an independent PASS using data from the registries. The reasons for this were both time and financial restraints as well as challenges related to SAE collections in clinics that primarily collect SAEs as part of commissioned safety studies.

Because of these limitations it was decided that BMSD would use already available PASS data to show that SAEs can be collected by the registries in a reliable manner. The chosen study was the MANUSCRIPT study by Roche where the comparator group includes various treatments and therefore provides a good comparison of SAEs between countries. The results from this Feasibility Study (please see the Feasibility Study Document) show that although there are some differences in the level of reported malignancies and serious infections these are still principally comparable between registries. Furthermore, some of the differences can be explained by different interpretations of the SAE definitions.

The Swedish and Danish MS registries provide mechanisms to link registry data national patient diagnosis cancer registries. As shown in the Feasibility Study, this approach provides SAE incidence rates comparable to the other BMSD registries whereas, in particular the Swedish registry, rates reported directly through the registry are lower. As a consequence, the Swedish MS registry from now on principally reports SAEs based on linked data in ongoing and future PASSs.

3.5 Potential to modify and extend data collection

Use of data from the BMSD registries in the current context is strictly secondary data use. In general, the BMSD as a network has no authority to instruct the registries to change or extend data items to be collected. That said, there have been recent examples when expressed needs from BMSD or other international efforts have indeed led to a coherent change in data collection routines across the BMSD registries highly relevant for safety studies. First, in 2018, all BMSD registries adopted the same principle to explicitly at each data entry ask for four classes of possible AEs: *malignancies*, *non-melanoma skin cancers*, *treatment related infections* and *other AEs*. At the onset of the Covid-19 pandemic in March 2020 a global consensus of how to collect Covid-19-related information was adopted by all BMSD registries. This provided a coordinated and efficient identification of treatment related risks of severe Covid-19 infections where the BMSD registries played important roles.

Accordingly, this shows that well-motivated modifications of data collection can indeed be achieved across the BMSD registries.

The BMSD registries are not engaged in primary collection of pharmacovigilance reports in the respective countries.

3.6 Availability of dates for important events

All BMSD registries are organized along the life-long journey defined by being diagnosed with
MS. Thus, the onset of MS disease is a cornerstone in the registration and is available for 98-100 % in the PASS relevant patient population (see Table 3 of the Core Protocol). Likewise, start of treatment date is mandatory for all BMSD registries (see RT document, Treatment information) and end of treatment is mandatory (four registries) or optional (two registries). For details around SAE reporting, please see the Feasibility Study document.

3.7 Additional quality management activities

Data quality measures are described in the Core Protocol under paragraphs 9.6, page 17 and 9.8, page 23. Some quality management activities are employed at the data collection stage, others at the data export stage and some are inherently project specific.

3.8 Protection of human subjects

Data protection principles are described in the Core Protocol in Chapter 10 on page 24. The BMSD registries employ a combination of pseudonymization and anonymization measures in different contexts. Typically, given the complexity of patient level data making true anonymization questionable, the principle applied by the BMSD registries is not to share other than aggregated data outside of the network. Within the network, conditions may be met to allow sharing of sometimes pseudonymized patient level data.

Further, even aggregated data can sometimes not be shared due to national legislations or practices. For instance, due to the “minimal cell” principle, Danish data containing less than 5 observations are not allowed to be shared.

3.9 Informed consent

As described under 1.2 Administrative information of the RT document, the practices of informed consent vary slightly between the BMSD registries, according to accepted national guidelines. As most BMSD registries required a signed consent formed, this is not required according to Danish legislations and in Sweden an opt-out principle is the practice with required documentation of patients having received information on registration in “national health care quality registries” such as the SMSreg.

3.10 Standard Protocol Template

The adopted Core Protocol document serves this purpose.

3.11 Final statement

It is our opinion that the BSMD EMA qualification opinion dossier has been significantly further developed since our previous attempt in 2021. Especially the

extended description of data quality measures, the development of a CDM, more detailed principles regarding drug exposure considerations as well as the improved descriptions and comparisons of the registries' ability to collect SAEs should hopefully contribute towards the EMA this time being willing to give the BMSD network a full qualification opinion.

List of Figures

List of Appendices

List of Abbreviations

- AE: Adverse Event
- BMSD: Big MS Data group
- CDM: Common Data Model
- CSF: cerebrospinal fluid
- CRO: Contract Research Organisation
- DICOM: Digital Imaging and Communications in Medicine
- DMT: Disease Modifying Therapy
- DQM: Data quality management
- EDSS: Expanded Disability Status Scale
- EMA: European Medicines Agency
- EUROCAT: European surveillance of congenital anomalies
- ICD: International Classification of Diseases
- MAH: Marketing Authorisation Holder
- MAD: Medico-administrative databases
- MedDRA: Medical Dictionary for Regulatory Activities
- MPA: Medical Products Agency
- MRI: Magnetic Resonance Imaging
- MS: Multiple Sclerosis.
- NIDs: Neuro-immunological diseases
- PASS: Post Authorisation Safety Study
- QO: Qualification Opinion
- RT: REQueST Tool document
- RWD: Real World Data
- SAE: Serious Adverse Event
- SAWP: Scientific Advice Working Party
- SOP: Standard Operating Procedure

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