Manual of Procedures (MOP) for

Italian Multiple Sclerosis and Related Disorders Register

Protocol Number: SM001 e SM002

Version Number: 4.0

Summary of Changes:

Number	Date	Affected Chapter(s)	Summary of Revisions Made:
1.0	15/07/2021	-	First issue
2.0	24/02/2023	All	Update of Chapters
3.0	15/06/2023	8	Addition of the chapter 8
4.0	21/05/2024	All	Update of Chapters

1 INTRODUCTION TO THE MANUAL OF PROCEDURES

1.1 Purpose

A Manual of Procedures (MOP) is a handbook that guides a study's conduct and operations. It supplements the study protocol by detailing the organization of the study, operational data definitions, recruitment, screening, enrollment, follow-up procedures, data collection methods, data flow, case report forms (CRFs), and quality control procedures. The purpose of the MOP is to facilitate consistency in protocol implementation and data collection across participants and clinical sites. Procedures in the MOP should be followed with the same degree of vigor as those documented in the protocol. The use of the MOP increases the likelihood that the results of the study will be scientifically credible and provides reassurance that participants' safety and scientific integrity are closely monitored.

This MOP is a reference document for policies and procedures related to the study entitled "Italian Multiple Sclerosis and Related Disorders Register". All staff members participating in the conduct of this study at participating institutions should have ready access to the MOP and be familiar with its contents.

The current version of this Manual is available on the website of the project at https://registroitalianosm.it/index.php?page=docprogetto.

The archive of the related documents and previous versions is available on a reserved section of the study website, available on request.

1.2 Updating

The MOP is a dynamic document that will be updated throughout the conduct of a study to reflect any protocol or consent amendments, as well as the refinement of the CRFs and study procedures. All clinical sites will receive a notification when the MOP will be updated and will be available on the study website.

2 ADMINISTRATIVE

2.1 Study Leadership Structure

2.1.1 Organizational Chart

The "Italian Multiple Sclerosis and Related Disorders Register" study is sponsored by the Research Unit "FISM – UNIBA" directly involved in all the phases of the study. The governance of the "Italian Multiple Sclerosis and Related Disorders Register" includes the following:

- Executive Committee;
- Scientific Committee (SC);
- Technical and Administrative Infrastructure (TAI–SAC, Struttura Amministrativa e di Coordinamento) coordinated by FISM;
- Technical Methodological Structure (TMS–STO, Struttura Tecnico Operativa), based at Mario Negri IRCCS Institute;
- Participating Centers Committee.

Moreover, the study recognizes the importance of having stakeholder advisory boards, including one of pharmaceutical companies (Amgen, Merck Serono, Novartis, Roche, Sanofi, Viatris, Biogen, Bristol Meyers Squibb, Alexion and Sandoz), providing their inputs and suggestions.

2.1.2 Roles and Responsibilities

The roster of contact persons is listed below:

Role/Institution	Name	e-mail	Issues
Sponsor Representative	FISM - Battaglia	m.a.battaglia@aism.it	Fund for the study
Executive Committee	FISM - Battaglia UniBA - Trojano	m.a.battaglia@aism.it maria.troiano@uniba.it	Organizational and administrative role
Scientific Committee	Trojano	maria.troiano@uniba.it	Scientific overview
Technical and Administrative Infrastructure (TAI)	Ponzio	michela.ponzio@aism.it registroitalianosm@aism.it	Study and centers coordination, research assistance and administration
Technical Methodological Structure (TMS)	Mosconi	paola.mosconi@marionegri.it smregistro@marionegri.it	Study and centers coordination, monitoring of data quality collection, development of CRFs and Web Application (RISM-App)
Data and analysis	Mosconi Lepore D'Ettorre Paletta Santucci Ponzio Salivetto	paola.mosconi@marionegri.it vito.lepore@marionegri.it ing.antonio.dettorre@gmail.com pasquale.paletta@marionegri.it claudia.santucci@marionegri.it michela.ponzio@aism.it marco.salivetto@aism.it	Data collection and data analysis, feasibility of research projects
Informatics	Rossi Vitali Corrado D'Ettorre DMSLab	lorenzo.rossi@marionegri.it massimo.vitali@marionegri.it donatella.corrado@gmail.com ing.antonio.dettorre@gmail.com l.marfisi@dmslab.it	Help Desk, eCRFs, RISM-App development and management, Website

2.2 Executive Committee

The Executive Committee is chaired by FISM and University of Bari (Unità di Ricerca FISM–UNIBA) and is responsible for the overall direction of the study.

FISM and UNIBA are jointly recognized as "Unità di Ricerca FISM - UNIBA".

2.2.1 Roles and Responsibilities

- Responsibility for the general design;
- Allocation of resources based on priorities of competing study demands;
- Review of study progress and implementation of necessary steps to ensure the achievement of study goals;

- Review and response to other general advice and/or recommendations;
- Changes in study procedures as appropriate;
- Relationship with European and International multiple sclerosis (MS) registers.

2.3 Scientific Committee

A SC oversees the study. The SC includes clinicians, methodologists, representatives of MS centers, and of the Italian Neurological Society (SIN, Società Italiana di Neurologia). Three representatives of MS centers are elected every 3 years by the network of the centers.

2.3.1 Roles and Responsibilities

The SC is involved in all the initiatives related to the study, promotes specific strategic projects, approves requests of access to centralized data for further research projects, and elaborates and prepares the operating protocol and the standardized operating procedures to homogenize the study activities of the various participating Centers. Regular meetings of the SC are organized by the Executive Committee. Meetings are chaired by the President of the SC on the basis of an agenda shared among members some days before the meeting. A minute of the meeting is drafted by the secretary of SC and then reviewed and approved by SC members.

2.3.2 Members

- Prof. Maria Trojano (Dipartimento di Biomedicina Traslazionale e Neuroscienze (DiBraiN), Aldo Moro University of Bari, Bari, "President");
- Prof. Mario Alberto Battaglia (Italian Multiple Sclerosis Foundation, Genova, "Vice-president");
- Dr. Paola Mosconi (Mario Negri IRCCS Institute, Milano);
- Dr. Claudio Gasperini (UOC di Neurologia e Neurofisiopatologia Azienda Ospedaliera S. Camillo-Forlanini, Roma, "Società Italiana Neurologia representative");
- Prof. Eleonora Cocco (Centro Regionale per la diagnosi e la cura della Sclerosi Multipla ASL8 P.O. Binaghi, Cagliari, "MS centers representative");
- Prof. Matilde Inglese (Centro per lo studio e la cura della Sclerosi Multipla e Malattie Demielinizzanti - Dipartimento di Neuroscienze, Riabilitazione, Oftalmologia, Genetica e Scienze Materno - Infantili, Clinica Neurologica - Ospedale Policlinico San Martino (DiNOGMI), Genova, "MS centers representative");
- Dr. Carla Tortorella (Centro Sclerosi Multipla - Az. Osp. S. Camillo Forlanini, Roma, "MS centers representative");
- Dr. Marco Capobianco (Centro Sclerosi Multipla, SC Neurologia, AO Santa Croce e Carle, Cuneo, "Secretary");
- Prof. Maria Pia Amato (Dipartimento NEUROFARBA, Sezione Neuroscienze, Università degli Studi di Firenze. Centro SM Neurologia 1, AOU Careggi, Firenze, "Expert");
- Prof. Giancarlo Comi (Centro Sclerosi Multipla Casa di Cura Igea, Milano, "Expert");
- Prof. Massimo Filippi (Centro Sclerosi Multipla - Ospedale San Raffaele, Milano, "Expert").

2.4 Technical and Administrative Infrastructure (TAI) and Technical Methodological Structure (TMS)

Two methodological and technical Infrastructures lead the study:

- TAI – Technical and Administrative Infrastructure, coordinated by FISM
- TMS – Technical Methodological Structure, based at Mario Negri IRCCS Institute.

2.4.1 Roles and Responsibilities

TAI – Technical and Administrative Infrastructure – deals with the secretarial functions, the requests for funding to support the infrastructure and the reporting processes in close collaboration with the TMS, the administrative management and the conservation of the assigned sums, the organization of meetings, the promotion and implementation of information and exchange flows between the participants, and any other operational fulfillment that is useful or necessary to ensure the proper functioning of the Research Unit.

TMS – Technical Methodological Structure – is responsible for the technical-operational coordination of the study, data analysis, and management of the central server that hosts the Web Application (called RISM-App) and the aggregated database, reports to the centers, analysis of the quality of data collected, and development of the RISM-App. The TMS guarantees the connectivity with the centers, back-up activities of the data stored on the server and takes appropriate security measures to protect such data. TMS also coordinates activities with centers and with Ethics Committees (ECs).

TAI and TMS share a section in the restricted area of the website, where all the data of the participating centers are stored and periodically updated.

2.4.2 Members

TAI - Technical and Administrative Infrastructure

Dr. Paola Zaratin: FISM Scientific director.

Dr. Michela Ponzio: senior researcher, TAI coordinator.

Dr. Marco Salivetto: researcher, clinical Post-Authorisation Safety Study (PASS) coordinator.

Dr. Alessia Elia: research assistant network manager

Mrs. Luciana Lunadei and Mrs. Maria Rita Di Fazio: administrative secretary.

Avv. Paolo Bandiera, Dr. Martina Bassi, Dr. Laura De Barbieri: Legal Office.

TMS - Technical Methodological Structure

Dr. Paola Mosconi and Dr. Vito Lepore: senior researchers and TMS coordinators.

Dr. Pasquale Paletta: researcher.

Dr. Pasquale Paletta and Dr. Antonio D'Ettorre: writing of periodical reports, evaluation of indicators, graphic presentation, and statistical analysis.

Dr. Pasquale Paletta, Dr. Claudia Santucci (Statistician), and Vito Lepore: feasibility of submitted projects (*sub-studies, see 2.7.4)*, and statistical analysis of ad hoc projects.

Dr. Lorenzo Rossi (Computer Engineer), Dr. Massimo Vitali (Computer Informatic Technicians), Dr. Antonio D'Ettorre (Computer Engineer), Dr. Donatella Corrado (Datawarehouse, Datamining developer, RISM-App developer), and DMSLab: database management and updating, data extraction, help-desk activities and online support to partecipant centres, creation and maintenance of the new web-based management system dedicated to the Register, backup activities.

Mrs. Sabrina Bidoli: administrative secretary; coordination of the contacts with the clinical centers and ECs.

2.5 Centers participants committee

The participant centers are recognized as the "Italian Multiple Sclerosis and Related Disorders Register Centers Group". The committee of Principal Investigators (PIs) of each center elects every three years 3 representatives who become part of the SC of the study.

2.5.1 Roles and Responsibilities

- Enrollment of eligible patients;

- Collection of Informed Consents;
- Data collection according to the protocol of the study;
- Storage of patients' documents.

2.5.2 Members

An up-to-date list of participant centers is available on the website of the study: https://registroitalianosm.it/index.php?page=dettagliocentri.

2.6. Staff and Training

2.6.1 Centers and clinicians

Each participant center signed and presented the protocol of the study to the pertinent local EC for approval.

Centers were required to include all the Multiple Sclerosis and Related Disorders cases in the study, to inform patients about the "Italian Multiple Sclerosis and Related Disorders Register", to request their consent to participate, and to transfer a standardized set of data using the RISM-App. Participation in "Italian Multiple Sclerosis and Related Disorders Register" is voluntary both from the neurologist's and the patient's side.

Each center is periodically invited to participate to regional or national meetings about the up-to-date of the study.

2.6.2 Research Assistants

In order to increase the quality of the data collected, a group of Research Assistants has been *ad hoc* trained for the study with the aim to foster the collection of good quality data in the Italian Multiple Sclerosis centers.

Research Assistants work in the study through a collaboration with FISM. To regulate the activities of Research Assistants at the centers, FISM asks the center to sign a "hospitality agreement" (*Accordo di ospitalità*) and gives the Research Assistants a mandate to process personal data (*Lettera di incarico al trattamento dei dati personali*).

Each Research Assistant is allocated to one or more centers, depending on the size and needs of the Multiple Sclerosis clinical center.

Research Assistants daily report by e-mail the TMS and the PI about the activities done in the visited center. Research Assistants report monthly all the activities to the TMS, and at least three times/year they are involved in meetings to discuss issues on their activities and on data collection.

All Research Assistants receive an *ad hoc* training on all aspects of the disease and of the protocol, in particular:

- Information about Multiple Sclerosis, Related Disorders and available treatments;
- Study objectives;
- Inclusion/Exclusion criteria;
- Patients visits schedule;
- Treatment, and follow-up;
- Laboratory evaluations;
- Investigator responsibilities;
- Essential document collection and storage;
- Informed consent procedures;
- RISM-App;
- Query process.

2.7 Policies and Procedures

2.7.1 Data Request Policy

The data are stored on the dedicated server at the Mario Negri IRCCS Institute in an encrypted form. The Research Unit FISM–UNIBA as "Co-Owner" - together with the network of Centers - has appointed the Mario Negri IRCCS Institute as responsible for the processing of personal data.

2.7.2 Publication and Presentation Policy

The data collected by the study are available according to the Executive Committee and SC.
Each participant center has full access to the data collected in its center.
Each participant center is requested to share with the TAI abstract or articles related to the study; an ad hoc section of the study website is dedicated to the publication/news regarding the study (https://registroitalianosm.it/index.php?page=documenti).
For the Type 1 and 2 studies (see 2.7.4) presented to the SC, each PI is requested to declare the policy of publication, according to the number of patients available in each center.

2.7.3 Organizational Chart

Each clinical site will maintain a delegation of responsibilities log in the essential documents' binder. This log associates investigator and/or clinical site staff names with specific study responsibilities. In particular, each center signs a specific document where the clinical center delegates the Italian Multiple Sclerosis and Related Disorders Register Infrastructure (Operating unit) to work for the study (*Mandato di adesione*).

2.7.4 Data for specific sub-studies

Data of the study are available to the participant centers for specific sub-studies. A standardized process for applications for research study has been developed. Each participating center can propose research studies addressing one of the high priority areas of the "Italian Multiple Sclerosis and Related Disorders Register". All the sub-studies are discussed by the SC before their acceptance. The submissions of sub-studies to the SC of the "Italian Multiple Sclerosis and Related Disorders Register" can be made at any time of the year and will be evaluated in the first meeting of the SC. It is possible to present two different types of sub-studies to the SC of the "Italian Multiple Sclerosis and Related Disorders Register":

- Type 1: studies promoted and coordinated by the SC, on its the spontaneous initiative or proposed by Centers/Institutions (public or private), in which all the Centers belonging to the "Italian Multiple Sclerosis and Related Disorders Register" will participate by right and obligatorily contributing with the "minimum dataset" (MDS).
- Type 2: collaborative studies between two or more clinical centers related to specific data sets, always within the MDS.

Firstly, the feasibility of proposals (i.e., variables availability, data completeness, sample size, methodological appropriateness etc.) is assessed by the TMS. Then, the members of the SC assess the proposals according to the scientific quality, the value of the study, and the alignment with priority areas of the study.
After the SC approval, the proponent center receives by the TAI a letter with its communication and (if available) suggestions by the SC, together with an agreement form for the use of the data. After the signature of the agreement, data are uploaded in a protected area of the RISM-App, and the responsible of the study is informed by e-mail. The proponent enters the protected area and downloads the file with the data.

All datasets sent are anonymous, the data are selected by macro area according to the project selection criteria. To ensure a higher level of data security and lower the probability of patient reidentification, the data within the datasets for the research projects will be further encrypted. By doing so, the encrypted code of each patient stored in the RISM-App will be different from the encrypted code randomly assigned to each patient for each dataset extraction.

3 REGULATORY

3.1 Regulations and Regulatory Bodies

This observational study is compliant with human subjects' regulations. Particularly, the study is conducted according to the Agenzia Italiana del Farmaco (AIFA) Determination, 20th March 2008.

3.1.1 Informed Consent/Assent Process

Informed consent is required for all subjects participating in the study. In obtaining and documenting the informed consent form, the investigator should comply with applicable regulatory requirements. Prior to the beginning of the study, the investigator must have the EC written approval for the protocol, and favorable opinion of the informed consent process and written form(s) and any other written information to be provided to the subjects.
The following different consent forms are used for the study:

Adults consent forms	To be delivered and signed to each eligible adult patient
Parent or Guardian consent forms	To be delivered and signed to parent/guardian of each eligible patient under 18 years of age
Under 12 years old consent forms	To be delivered to each eligible patient under 12 years of age
12-18 years old consent forms	To be delivered to each eligible patient 12-18 years of age

In each participant center, all informed consent forms properly filled and signed are filed in a dedicated binder. Original, or a copy, of consent forms is stored only in the participating center; the TAI and the TMS do not receive any copy of this document.
After having collected the consent forms, clinicians of participant centers must fill-in an appropriate field on the RISM-App CRF.
Currently, those documents are available in three languages according to centers' needs: Italian, English and German.

3.1.2 Re-consenting for Protocol Changes or Safety Updates

If a consent document is revised due to changes in study procedures, subjects who were enrolled prior to the change, but are affected by the change, will be informed and will sign the amended consent document. If a consent document is revised due to changes in the risks or safety of the study, all active participants must sign the revised consent.

3.1.3 Privacy Rule

A detailed document about the privacy of data collected "Informativa e manifestazione di consenso al trattamento dei dati personali ai sensi dell'Art. 13 del Reg. UE 2016/679" (Versione n. 3 – 25/02/2021) accompanies the informed consent form. People with MS sign this document before entering the study.

A PIA (Privacy Impact Assessment) document of the study has been prepared jointly by FISM and the TMS. The final version has been signed in October 2020.

3.2 Essential Documents

Essential documents are those that individually and collectively permit evaluation of both the conduct of a clinical study and the quality of the data produced. Paper versions of non-subject specific site documents will be filed in the study-specific Essential Documents binder.

3.2.1 Required Documents

The following essential documents must be retained at the study site, must be accurately maintained, and may be verified.

Site-specific documents:

- The protocol and all protocol amendments;
- All versions of EC approved consent documents;
- EC documentation, approvals, and correspondence;
- Study communication;
- Delegation of responsibilities log;
- Documentation of clinical research and study training;
- Documentation of clinical site Research Assistant visits.

Subject-specific documents are not stored at central level. Each participant center has the responsibility to collect and store the following documents:

- Source documents (e.g., lab reports, ECG tracings, X-rays, radiology reports, etc.);
- Signed consent document.

3.2.2 Document Maintenance

The documentation pertaining to this protocol is preserved for 10 years, and the Sponsor permission is required prior to destruction of records.

4 SITE QUALITY MANAGEMENT PLANS

The Register does not provide formal site visits to participating centers. 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, on the basis of specific needs related to research studies, carry out formal checks on the data collected.

A set of performance indicators has been identified and adopted with the aim to improve the quality, completeness of the data, generalization and representativeness of the collected data. For every examined indicator or domain, each participating center was assigned a score of 5 for the highest performance, while lower scores of 4 to 1 were attributed for progressively lower performance. Every six months, each participating center receives a report where data and performance indicators of its own center are benchmarked with the whole sample, so that each center can assess the most critical performances and the level of improvement with time.

5 PROTOCOL IMPLEMENTATION

5.1 Recruitment and Enrollment

5.1.1 Recruitment Methods

Each participant center recruits patients according to its clinical activity.

Some of the participating centers started their data collection before 2000, in the framework of the Italian Multiple Sclerosis Database Network (MSDN). This network used the iMed© software system, progressively replaced by a web-based system, developed ad hoc for the study: the RISM-App.

5.1.2 Informed consent

Each eligible patient enrolled is required to sign a written informed consent form to enter the "Italian Multiple Sclerosis and Related Disorders Register". Since in some of the participant centers data were collected before the starting of the "Italian Multiple Sclerosis and Related Disorders Register" (through iMed© or other data-entry), according to the local laws and regulations, data collected retrospectively can also be included.

5.1.3 Establishing Eligibility

Patients eligible for the study are:

- those with a diagnosis - or a possible diagnosis - of Multiple Sclerosis and Related Disorders;
- those diagnosed with Clinically Isolated Syndrome (CIS), i.e., neurological episode (symptom or sign), lasting at least 24 hours, that it is compatible with a demyelinating disease of the central nervous system;
- those with diseases from the Neuro Myelitis Optic Spectrum Disorder (NMOSD) and those associated with the presence of anti-MOG antibodies (MOGAD).

Physicians refer to the McDonald criteria for the MS diagnosis.

5.1.4 Assigning Participant Center Identification Numbers

Each center is identified by a code (2-letters and 3-numbers) attributed uniquely by TAI.

5.2 Enrollment Procedures

For each center, TMS records the information related to the PI in the RISM-App, enabling him/her to access it. The software automatically sends an e-mail to the PI confirming the registration in the system.

The password assigned to the PI is temporary, must be changed at the first access to the system and has a duration of three months. After three months, the system asks the user to change the access password.

Within each center, the PI can appoint one or more users delegated to input the data of the patients. The names of the authorized persons are communicated via e-mail by the PI to TMS, which requests the IT support to activate the new accounts, repeating the assignment procedure described above.

To further improve the system security, the following requirements have been implemented:

- password not shorter than 12 characters;
- reCAPTCHA, Completely Automated Public Turing test to tell Computers and Humans Apart;
- A two-factor authentication;
- it i mandatory to change the password when using the system for the first time and every three months thereafter;
- password complexity check: it must contain at least three characters between numbers, upper- and lower-case alphabetic characters as well as special characters;
- no reuse of the last 4 passwords.

Password storage has been implemented with a new, more secure one-way hashing algorithm (*bcrypt*).

5.3 FAQ – Frequently asked questions

In order to increase the standardization of procedures and the quality of data collection a section of the RISM-App is dedicated to frequent questions. For each question is provided an explanation with practical guidelines. This section is periodically updated by TMS.

6 PROCESS RESPONSIBILITIES

6.1 Detailed Description of Study Procedures

For each patient enrolled, a new form must be filled-in in the RISM-App system.

The system assigns a code number to each new patient.

6.1.1 Schedule of Events

Each patient will be followed according to the clinical center activities.

According to the protocol of the study, a clinical examination every six months and an Expanded Disability Status Scale (EDSS) assessment as periodic follow-up are requested for each patient.

6.1.2 Side effects

In the RISM-App, a section is dedicated to specific MS treatments. For every MS drug available on the market in Italy, an assessment of the clinical risk is available with tables indicating tests and schedule to be foreseen during the administration.

A section is also available for collecting adverse events, reporting type, date and drug-adverse event correlation.

6.1.3 Clinical risk management

In the RISM-App, a section is dedicated to the management of the clinical risk associated to the Disease Modifying Therapies (DMTs) available on the market in Italy. This section is created on the basis of the available recommendations from the main regulatory bodies (European Medicines Agency - EMA, Food and Drug Administration - FDA and AIFA) and helps clinician scheduling all the tests and examinations needed for the administration of a specific DMT.

6.1.4 Transfer of cases among centers

RISM-App allows the transfer of a case, and all its data, from one participating center to another. After that the patient provides a formal approval for this transfer, the clinician operationally, via the “Patient Transfer” section on the RISM-App, requests it. To facilitate this function, a 30-day time limit for accepting or rejecting the transfer of a case has been implemented. Once this limit is exceeded, the case is automatically transferred to the requesting center.

In case of decline to transfer request, a note field is available to specify the reasons.

7 DATA MANAGEMENT

7.1 Data Collection Methods

Data are collected through a web-based system - the RISM-App - developed *ad hoc* for the study, and available at https://registroitalianosm.it/index.php?page=areariservata. Each center can enter the data after identification through a personalized password (direct login at https://registroitalianosm.it/index.php?page=areariservata).

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.

7.2 Source Documentation Requirements

All source documents should be filled in by the local PI, study coordinator, their assistants or Research Assistant.

7.3 Study Forms

The SC agreed, by consensus, on a compulsory common MDS of selected information according to the principles of relevance. The MDS ensures the collection of sufficient data for the clinical characterization of each single patient. The list of the mandatory variables of interest, identified on the basis of the existing guidelines and the recommendations of the SC, ensures:

- participation of a large and representative number of centers;
- easy and simple data collection;
- ability to achieve the maximum completeness and quality of data for each center;
- possible development of linkage procedures with regional information, flows of health administrative data (hospital discharges, drug prescriptions, ticket exemptions, registers of patients, outpatient specialist).

No paper data collection is available, copy of the CRF is available on the website of the study https://registroitalianosm.it/index.php?page=documenti.

In 2022, the data collection platform was expanded with a new module for patients with NMOSD and MOGAD. Although they share with MS the autoimmune nature and similar clinical phenotypes, they constitute distinct entities in terms of natural history and disease characteristics. Careful data collection for these rare diseases will allow the development of clinical and therapeutic management studies over the coming years. Therefore, sections were extended, leading to the development of specific features for them and implementing others for MS.

According to the current clinical practice, the following information is requested in the RISM-App:

- Identification/Personal data;
- Onset and Diagnosis (Anamnesis);
- Follow-up visits – EDSS, Safety;
- Relapses;
- Adverse events (clinical events);
- Treatments;
- Non-pharmacological treatments;
- Risk assessment;
- Pregnancies;
- COVID-19;
- Co-morbidity;
- Familiar anamnesis;
- Tests and scales;
- Laboratory exams;
- Magnetic Resonance, Liquor, Evoked Potentials;
- EEG, ECG, Blood pressure;
- Eye examination;

- Optical Computerized Tomography.

The following standardized databases are implemented in the RISM-App with the aim of harmonization of data collection:

- FarmaDati, a database of Medicines, Parapharmaceutical and Medical Device, https://www.farmadati.it/;
- MedDRA, a specific standardised medical terminology, https://www.meddra.org/;
- ICD9CM, International Classification of Disease - a nomenclature of diagnoses, trauma, surgical interventions and diagnostic and therapeutic procedures. Each term is associated with a numeric or alphanumeric code;
- EUROCAT, for the input of the congenital anomalies https://eu-rd-platform.jrc.ec.europa.eu/eurocat_en.

An *ad hoc* section is dedicated to the collection of data regarding cases diagnosed in subject under 18 years of age, or diagnosed when they were younger than 18. According to the clinical practice, the following information is requested in the RISM-App:

- Identification/Personal data;
- Onset and Diagnosis (Anamnesis);
- Follow-up visits – EDSS, Safety;
- Relapses;
- Adverse events (clinical events);
- Treatments;
- Non-pharmacological treatments;
- Risk assessment;
- Pregnancies;
- COVID-19;
- Anamnesis and Risk Factors;
- Tests and scales;
- Laboratory exams;
- Magnetic Resonance, Liquor, Evoked Potentials;
- EEG, ECG, Blood pressure;
- Eye examination;
- Optical Computerized Tomography.

The same information is requested for patients diagnosed with NMOSD and MOGAD, maintaining the different collection for adult patients and under 18 onset patients.

7.4 Data Error Detection and Correction

Each center has the full responsibility for the data collected.
The Research Assistants of the study interact with the neurologists in charge of the study and enter the data or review the data collected.
Every six months, each center receives a personalized report with the situation of the center and a document on data quality indicators.

7.5 Data Quality Management

7.5.1 Data tracking

A module has been implemented to log all accesses to the database and all operations both in reading and in writing that are performed through the RISM-App.
Access logs to individual personal data must follow the rules specified by the Linee guida del Garante. As established by the Linee Guida del Dossier Sanitario (Health Dossier Guidelines), the system keeps track of the following data:

- identification of the person in charge who carried out the access operation;
- date and time of execution;
- identification of the workstation used;
- identification of the patient whose medical record is affected by the access operation by the person in charge;
- type of operation performed on the data (including consultation).

All these records are encrypted in appropriate log files.

7.5.2 Data entry, data editing and updating

Each authorized center receives a password to enter the system.
The access to the resources available within the portal - personal and clinical data of patients with MS or Related Disorders; statistical reports on local and national data - is reserved for authorized personnel. Each operator who wants to make his or her contribution must be part of an Italian center participating in the study.

7.5.3 Reporting

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

7.6 Data Provided from an Entity Other than the Clinical Site

As the nature of this study, observational study according with local clinical practice, at the moment are not available standard guideline for the collection of data regarding for example laboratory data or Magnetic Resonance Imaging (MRI) assessment.

7.7 Long Term Storage of Case Report Forms

Considering the nature of this study, location and time of the storage of documents will be maintained by each clinical center. Administrative data and information about the study will be maintained by the TMS and the TAI for a period of ten years.

7.8 Maintaining Data Privacy

The Web Application, called RISM-App, has been developed using the PHP Laravel framework (framework version 10.48.3 - PHP version 8.2.17), which guarantees protection from the main security risks highlighted by Open Web Application Security Project (OWASP).RISP-Appprovides for the storage of data, in accordance with the study protocol approved by the Coordinating center EC and the local ECs. Patient identification information (name, surname and social security number) entered in the RISM-App is collected on the central server database and made accessible only to authorized healthcare professionals of the participating centers.
In the RISM-App the personal data sheet is logically separated from the rest of the cards.

The RISM-App was designed and developed with full respect for the privacy of both investigators and patients. In particular, the privacy of patients is guaranteed by associating each of them with a completely anonymous numeric identification code. Data related to personal information of each patient are stored in encrypted form, i.e., encoded with specific cryptographic algorithms whose purpose is to obtain "obfuscated" data, not understandable/intelligible by people not authorized to read them.

7.9 Data retention/encryption

The data collected are stored in encrypted form on the dedicated server at the Mario Negri IRCCS Institute. 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.

7.10 Storage

The database for data storage (Oracle MySql v. 5.7.29) uses the Binary Log mode which allows to keep a copy of each transaction that makes changes to the database (in practice a continuous incremental over time). This modality allows point-in-time recovery of the database by restoring it up to the last transaction made or up to a certain point. Two procedures are used for this purpose:

- a procedure performed once a week (at 01:00 on Sunday), which performs a complete dump of the database in order to guarantee a starting point for the recovery;
- a procedure in continuous execution that archives in real time every single transaction that makes changes to the database.

Both procedures store the copy of the data on storage located in a building separate from the one where the database resides.

In case of need for recovery, the last complete dump of the database is restored and subsequently all the transactions carried out from the moment of the dump onwards, up to the last archived or until the moment in which it is necessary to restore the state of the database.

All copies made by the two procedures (both full weekly dumps and archived binary logs) are kept for 90 days. This allows to completely restore the database to the state it was in at any point in the last three months, without any loss of information.

7.11 Software and hardware configuration of the devices used

The RISM-App does not require any software installation at the participating clinical centers. The server and support-operating environment has the following characteristics:

Frontend

- AngularJS 1.8.3

Backend

- Linguaggio di programmazione: PHP 8.2.17
- Laravel versione 10.48.3

WebServer
- Sistema operativo: Ubuntu 22.04.4 LTS
- Web server: Apache v. 2.4.58
- Protezione sito web: certificato SSL/TLS versione 3

DB Server
- Sistema operativo: CentOS Linux release 8.1.1911
- DBMS: Oracle MySql v. 5.7.29

8. PROCEDURES FOR DATA QUALITY MONITORING FOR POST-AUTHORISATION SAFETY STUDIES (PASS)

8.1.1 Introduction

8.1.2 Purpose

This document aims to set up the procedures for data quality monitoring to improve the completeness and quality of data requested by the ongoing Post-Authorisation Safety Studies (PASS) within the observational study "The Italian Multiple Sclerosis and Related Disorders Register". The procedures are focused on two activities:

- the retrieval of missing data;
- the validation and the update of (serious) adverse events by participating centers, with a focus on the causal-effect relationship with the drug which should be reported in the section "Eventi clinici" on the RISM-App.

In "Appendix A" the ongoing PASS are reported.

8.1.2 Documents

The following procedures and all the PASS-related activities are strictly linked with the organization of the "The Italian Multiple Sclerosis and Related Disorders Register" study, whose documents are available on the website: https://registroitalianosm.it/index.php?page=docprogetto.

8.2 Procedures

8.2.1 Export and creation of the "Lista soggetti PASS"

Every six months (in occurrence of the data exports of 31 January and 31 July), PASS data are extracted and updated, as requested in the different protocols or in accordance to the Statistical Analysis Plan (SAP).

The complete dataset is extracted anonymously by the TMS in SAS, Access and Excel formats, as agreed, and sent to the PI for PASS, who forwards them to the dedicated Statistician (ST).

The data are provided with a track record that describes each field according to formats and modalities.

The selected patients for each PASS, already enrolled in the Register, are identified according to *ad hoc* inclusion and exclusion criteria that are detailed in each specific PASS protocol, thus representing only a sub-sample of the total number of patients.

Following the identification of the study population, specific variables are selected for the analysis on the basis of the information outlined in the protocol/SAP.

Before data analysis, a Data Management step is needed, during which the ST extracts the list of patients with missing information or incoherent data.

As regards adverse events, it is important to make a clear distinction between update and validation. The update refers to the activities established to raise awareness on the importance of

completeness and accuracy of data collection. Validation refers to the activities performed after the data are extracted.
The retrieval of this information will improve data accuracy and the power for the analysis. Moreover, it will provide the opportunity to investigate unexplored clinical questions in the "Italian Multiple Sclerosis and Related Disorders Register" study.
As described in this document, the Register is classified as an observational study and not as a publicly established disease registry, thus the upload of information on the RISM-App, such as adverse events, is not mandatory but it is recommended to clinical centers that voluntarily participate in the Register.
To monitor and check data collected and according to the PASS considered, an Excel file list of patients with missing information is downloaded. This Excel file is forwarded to the Study Coordinator for the PASS based at TAI headquarter.
Non-substantial changes are performed by the Study Coordinator to the Excel file to facilitate the understanding and usage of the document by the participating centers. The Study Coordinator prepares a center-specific list in an *ad hoc* Excel file, entitled "Lista soggetti PASS" (PASS subjects list).

8.2.2 Contact of the clinical centers

The Study Coordinator, according to the organizational infrastructures of the Register (the TAI and the TMS), informs, usually via e-mail, the referring neurologist at the clinical center about the need of a data update for the patients included in the PASS. In particular, the Study Coordinator asks the clinical center to update the information on patients' profiles on the basis of the file Lista soggetti PASS and shared through the restricted area on the RISM-App. The Study Coordinator notifies the research assistant, if any, that the communication has been sent, keeps them updated, and asks for their support in performing the update.

8.2.3 Execution of the activity

After an appropriate time, depending on the type and workload required, the frequency of the center visits by the research assistant (if present), and indicatively within the time-frame of one month, the Study Coordinator asks the clinical center a report. The procedure for the two planned activities (see 8.1.2) is described below.

8.2.3.1 Retrieval of missing data

Each clinical center, on the basis of the file Lista soggetti PASS received, updates the patient records on the RISM-App. The center completes the file Lista soggetti PASS indicating whether the data were retrieved or not. Particularly:

- If the data were retrieved and entered on the RISM-App: enter "SI" in the specific field for that data;
- If the data are lost or unrecoverable: enter "NO" in the specific field.

Any additional information can be entered in the field "Note". Then the referring neurologist, or the research assistant on behalf of the clinical center, contacts the Study Coordinator to report the work performed and uploads the updated file Lista soggetti PASS through the restricted area of the RISM-App. If the center is found to be non-respondent to the survey, in the notes field of the file Lista soggetti PASS the Study Coordinator enters for patients referred to that center "CENTRO NON RISPONDENTE."

8.2.3.2 Validation and update of adverse events (serious and non-serious)

Regarding the validation and updating of adverse events (serious and non-serious), the clinical center reviews the file Lista soggetti PASS - section adverse events monitored in such studies (e.g., progressive multifocal leukoencephalopathy – PML, opportunistic infections, neoplasms).
The center verifies the details of the adverse event entered to the RISM-App and updates the related form if there is new information. The center then updates the file Lista soggetti PASS received by entering the following:

- If the event is confirmed and updated on the RISM-App: enter "AGGIORNATO" in the specific field corresponding to the event;
- If the event is confirmed but there are no updates: enter "VALIDATO" in the specific field corresponding to the event;
- In case there were mistakes in the completion of the event or in case of subsequent clinical developments leading to substantial changes in the event itself (e.g., new diagnosis): enter "RIVALUTATO" in the specific field corresponding to the event.

Any additional information can be entered in the field "Note".
Then the referring neurologist, or the research assistant on behalf of the clinical center, contacts the Study Coordinator to report the work done and sends the updated file Lista soggetti PASS through the restricted area of the RISM-App. The Study Coordinator can arrange a remote meeting with the referring neurologist of the clinical center (and the research assistant if present) for any clarification regarding individual events.
If the center is found to be non-respondent to the survey, the Study Coordinator enters for patients referred to that center "CENTRO NON RISPONDENTE" in the notes field of the file Lista soggetti PASS.

8.2.4 Final report of the activity

The Study Coordinator will provide a summary of the activity to the PI and the ST, reporting any critical issues. A number of parameters will be considered to evaluate the performance of the activity executed:

- Percentage of responsiveness from clinical centers;
- Percentage of retrieved data (based on the file Lista soggetti PASS updated by centers or by comparing the percentages of data entered between the extractions from the Register before and after the activity);
- Percentage of validated/updated adverse events (on the basis of the file Lista soggetti PASS updated by centers).

8.2.5 Archiving

The Study Coordinator collects communications and feedback received from clinical centers and research assistants and archives the file Lista soggetti PASS updated.

8.3 Description of the current PASS

1. Title of PASS: An observational study utilising data from the US Tysabri TOUCH programme and select EU MS Registries to estimate the risk of PML and other serious opportunistic infections among patients who were exposed to an MS disease modifying treatment prior to treatment with Tysabri

- Short study title: Tysabri DMT switch PASS
- Investigational drug: Natalizumab (Tysabri)

- Study population: patients with multiple sclerosis who have switched from DMTs and have one or more infusion(s) of Tysabri
- Data collection period: retrospective component (data captured prior to 1 January 2016) and prospective component (data captured, and patients followed-up, from 1 January 2016 through 31 December 2023)

2. Title of PASS: Long-Term Surveillance of Ocrelizumab Treated Patients With Multiple Sclerosis

- Short study title: Manuscript Study
- Investigational drug: Ocrelizumab (Ocrevus)
- Study population:
  - Patients with multiple sclerosis who must be newly treated with ocrelizumab during the study observational period;
  - Patients with multiple sclerosis who have never received treatment with ocrelizumab and must be newly treated with an approved DMT other than ocrelizumab during the study observational period;
  - Patients with multiple sclerosis who have never received ocrelizumab or any other DMT within the complete history recorded in the available medical records and during individual follow-up in the study observational period.
- Data collection period: 2018 - 2028

3. Title of PASS: Long term, prospective, observational cohort study evaluating the safety profile in patients with highly active relapsing MS newly started on oral cladribine

- Short study title: Clarion
- Investigational drug: Cladribine (Mavenclad)
- Study population:
  - Patients with MS who must be newly treated with oral cladribine during the study observational period;
  - Patients with MS who must be newly treated with fingolimod during the study observational period.
- Data collection period: 2018 - 2033

4. Title of PASS: Kesimpta long-term retrospective safety study utilizing real-world data from existing multiple sclerosis registries and databases from multiple countries

- Short study title: Kesimpta long-term PASS
- Investigational drug: Ofatumumab (Kesimpta)
- Study population:
  - Patients with multiple sclerosis who must be newly treated with ofatumumab during the study observational period;
  - Patients with multiple sclerosis who have never received treatment with ofatumumab and must be newly treated with an approved DMT other than ofatumumab during the study observational period;

Data collection period: 2021 - 2032

9 SITE MONITORING

The study does not foresee specific monitoring visits. Centers with a Research Assistant receives periodic visits. The research assistant checks the entered data and enters new data.

10 FINAL STUDY

According to the protocol, the study will end in 2025. This date is however indicative and will be subjected to a specific amendment in order to further extend the study.

11 APPENDIX A: LIST OF ABBREVIATIONS

AIFA	Agenzia Italiana del Farmaco
CIS	Clinically Isolated Syndrome
CRF	Case Report Form
DMT	Disease Modifying Therapy
EC	Ethics Committee
EDSS	Expanded Disability Status Scale
EMA	European Medicines Agency
FDA	Food and Drug Administration
FISM	Fondazione Italiana Sclerosi Multipla
IRCCS	Istituto di Ricovero e Cura a Carattere Scientifico
MDS	Minimum Dataset
MOGAD	MOG antibody disease
MOP	Manual of Procedures
MRI	Magnetic Resonance Imaging
MS	Multiple Sclerosis
NMOSD	Neuro Myelitis Optic Spectrum Disorder
OWASP	Open Web Application Security Project
PASS	Post-Authorisation Safety Studies
PI	Principal Investigator
PIA	Privacy Impact Assessment
PML	Progressive Multifocal Leukoencephalopathy
SAC	Struttura Amministrativa e di Coordinamento
SAP	Statistical Analysis Plan
SC	Scientific Committee
SIN	Società Italiana di Neurologia
ST	Statistician for PASS
STO	Struttura Tecnico Operativa
TAI	Technical and Administrative Infrastructure
TMS	Technical Methodological Structure