Manual of Procedures (MOP) for

Italian Multiple Sclerosis and Related Disorders Register

Protocol Number: SM001 e SM002

Version Number: 5.0

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
5.0	20/06/2025	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" (RISM). 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 repository, 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 RISM website.

2 ADMINISTRATIVE

2.1 Study Leadership Structure

2.1.1 Organizational Chart

RISM is sponsored by the Research Unit "FISM – UNIBA" (see 2.2) directly involved in all the phases of the study. RISM governance includes the following:

- Executive Committee;
- Scientific Committee (SC);
- Technical Methodological and Coordinating Structure (STOC, Struttura Tecnico Operativa e di Coordinamento) coordinated by FISM;
- Participating Centers Committee.

Moreover, the study recognizes the importance of having Stakeholder Advisory Boards, including one with 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 persons and their contacts 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 Methodological and Coordinating Structure STOC	Ponzio	michela.ponzio@aism.it registroitalianosm@aism.it	Project, centers, research assistants and administrative coordination
Data and analysis	Ponzio Mosconi Lepore D'Ettorre Paletta Salivetto Bacchi Graziano	michela.ponzio@aism.it rims.mosconi@fismets.it leporevito792@gmail.com ing.antonio.dettorre@gmail.com pasquale.paletta@fismets.it marco.salivetto@aism.it sara.bacchi01@universitadipavia.it giusi.graziano78@gmail.com	Data collection and data analysis, monitoring of data quality collection, development of CRFs and collaboration for Web Application (RISM-App) development, feasibility of research projects
Informatics	Burelli Corrado D'Ettorre DMSLab	ivan.burelli@aism.it donatella.corrado@gmail.com ing.antonio.dettorre@gmail.com l.marfisi@dmslab.it a.damico@dmslab.it	Help Desk, eCRFs, RISM-App development and management, Website

2.2 Executive Committee

The Executive Committee is chaired by Fondazione Italiana Sclerosi Multipla (FISM) and University of Bari (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 RISM. The SC includes clinicians, methodologists, representatives of MS centers, and of the Italian Neurological Society (SIN, Società Italiana di Neurologia). The committee of Principal Investigators (PIs) of each center elects every three years 3 representatives who become part of the SC of the study.

2.3.1 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 STOC and then reviewed and approved by SC members.

2.3.2 Members

- Prof. Maria Trojano ("President");
- Prof. Mario Alberto Battaglia ("Vice-president");

- Prof. Eleonora Cocco (Centro Regionale per la diagnosi e la cura della Sclerosi Multipla ASL8 P.O. Binaghi, Cagliari, "MS centers representative");
- Dr. Claudio Gasperini (UOC di Neurologia e Neurofisiopatologia Azienda Ospedaliera S. Camillo-Forlanini, Roma, "Società Italiana Neurologia 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. Paola Mosconi;
- 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. Massimo Filippi (Centro Sclerosi Multipla - Ospedale San Raffaele, Milano, "Expert").

- Members of the STOC (Michela Ponzio, Paola Mosconi and Vito Lepore) attend the Scientific Committee meetings.

2.4 *Technical Methodological and Coordinating Structure (STOC)*

The STOC is the methodological and technical infrastructure that leads the study:

2.4.1 Roles and Responsibilities

STOC is responsible for the technical-operational coordination of RISM, data analysis, 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. STOC deals with:

- the secretarial functions,
- the requests for funding to support the infrastructure,
- the reporting processes,
- the administrative management and the conservation of the assigned sums,
- the organization of meetings including the presence at International Congress with dedicated booth,
- the promotion and implementation of information and exchange flows between the participants,
- the organization of training for centers and research assistants
- any other operational fulfillment useful or necessary to ensure the proper functioning of the Research Unit.

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. Finally, STOC coordinates activities with centers and with Ethics Committees (ECs).

2.4.2 Members

Dr. Paola Zaratin: FISM scientific director.
Dr. Michela Ponzio: senior researcher, STOC coordinator.
Dr. Paola Mosconi and Dr. Vito Lepore: senior researchers.
Dr. Marco Salivetto: researcher, clinical Post-Authorisation Safety Study (PASS) coordinator.
Dr. Pasquale Paletta: researcher.
Mrs. Sabrina Rutigliano and Mrs. Luciana Lunadei: coordination of the contacts with the clinical centers and ECs, research assistant network; Mrs. Maria Rita Di Fazio administrative office.
Mr. Ivan Burelli (Information Technology coordinator), 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 participant centres, creation and maintenance of the new web-based management system dedicated to the Register, backup activities.
Avv. Paolo Bandiera, Avv. Laura Debarbieri, Dr.ssa Martina Bassi, Dr. Lorenzo Garzarelli: Legal and Compliance Office.

2.5 Centers participants committee

The participant centers are recognized as the "RISM Centers Group".

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 RISM study to the pertinent local EC for approval.
Centers were required to include all the MS and Related Disorders cases in the study, to inform patients about the RISM, to request their consent to participate, and to transfer a standardized set of data through the RISM-App.
Participation in RISM 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 (RAs) has been *ad hoc* trained for the study with the aim to foster the collection of good quality data in the Italian MS participant centers. RAs work in the study through under the supervision and in collaboration with the STOC.
A "hospitality agreement" (*Accordo di ospitalità*) is signed by FISM and the center to regulate RAs activities. Each RA is allocated to one or more centers, depending on the size and needs of the MS clinical center. RAs plan their visits at clinical centers on a monthly basis, and daily report by e-mail to the STOC and the PI of the visited center about the activities done. RAs, at least three times/year, are involved in meetings to discuss issues on their activities and on data collection.
All RAs receive an *ad hoc* training on all aspects of the disease, protocol, and RISM-App, in particular:

- Information about MS, Related Disorders and available treatments;
- Study objectives;
- Inclusion/Exclusion criteria;
- Patients visit schedule;
- Treatments and follow-up;
- Laboratory evaluations;
- Investigator responsibilities;
- Essential document collection and storage;
- Informed consent procedures;
- RISM-App;
- Query process;
- Frequently Asked Questions (FAQ).

2.7 Policies and Procedures

2.7.1 Data Request Policy

Data are stored in encrypted form on a flexible Microsoft Azure database server for MySQL with location Northern Italy.

2.7.2 Publication and Presentation Policy

Data collected within RISM are available according to the Executive Committee and SC.
Each participant center has full access to its own collected data.

Each participant center is requested to share with STOC 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 links investigator and/or clinical site staff names with specific study responsibilities. In particular, each center signs a specific document where to delegate the RISM 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 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 SC before their acceptance. The submissions of sub-studies to the SC can be made at any time of the year and will be evaluated in the first SC meeting. It is possible to propose two different types of sub-studies:

- Type 1: studies promoted and coordinated by the SC, on its spontaneous initiative or proposed by Centers/Institutions (public or private), in which all the Centers belonging to the RISM 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 datasets, always within the MDS.

Firstly, the feasibility of proposals (i.e., variables availability, data completeness, sample size, methodological appropriateness etc.) is assessed by STOC. 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 from STOC a letter with its communication and (if needed) suggestions by the SC, together with an agreement form for the data usage. After the signature of the agreement, a subset of data according to the selection criteria of the proposal are uploaded in a protected section of the RISM-App, and the proponent of the study is informed via e-mail. The proponent can download the extracted dataset entering the protected section of the RISM-App, and is also requested to delete the file immediately after the download.
All datasets sent are anonymous. To ensure a higher level of data security and lower the probability of patient reidentification, the data within the datasets for the research projects are 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 DM 30/11/2021 related to not for profit studies and Agenzia Italiana del Farmaco (AIFA) Determination del 08.08.2024 to the extent applicable.

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 provide to the subjects.
The following different consent forms are used for the study:

Adults consent forms	To be delivered to and signed by each eligible adult patient
Parent or Guardian consent forms	To be delivered to and signed by 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; STOC does not receive any copy of this document.
After having collected the consent forms, clinicians of participant centers fill-in a compulsory appropriate field on the RISM-App.
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 by FISM. The current has been signed in October 2020 a new version will be released in summer 2025.

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 RA visits.

Subject-specific documents are not stored at a central level. Each participant center has also 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 20 years, and the Sponsor permission is required prior to destruction of records.

4 SITE QUALITY MANAGEMENT PLANS

RISM 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. RAs regularly visit the centers and, 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.

FISM as sponsor also reserves the right to conduct site visits if necessary.

5 PROTOCOL IMPLEMENTATIONS

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 asked to sign a written informed consent form to enter the RISM. Since in some of the participant centers data were collected before the starting of the RISM (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 MS or 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 and following updates 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 STOC.

5.2 Enrollment Procedures

For each center, STOC 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 STOC, 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 is 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 STOC.

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 patient, and all its data, from one participating center to another. After 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 patient has been implemented. Once this limit is exceeded, the patient's case-history 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 RISM, each patient has a unique valid code identifier, obtained through the patient encrypted fiscal code.
Each patient is assigned to a center.
The manual "Guida Rapida" to introduce RISM-App, its characteristics and features and the manual for the queries facilities "RISM_App_Queries_Manuale_Operatore" are available in the restricted area (Manual Section). Moreover, is available a document to evaluate the clinical risk of treatments ("Informazioni su schede Gestione Rischio Clinico" https://registroitalianosm.it/index.php?page=docprogetto).
A document describing technical characteristics of the RISM-App is available as Appendix B.

7.2 Source Documentation Requirements

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

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, copies of the CRFs are 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 subject with an onset prior the 18 years of age. 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 RAs interact with the neurologists in charge of the center 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 STOC for a period of 20 years.

7.8 Maintaining Data Privacy

The RISM-App has been developed using the PHP Laravel framework (framework version 10.48.3), which guarantees protection from the main security risks highlighted by Open Web Application Security Project (OWASP). RISP-App provides for the storage of data, in accordance with the study protocol approved by the Coordinating center EC and the local ECs (see Appendix B for technical information). 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

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.

7.10 Storage

The database for data storage (Oracle MySql v. 8.0.40-azure) 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.
The system performs a Database backup once a day (around 11.20 a.m.) and keeps the last 7 copies.

7.11 Software and hardware configuration of the devices used

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

Web: Service app Azure

- SKU e dimensions: PremiumV3 P3v3 (site: Italy North)
- Operating system: Linux / stack di runtime Php 8.3
- Development technologies:
    - front-end**:** AngularJS v1.8.3
    - back-end**:** Laravel framework version 10.48.3

DB: Server flessibile di Database di Azure per MySQL

- Calculation size: Standard_D2ds_v4 (2 vCore, 8 GiB di memoria, 3200 operazioni di I/O al secondo max)
- MySQL version: 8.0
- Site: Italy North

Application gateway

- Level: WAF V2
- Site: Italy North (zones 1, 2, 3)

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 RISM. 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.

The ongoing PASS are reported below (see 8.3).

8.1.2 Documents

The following procedures and all the PASS-related activities are strictly linked with the organization of the RISM 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"

The complete dataset is extracted anonymously by the STOC in SAS, Access and Excel formats, as agreed, and sent to the PI for PASS, who forwards them to the dedicated Statistician (ST). PASS data are processed and analysed in accordance to the Statistical Analysis Plan (SAP).

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 RISM 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 STOC 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 (STOC), 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 RAs, 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 RA's center visits (if present), and indicatively within the time-frame of one month, the Study Coordinator asks the clinical center for 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 RA 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 RA 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 RA 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

If requested, 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 RAs and archives the file Lista soggetti PASS updated.

8.3 Description of the current PASS

1. Title of PASS: Long-Term Surveillance of Ocrelizumab Treated Patients With MS

- Short study title: Manuscript Study
- Investigational drug: Ocrelizumab (Ocrevus)
- Study population:
  - Patients with MS who must be newly treated with ocrelizumab during the study observational period;
  - Patients with MS 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 MS 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

2. 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

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

- Short study title: Kesimpta long-term PASS
- Investigational drug: Ofatumumab (Kesimpta)
- Study population:
  - Patients with MS who must be newly treated with ofatumumab during the study observational period;

- Patients with MS 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 RA receive regular visits. The RA 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
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
RA	Research Assistant
SAP	Statistical Analysis Plan
SC	Scientific Committee
SIN	Società Italiana di Neurologia
ST	Statistician for PASS
STOC	Technical Methodological and Coordinating Structure (Struttura Tecnico Operativa e di Coordinamento)

12 APPENDIX B: RISM-APP FEATURES

Conservazione dati/crittografia

I dati sono conservati in forma criptata su un server flessibile di database di Microsoft Azure per MySQL con località Italy North.

I dati anagrafici sono criptati nel seguente modo:

1. utilizzo del modulo di crittografia del sw di Database che prevede che i dati identificativi siano cifrati con chiave simmetrica di almeno 128 bit diversa da quella utilizzata per la cifratura dei dati clinici (anche essa di almeno 128 bit). Le chiavi simmetriche devono essere cifrate a loro volta, preferibilmente con chiavi asimmetriche di almeno 2048 bit;
2. impegno dei ricercatori riceventi ad utilizzare algoritmi di crittografia equivalenti nei loro studi;
3. gestione delle chiavi che preveda il cambio chiavi simmetriche almeno ogni 2 anni;
4. revisioni biennale degli algoritmi di crittografia sulla base dei rapporti Encrypt o equivalenti.

2

Titolari e responsabili dati

L'Unità di Ricerca FISM (Fondazione Italiana Sclerosi Multipla ETS) – UNIBA (Università degli Studi di Bari "Aldo Moro" Dipartimento di Biomedicina Traslazionale e Neuroscienze – DiBraiN) sono co-titolari dei dati, assieme ad ogni centro partecipante.

Ogni centro è titolare autonomo dei propri dati.

La Fondazione Italiana Sclerosi Multipla ETS, a sua volta, ha nominato dei sub-responsabili del trattamento dei dati ai sensi e per gli effetti dell'art. 28 del GDPR 679/2016.

Solo il web master della RISM-App ha accesso all'intero database.

3

Operativamente

Il centro, dopo aver ricevuto approvazione dal Comitato Etico e Delibera Aziendale (se richiesta), raccoglie i dati del paziente e li inserisce, con modalità protetta da password, nella RISM-App.

Il centro, nella propria sezione dedicata, vede in chiaro tutti i dati dei propri pazienti. Ogni caso ha un ID.

I dati vengono trasferiti in maniera criptata su un server flessibile di database di Microsoft Azure per MySQL con località Italy North (*Dimensioni di calcolo: Standard_D2ds_v4 [2 vCore, 8 GiB di memoria, 3200 operazioni di I/O al secondo max] e Risorsa di archiviazione: 247 GiB*).

In tutti i file di dati disponibili per le analisi i pazienti sono identificati solo attraverso l'ID. Solo il webmaster autorizzato ha la possibilità di vedere tutti i dati in chiaro.

Tutte le comunicazioni tra centro e Struttura Tecnico Operativa e di Coordinamento avvengono identificando i casi tramite ID e in una sezione protetta della RISM-App.

4

Tracciabilità e registrazione accessi

È possibile tracciare tutti gli accessi al database sia in lettura che in scrittura.

I tracciamenti, in conformità alle Linee guida del Garante, avvengono tramite la registrazione dei seguenti dati:

- identificativo del soggetto incaricato che ha posto in essere l'operazione di accesso;
- data e l'ora di esecuzione;
- identificativo della postazione di lavoro utilizzata;
- identificativo ID del paziente la cui cartella clinica è interessata dall'operazione di accesso da parte dell'incaricato;
- tipologia dell'operazione compiuta sui dati (anche operazioni di pura consultazione).

Tutte dette registrazioni sono criptate in opportuni file di log.

5

Sicurezza accesso - Password

All'interno di ogni centro, vengono assegnate al Principal Investigator le credenziali di accesso alla RISM-App. Tali credenziali sono definite dal supporto informatico della Struttura Tecnico Operativa e di Coordinamento e comunicate alla segreteria tramite email, la quale provvederà ad inviare formale email all'utente in questione.

La password assegnata al Principal Investigator è temporanea e va obbligatoriamente cambiata al primo accesso al sistema ed ha una durata di 3 mesi. Scaduti i 3 mesi, il sistema richiede all'utente di modificare obbligatoriamente la password di accesso.

All'interno di ogni centro, il Principal Investigator può nominare uno o più utenti delegati all'input dei dati dei pazienti in cura. I nominativi delle persone autorizzate vengono comunicati per iscritto alla segreteria della Struttura Tecnico Operativa e di Coordinamento, che richiede al supporto informatico di attivare i nuovi account per il Centro, ripetendo la procedura di assegnazione descritta sopra.

6

Sicurezza accesso (2)

Per migliorare ulteriormente la sicurezza del sistema è stato implementato un meccanismo di:

- verifica lunghezza password non inferiore a 12 caratteri;
- obbligatorietà del cambio della password al primo utilizzo del sistema e successivamente ogni 3 mesi;
- controllo della complessità della password che dovrà contenere almeno 3 caratteri tra numeri, caratteri alfabetici in maiuscolo e minuscolo nonché caratteri speciali;
- non riutilizzo delle ultime 4 password.

La memorizzazione della password è stata implementata con un nuovo algoritmo di hashing one-way più sicuro (bcrypt).

E' stato attivato CAPTCHA (Completely Automated Public Turing test to tell Computers and Humans Apart), una misura di sicurezza nota come autenticazione Challenge/Response. Essa protegge gli utenti dallo spam e dalla decriptazione delle password chiedendo loro di superare un semplice test che attesti che l'utente è una persona e non un computer.

È stata implementata l'autenticazione a due fattori (2FA), mediante l'utilizzo dell'app Microsoft Authenticator o dell'app Google Authenticator.

7

Modalità di archiviazione (back-up)

Il database utilizzato per l'archiviazione dei dati consente di mantenere una copia di ogni transazione che apporta una modifica al database.

Il server flessibile di Azure per MySQL crea automaticamente i backup e li archivia in modo sicuro nella risorsa di archiviazione con ridondanza locale all'interno dell'area. I backup possono essere usati per ripristinare il server a un momento specifico. Il periodo di conservazione dei backup è pari a 7 giorni.

Applicativo 1 backup ogni ora con 240 restore point
DB 1 backup al giorno con 7 giorni di restore point

È in corso di valutazione un ulteriore backup dell'infrastruttura in diverso datastore con funzione di immutabilità del dato.

8

Configurazione Servizi

RISM-App è un applicativo web-based ospitato su cloud Microsoft Azure che utilizza i seguenti servizi:

Web: Servizio app Azure
- SKU e dimensioni: PremiumV3 P3v3 (località: Italy North)
- Sistema operativo: Linux / stack di runtime Php 8.3
- Tecnologie di sviluppo:
  - front-end: AngularJS v1.8.3
  - back-end: Laravel framework versione 10.48.3

DB: Server flessibile di Database di Azure per MySQL
- Dimensioni di calcolo: Standard D2ds_v4
- Versione MySQL: 8.0
- Località: Italy North

Application gateway
- Livello: WAF V2
- Località: Italy North (zona 1, 2, 3)

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