Manual of Procedures (MOP) for

Italian multiple sclerosis register and related disorders

Protocol Number: SM001 e SM002

Version Number: 1.0

Summary of Changes:

Number	Date	Affected Chapter(s)	Summary of Revisions Made:
1.0	15/07/2021	-	First issue

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 a study's organization, operational data definitions, recruitment, screening, enrollment, and 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. Use of the MOP increases the likelihood that the results of the study will be scientifically credible and provides reassurance that participant safety and scientific integrity are closely monitored.

This MOP is to be used as a reference document for policies and procedures related to the study entitled "Italian multiple sclerosis register and related disorders". 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 the MOP is available on the website of the project https://registroitalianosm.it/. The archive of the related documents and previuos versions are 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 be notified that the MOP has been updated and is available on the study website.

2 ADMINISTRATIVE

2.1 Study Leadership Structure

2.1.1 Organizational Chart

The "Italian multiple sclerosis register and related disorders" 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 register and related disorders" includes the following:

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

Moreover, the study recognises the importance of having stakeholder advisory boards, including a stakeholder advisory board of pharmaceutical companies (Almirall, Merck Serono, Novartis, Roche, Sanofi, Teva, Mylan, Biogen and Celgene) 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 Committe	FISM-Battaglia UniBA-Trojano	m.a.battaglia@aism.it maria.troiano@uniba.it	Organizational and administrative role
Scientific Committe	Trojano	maria.troiano@uniba.it	Scientific overview
Struttura amministrativa e di coordinamento (SAC)	Ponzio	michela.ponzio@aism.it registroitalianosm@aism.it	Coordination of study, centers, research assistance and administration
Struttura Tecnico Operativa (STO)	Mosconi	paola.mosconi@marionegri.it smregistro@marionegri.it	Coordination of study, centers and data collection. Conduct of the study, development of CRF and web
Data and analysis	Mosconi Lepore Ponzio	paola.mosconi@marionegri.it vito.lepore@marionegri.it michela.ponzio@aism.it	Data collection and data analysis
Informatics	Rossi Vitali Bazzi D'Ettorre Corrado DSMLab	lorenzo.rossi@marionegri.it massimo.vitali@marionegri.it davide.bazzi@marionegri.it ing.antonio.dettorre@gmail.com donatella.corrado@gmail.com l.marfisi@dmslab.it	Help Desk, eCRF, Web application

2.2 Executive Committee

The Executive Committee is chaired by FISM and University of Bari (Unità di Ricerca FISM–UNIBA) and it 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 SM registers.

2.3 Scientific Committee

A scientific committee oversees the study. Scientific Committee includes clinicians, methodologists, representatives of MS centers, and of the Italian Neurological Society (SIN). Three representatives of MS centers are elected every 3 years by the network of the centers.

2.3.1 Roles and Responsibilities

The scientific committee 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 Scientific Committee - every month/ every last Friday - are organized by the Executive Committee. Meeting are chaired by the President of the Scientific Committee on the basis of an agenda circulated among members some days before the meeting. A minute of the meeting is approved among members.

2.3.2 Members

- Prof.ssa Maria Trojano (Dipartimento Scienze Mediche di Base, Neuroscienze ed Organi di Senso, Università degli Studi Aldo Moro, Bari, "Presidente");
- Prof. Mario Alberto Battaglia (Fondazione Italiana Sclerosi Multipla, Genova, "Vice-presidente");
- Dr. Marco Capobianco (Centro Di Riferimento Regionale Per La SM (CRESM) - SCDO Neurologia - AOU San Luigi, Orbassano, "Rete dei centri SM");
- Prof.ssa Maura Pugliatti (Centro Di Servizio E Ricerca Sulla Sclerosi Multipla AOU Di Ferrara, Ferrara, "Rete dei centri SM");
- Dr.ssa Monica Ulivelli (UOC Neurologia e Neurofisiologia Clinica - Università degli Studi di Siena, Siena, "Rete dei centri SM");
- Dr.ssa Paola Mosconi (Istituto di Ricerche Farmacologiche Mario Negri IRCCS Institute, Milano, "Rappresentante IRFMN");
- Prof. Francesco Patti (Centro Sclerosi Multipla AOU Policlinico Vittorio Emanuele, Catania, "Esperto");
- Dr. Claudio Gasperini (UOC di Neurologia e Neurofisiopatologia Azienda Ospedaliera S. Camillo-Forlanini, Roma, "Rappresentante Società Italiana Neurologia");
- Prof.ssa Maria Pia Amato (Centro Sclerosi Multipla AOU Careggi, Firenze, Rappresentante "Esperto");
- Dr. Roberto Bergamaschi (Centro Interdipartimentale Sclerosi Multipla, Fondazione Istituto Neurologico C. Mondino, Pavia, "Esperto/Segretario");
- Prof. Giancarlo Comi (Direttore Dipartimento di Neurologia, IRCCS Ospedale San Raffaele, Milano, "Esperto").

2.4 Struttura Amministrativa e Coordinamento (SAC) e Struttura Tecnico Operativa (STO)

Two methodological and technical Infrastructures lead the study:

- SAC Struttura Amministrativa e di Coordinamento (Technical and Administrative Infrastructure) coordinated by FISM and
- STO Struttura Tecnico Operativa (Technical Methodological Structure) based at IRCCS Istituto Ricerche Farmacologiche Mario Negri IRCCS Institute.

2.4.1 Roles and Responsibilities

SAC - Struttura Amministrativa e di Coordinamento deal with the secretarial functions, the requests for funding to support the infrastructure and the reporting processes in close collaboration with the Technical Operational Structure, 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.

STO - Struttura Tecnico Operativa is responsible for the technical-operational coordination of the study, data analysis, management of the central server that hosts the Web Application and the aggregated database, report to the centers, analysis of quality of data collected, development of Web Application. STO guarantees the connectivity with the centers, activities to back up the data stored on the server and to take appropriate security measures to protect such data. STO coordinates activities with centers, and Ethical Committee.

SAC and STO share a section in the restricted area of the websiste where all the data of the centers participant are stored and periodically updated.

2.4.2 Members

SAC - Struttura Amministrativa e di Coordinamento
Scientific director FISM, Dott.ssa Paola Zaratin con compito di raccordo tra strutture operative (SAC e STO) ed Executive Committee.
Ricercatori senior con compiti di coordinamento delle attività Dr.ssa Michela Ponzio.
Segretarial, Sig.ra Luciana Lunadei, Maria Rita Di Fazio (administrative secretary)
Legal Office, Avv Paolo Bandiera, Dott.ssa Martina Bassi

STO - Struttura Tecnico Operativa
Ricercatori senior con compiti di coordinamento delle attività della Struttura Tecnico Operativa, Dr.ssa Paola Mosconi e Dr. Vito Lepore.
Figure professionali per gestione e aggiornamento database iMed-Web Application (vecchia versione e 2.0), estrazione dati, attività di help-desk e supporto online ai centri partecipanti, realizzazione e manutenzione del nuovo sistema di gestione web-based dedicato al Registro, attività di backup: Ing. Lorenzo Rossi (Computer Engineer), Dr. Davide Bazzi e Dr. Massimo Vitali (Computer Informatic Technicians), Ing. Antonio D'Ettorre (Computer Engineer), Dr.ssa Donatella Corrado (Datawarehouse, Datamining developer, and Web developer), DSMLab.
Ricercatori per reportistica, valutazione indicatori, presentazione grafica, analisi statistiche, scrittura report e articoli: Dr.ssa Cristina Bosetti, Dr.ssa Claudia Santucci (coordinamento Dr. Valter Torri) e Ing. Antonio D'Ettorre.
Figure professionali per coordinamento e rapporto con i centri partecipanti, Comitati Etici, compiti di segreteria e di assistenza alla attività di coordinamento: Guya Sgaroni.

2.5 Centers participants committee

The participant centers are recognized as the "Italian Multiple Sclerosis Register and related disorders Centers Group". The committee of principal investigator of each center elects every three years 3 representatives that become part of the Scientific Committee of the study.

2.5.1 Roles and Responsibilities

- Enrollment of eligible patients;
- Collection of Inform Consent;
- Data collection according with the protocol of the study;
- Storage of patients' documents.

2.5.2 Members

An up-to-date list of participants centers is available on the website of the study: https://registroitalianosm.it/.

2.6. Staff and Training

2.6.1 Centers and clinicians

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

The centers were required to include all the multiple sclerosis (and related disorders) cases in the study, to inform people about the "Italian multiple sclerosis register and related disorders", request their consent to participate, and to transfer a standardized set of data using the Web Application.

Participation in "Italian multiple sclerosis register and related disorders" is voluntary both from the neurologist's and the patient's side.

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

2.6.2 Research Assistance

In order to increase the quality of the data collected, a group of 17 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 (research fellowship) (*Lettera di assegnazione Borsa di ricerca*). To regulate the activities of researchers at the centers, FISM asks the center to sign a "hospitality agreement" (*Accordo di ospitalità*) and gives the researcher a mandate to process personal data (*Lettera di incarico al trattamento dei dati personali*).

Each assistant is allocated to one or more centers, depending of the size of the Multiple Sclerosis clinical center.

Research assistants report daily by mail the activities done in the visited center, in copy the local PI. Research assistants report monthly the all activities to the STO, and at least three/times year they are involved in meeting to discuss problems of data collection.

All research assistances receive ad hoc training on all aspects of the disease and the protocol, in particular:

- Information about multiple sclerosis and treatment available;
- Study Objectives;
- Inclusion/Exclusion Criteria;
- Subject Visit Schedule;
- Screening, Treatment, and follow-up;
- Laboratory Evaluations;
- Investigator Responsibilities;
- Essential Document Collection and Storage;

- Informed Consent Procedures;
- Web Application;
- Query Process.

2.7 Policies and Procedures

2.7.1 Data Request Policy

The data is stored on the server dedicated to the Mario Negri IRCCS Institute in an encrypted form. The Research Unit FISM–UNIBA as "Co-Owners" - together with centers of 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 with Executive Committee and Scientific Committee.
Each participant center has full access of data collected in its center.
Each participant center is requested to share with SAC abstract or articles related with the study; an ad hoc section of the study website is dedicated to the publication/news regarding the study.
For the Type 1 and 2 studies (see 2.6.4) presented to the Scientific Committee each PI is requested to declare the policy of publication, according with the number of patients available in each center.

2.7.3 Organizational Chart

Each site will maintain a delegation of responsibilities log in the essential documents binder. This log associates investigator and/or site staff names with specific study responsibilities. In particular, each center signs a specific document where the clinical center delegates the Italian MS Register and related disorders infrastructure (Operating unit) to work for the study (*Mandato di adesione*). In addition, FISM ask to Center to be designate to manage personal data through an act of appointment as an external person in charge of the processing of personal data (*Atto di nomina per responsabile esterno dei dati personali*).

2.7.4 Data for specific sub-studies

Data of the study are available for the participant centers for specific sub-studies. A standardized process for applications of research study has been developed. The applications are submitted through https://www.aism.it/bandiregistro website after registration of the study responsible. Through this website of the FISM, each participating center can propose research studies addressing one of the high priority areas of the “Italian multiple sclerosis register and related disorders”. All the sub-studies are discussed by Scientific Committee before their implementation. The submissions of sub-studies to the Scientific Committee of the “Italian multiple sclerosis register and related disorders” can be made at any time and will be evaluated in the first meeting of the Committee. It is possible to present two different types of sub-studies to the Scientific Committee of the “Italian multiple sclerosis register and related disorders”:

- Type 1 studies: studies promoted and coordinated by the Scientific Committee, on the spontaneous initiative of the Scientific Committee or proposed by Centers / Institutions (public or private), in which all the Centers belonging to the “Italian multiple sclerosis register and related disorders” will participate by right and obligatorily contributing with the "minimum data set ".
- Type 2 studies: collaborative studies between 2 or more Clinical Centers relating to specific data sets always within the minimum data set.

Operatively, firstly, the feasibility of proposals (i.e., variables availability, completeness of data, size of the sample, methodological appropriateness etc.) is assessed by STO. Then, the members of the Scientific Committee assess the proposals according to scientific quality, value of the study, and alignment with priority areas of the study.
After the approval, proponent center receives by SAC a letter with the communication of the approval of the study and, if presents suggestions from the SC together with and agreement form for the use of the data. After the signature of the agreement data are uploaded in a protected area of register website and the responsible of the study is informed by mail. Through a specific temporary password, the proponent enters the protected area and downloads the file of data.
All data set sent is anonymous.

3 REGULATORY

3.1 Regulations and Regulatory Bodies

This observational study is compliant with human subjects' regulations, in particular the study is conduct according to AIFA Determination 20 March 2008.

3.1.1 Informed Consent / Assent Process

Informed consent is required for all subjects participating in the study. In obtaining and documenting informed consent, the investigator should comply with applicable regulatory requirements. Prior to the beginning of the study, the investigator must have the Ethic Committee's (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 old
Under 12 years old consent forms	To be delivered to each eligible patient under 12 years old
12-18 years old consent forms	To be delivered to each eligible patient 12-18 years old

In each participant centers, all consent forms properly filled and signed are filed in a dedicated binder. Copy of consent forms is stored only in the participating center; SAC and STO do not receive copy of these documents.
After having collected the consent forms, clinicians of participants centers must fill in an appropriate field on the Web Application CRF.

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 of the changes 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

Regarding the people with multiple sclerosis involved in the study, a document with details of 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 multiple sclerosis signs this document before enter the study.

A document concerned the PIA - Privacy Impact Assessment of the study has been jointly prepared by FISM and STO-Mario Negri. The final version has been signed in October 2020.

3.2 Essential Documents

Essential documents are those documents 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 during study monitoring visits.

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 documents.

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. The centers are periodically achieved by e-mail with updates regarding 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 survey, timeliness, generalization and representativeness of the collected data. For each examined indicator or domain each participating center was awarded with a score of 5 for the highest performance, while lower scores of 4 to 1 were attributed for

progressively lower performance. Every 6 months, each participating center receives a report where data and performance indicators of its own center are benchmarked with the whole sample: in this way each center can assess the most critical performances and the level of improvement with time.

5 PROTOCOL IMPLEMENTATION

5.1 Recruitment, Screening, and Enrollment

5.1.1 Recruitment Methods

Each participant center recruit patients according with its clinical activity.
Some of the participant center started their data collection in 2000 in the framework of the Italian Multiple Sclerosis Database Network (MSDN). This network used the iMed© software's system, progressively replaced by a web-based system developed ad hoc for the study, the Web Application.

5.1.2 Informed consent

Each eligible patient enrolled is required to sign a written informed consensus to enter into the "Italian multiple sclerosis register and related disorders". Since in some of the participant centers data were collected before the starting of the "Italian multiple sclerosis register and related disorders" (through iMed© or other data-entry), according to the local laws and regulations, data collected retrospectively can be also included.

5.1.3 Establishing Eligibility

Are eligible for the study:

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

Regarding the diagnosis of multiple sclerosis physicians refer to the Mac Donald criteria.

5.1.4 Assigning Participant Identification Numbers

Each center is identified by a 2-character numeric code attributed uniquely by SAC.

5.2 Enrollment Procedures

For each center STO records the information related to the Principal Investigator in the Web Application, enabling it to access the Web Application. The software automatically sends an email to the Principal Investigator confirming registration in the system.
The password assigned to the Principal Investigator is temporary and must be changed at the first access to the system and has a duration of 3 months. After 3 months, the system asks the user to change the access password.
Within each center, the Principal Investigator can appoint one or more users delegated to input the data of the patients. The names of the authorized persons are communicated by the Principal Investigator by email to the STO which requests the IT support to activate the new accounts for the Center, repeating the assignment procedure described above.
To further improve the security of the system, the following has been implemented:

- password length not less than 8 characters;
- it is mandatory to change the password when using the system for the first time and every 3 months thereafter;
- password complexity check which must contain at least 3 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*).

6 PROCESS RESPONSIBILITIES

6.1 Detailed Description of Study Procedures

For each patient enrolled a new form must be filled in in the Web Application system.

The system assigns a code number to each new patient.

6.1.1 Schedule of Events

Each patient will be followed according with the clinical center activities.
According with the protocol of the study, for each patient is requested a clinical examination every 6 months together with an EDSS assessment as periodic follow-up.

6.1.2 Side effects

In the Web Application a section is dedicated to multiple sclerosis treatment specific. For every multiple sclerosis 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.

7 DATA MANAGEMENT

7.1 Data Collection Methods

Data are collected through a web-based system - Web Application - ad hoc developed for the study available at https://registroitalianosm.it/. Each center can enter the data after identification through a personalized password (direct login at https://app.registroitalianosm.it/).
In the "Italian multiple sclerosis register and related disorders", each patient has a unique valid code identifier, through the patient encrypted fiscal code.
Each patient is assigned to a center.
The web application system admits the possibility that a subject is followed by two participating centers - for example in a rehabilitation center and in a drug center.

7.2 Source Documentation Requirements

All source documents should be filled out by the local study coordinator, their assistants or research assistance.

7.3 Study Forms

The Scientific Committee agreed, by consensus, on a compulsory common minimum dataset (MDS) of selected information according to the principles of relevance. MDS ensures the

collection of sufficient data for the clinical characterization of the single patient. The list of the mandatory variables of interest, identified on the basis of the existing guidelines and the recommendations of the Scientific Committee, ensures:

- participation of a large and representative number of centers;
- easy and simple data collection;
- ability to each center to achieve maximum completeness and quality of data;
- possible development of linkage procedures with regional information flows of health administrative data (hospital discharges, prescription drugs, ticket exemptions, register 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.

According with the clinical practice the following information are requested in the Web Application:

- Identification/Anagrafic data;
- Onset and Diagnosis (Anamnesis);
- Follow-up visits – EDSS, Safety;
- Relapses;
- Adverse events (clinical events);
- Pregnancies;
- Treatment specific;
- Treatment symptomatic;
- Risk assessment;
- Co-morbidity;
- Familiar anamnesis;
- Laboratory exams;
- Magnetic Resonance, Liquor, Evoked Potentials;
- EEG, ECG, Blood pressure.

The following standardized database are implemented in the Web Application with the aim of the 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 old or diagnosed when they are less than 18 years old. According with the clinical practice the following information are requested in the Web Application:

- Identification/Personale data;

- Onset and Diagnosis (Anamnesis);
- Follow-up visits – EDSS, Safety;
- Relapses;
- Adverse events (clinical events);
- Treatment specific;
- Treatment symptomatic;
- Risk assessment;
- Anamnesis and Risk Factors;
- Tests and scales;
- Laboratory exams;
- Magnetic Resonance, Liquor, Evoked Potentials;
- EEG, ECG, Blood pressure.

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 Web Application.
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 multiple sclerosis; statistical reports on local and national data - is reserved for authorized personnel. Each operator who wants to make their 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 MRI assessment.

7.7 Long Term Storage of Case Report Forms

As the nature of this study location and length of time of documents will be maintained by each clinical centers. Administrative data and information about the study will be maintained by STO and SAC for a period of ten years.

7.8 Maintaining Data Privacy

The Web Application 2.0 has been developed using the PHP Laravel framework (framework version 6.20.18 - PHP version 8.0.3) which guarantees protection from the main security risks highlighted by OWASP.
The Web Application 2.0 provides for the storage of data, in accordance with the study protocol approved by the Coordinating center Ethics Committee and the local Ethics Committees. Patient identification information (name, surname and social security number) entered in the Web Application 2.0 are collected on the central server database and made accessible only to authorised healthcare professionals of the participating centers.
In the Web Application 2.0 the personal data sheet is logically separated from the rest of the cards. The Web Application 2.0 was designed and developed with full respect for the privacy of both the investigators and the patients. In particular, the privacy of patients is guaranteed by associating each of them with a completely anonymous numeric identification code. Data relating to the 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 is stored in encrypted form on the server dedicated at the Mario Negri Institute IRCCS. 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 (MySQL 5.7) 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 mode 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 3 months without any loss of information.

7.11 Software and hardware configuration of the devices used

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

Frontend Application

- Operating System: CentOS Linux release 8.1.1911;
- Programming language: PHP 8.0.3;
- Web server: Apache v. 2.4.37;
- Website protection: certificato SSL/TLS.

Backend Database

- Database: Oracle MySql v. 5.7.29

8 SITE MONITORING

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

9 FINAL STUDY

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

10 APPENDIX A: LIST OF ABBREVIATIONS

AE	Adverse Event/Adverse Experience
AIFA	Agenzia Italiana del Farmaco
CIS	Clinically Isolated Syndrome
CRF	Case Report Form
EC	Ethic Committee
eCRF	Electronic Case Report Form
ECG	Elettrocardiogramma
EDSS	Expanded Disability Status Scale

EEG	Elettroencefalogramma
FISM	Fondazione Italiana Sclerosi Multipla
GCP	Good Clinical Practice
IRCCS	Istituto di Ricovero e Cura a Carattere Scientifico
MDS	Minimum Dataset
MOGAD	MOG antobodies
MOP	Manual of Procedures
MRI	Magnetic Resonance Imaging
NMOSD	Neuro Myelitis Optic Spectrum
OWASP	Open Web Application Security Project
PHP	Hypertext Preprocessor
PI	Principal Investigator
QA	Quality Assurance
QC	Quality Control
SAC	Struttura Amministrativa e di Coordinamento
SAE	Serious Adverse Event/Serious Adverse Experience
SOP	Standard Operating Procedure
STO	Struttura Tecnico Operativa
TAI	Technical and Administrative Infrastructure
TMS	Technical Methodological Structure
UNIBA	Università degli Studi di Bari