



Clinical trial

The Argentinean multiple sclerosis registry (RelevarEM): Methodological aspects and directions

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ABSTRACT

Despite that different registries already exist in various countries in Europe and North America, no ongoing nationwide registry exists in Latin America (LATAM), a region where the disease behaves differently than in other regions. The objective of this document is to describe the methodology behind RelevEM, the first nationwide MS registry in Argentina and LATAM.

Methods: In this article, we described the creation, implementation and data management of the nationwide MS registry in Argentina. The registry contains information on the structure, ethical aspects, implementation and variables of the registry (Clinical Trials registry number NCT NCT03375177).

Conclusion: RelevEM is the first MS nationwide registry in Argentina, as well as in LATAM, with the objective of providing reliable real-world data of MS in the country.

1. Introduction

Multiple sclerosis (MS) is a chronic disease of the CNS, pathologically featured by the presence of multiple inflammatory lesions that progress in time and that lead to significant disability in most affected patients 20 or 30 years after disease onset (Noseworthy et al., 2000; Trapp et al., 1998; Kremenutzky et al., 2006; Müller et al., 2005). Based on the predominance of episodic demyelinating events and the neurodegenerative process, the clinical course is defined either as relapsing remitting, which represents approximately 85% of prevalent cases (RRMS), or as progressive (primary, if progression starts from onset, or secondary if it begins after a preceding RRMS) (Lublin and Reingold, 1996; Lublin et al., 2014).

Clinical registries comprise a set of systematic collected and stored data focused on a specific condition (Trojano et al., 2017). The information stored in a registry provides relevant information about a disease and, through a process of error detection, ensures data quality and reliability (Trojano et al., 2017). Systematic data collection is characteristic of a well-designed registry, and its quality depends directly on the completeness and validity of the data contained therein (Trojano et al., 2017; Trojano et al., 2018).

MS registries are essential tools for providing relevant information such as epidemiological aspects of the disease, safety issues and treatment effectiveness (Trojano et al., 2018), (Flachenecker et al., 2014). Currently there are many registries from various countries from Europe and North America that describe how the disease behaves in those regions (Flachenecker et al., 2014); however, no ongoing nationwide registry exists in Latin America (LATAM), a region where the disease behaves in a different way in terms of lower frequency of the disease (lower prevalence as well as incidence) and probably a different disease course severity when compared with other regions and hemispheres (Cristiano and Rojas, 2017).

The objective of this document is to describe the methodology behind RelevEM, the first nationwide MS registry in Argentina and Latin America (Clinical Trials registry number NCT NCT03375177).

2. Methods

2.1. Definition and objectives of the registry

RelevEM is a longitudinal, strictly observational MS registry in Argentina. The registry is open to all practicing neurologists, MS specialists and their teams across the country. It tracks the outcomes of routine clinical practice of patients with MS.

The primary objective of the registry is to create an MS physicians network in Argentina that captures pragmatic and relevant information from MS patients in terms of clinical and demographic aspects. The secondary objective includes safety aspects and access to healthcare,

and the tertiary objective is related to treatment effectiveness (Table 1). For the treatment effectiveness outcome, information about relapses, EDSS progression and new MRI lesion from included patients on treatment will be used.

2.2. Structure of the registry

The structure of the registry includes an executive committee with an administrative and organizational role; a scientific committee which oversees the scientific initiatives, promotes specific strategic projects and approves requests of access to centralized data for further research projects; a methodological and regulatory team which provides the methodological support of the registry and ensures the regulatory aspects in each center; a group of technical programmers that develop and provide support to the web-based platform that allows researchers to register and follow up their patients. The structure of the record is shown in Fig. 1.

2.3. Ethical aspects

The Argentinean MS registry was approved as the coordinating center by the Ethics Committee of the Hospital Italiano de Buenos Aires, Argentina. Later, individual regulatory and data protection requirements were fulfilled according to all applicable local regulations and laws in each participant center and practice. Each principal investigator of the registry (or those delegated to the centre as co-investigators) fully explains the objective of the registry to all potential participants and encourages their questions. All patients willing to participate in the registry are required to provide an oral or signed consent form (pending

Table 1
Information collected by the Argentinean MS registry.

Module	Description
Baseline	Patient identification Center Informed consent Administrative information Disease onset, course, symptoms, recovery Comorbidities
Follow up	Date EDSS Bouts Treatment used for MS
Paraclinical tests	MRI date MRI new lesions CSF findings
Safety	Adverse events

MRI = magnetic resonance imaging; EDSS expanded disability status scale.

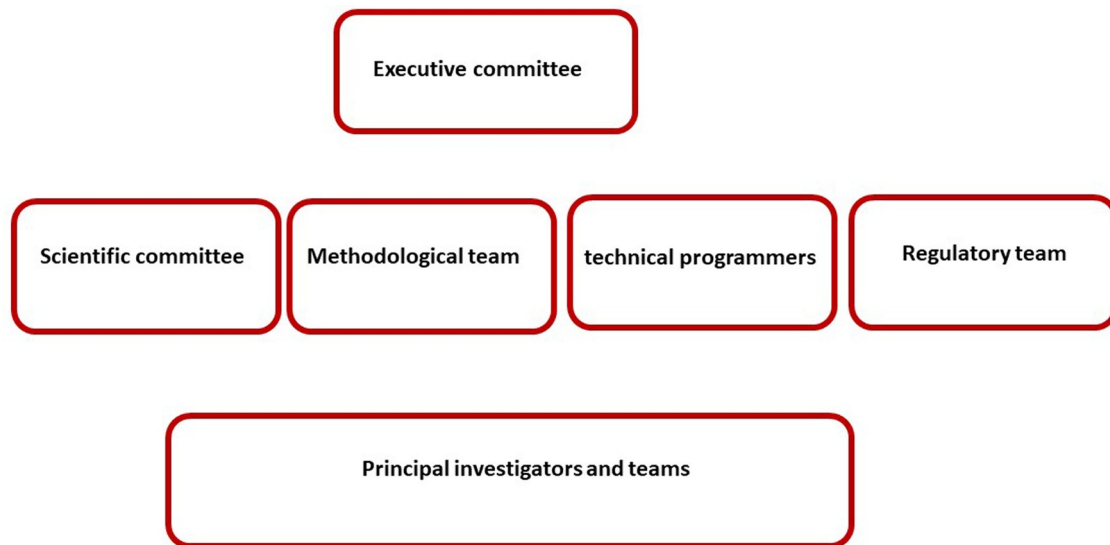


Fig. 1. Structure of RelevaEM.

on each approval) authorizing release of their coded medical information anonymized to the central registry. To be included in the registry, every researcher must fulfill the ethical and regulatory conditions.

2.4. Population

Any patient diagnosed with MS, a clinically isolated syndrome, a radiologically isolated syndrome or a neuromyelitis spectrum disorder defined by validated diagnostic criteria (for MS and NMOSD) (Wingerchuk et al., 2015; Thompson et al., 2018) can be entered into the registry. To ensure the correct use of the diagnostic criteria for MS and NMOSD in each center, the executive committee invite to all MS centers and physicians involved in the care of affected patients in Argentina. To reduce the possibility of bias in the selection, each participating physician should aim to include all patients seen in their practice or clinic.

2.5. MS centers and physicians involved

Medical assistance to MS patients in Argentina is mainly provided by qualified physicians and MS centers. The goal of the registry is to include all MS patients in Argentina and, consequently, all MS centers and physicians involved in the care of affected patients. Qualified centers and PI were selected based on their experience in disease management (number of MS patients seen per year), the possibility to perform clinical and paraclinical procedures (oligoclonal bands on CSF, MRI exams, etc.) and activities involved in education and research in MS in Argentina. All qualified physicians and centers were contacted by the executive committee in order to explore their willingness to participate in the Registry project. Participation in the Registry is voluntary for both the neurologist and the patient. From May 2018 to September 2018, the centers and PIs were contacted and incorporated into the Registry. Centers were incorporated in stages, starting with Buenos Aires, and later extending to other centers by region. Up to November 2018, 56 centers and 98 professionals distributed throughout Argentina have become part of the Registry (Fig. 2).

2.6. Data collection and patient confidentiality

Prevalent and incident cases are included in the Registry by each physician. Once the patient is identified and has consented to participate, the requested data is included in a web platform specifically designed for the purpose of the Registry.

The data is uploaded by the principal investigators of each participating center. The Scientific Committee agrees, by consensus, on a compulsory common minimum dataset consisting of selected information according to the principles of relevance to ensure the collection of enough data for the clinical characterization of the single patient. The list of the mandatory variables of interest at Registry entry, as well as during the follow-up, is shown in Table 1. Information about the characteristics of the disease, both at the beginning and during follow-up, is collected throughout by each PI on the data collection form (Table 1).

At all times, the protection of the patient's identity and data is observed in accordance with the legal regulations in force under the National Law of Protection of Personal Data 25.326 (Habeas Data), in accordance with the international legislation on registration of diseases and protection of personal and private data, according to the 18th World Medical Assembly of Helsinki (1964), when applicable. The right to non-participation in the registry is always respected without this implying in any case any type of discrimination, differential treatment or mistreatment towards the patient.

The entire process regarding informed consent, patient evaluation, data entry, data sharing and other procedures of the Registry were standardized in an operation procedure described in documents of the Registry function.

2.7. Data monitoring

All the variables at the time of entry and during the follow-up are mandatory full load. In this way, data loss is ensured to be kept at a minimum. Data are centrally monitored by the methodological team to guarantee a high level of quality for the information collected. Centers are periodically contacted with ad hoc reports with queries on missing data, inconsistencies among variables collected and any duplicates for their resolution.

2.8. Research projects

The mission of the Registry is not limited to assuring quality healthcare for patients with MS but also to promote research projects that address high-priority issues. The philosophy underpinning the registry seeks to reflect the collaborative nature of the project and to encourage epidemiological research efforts in MS in Argentina. Any researcher who is part of the Registry may propose a research project that will be evaluated by the scientific committee and, if relevant, will



Fig. 2. States and centers involved in the registry.

be approved for its realization. The data contained in the Registry will be used in the research project and, in this way, the performance of various epidemiological studies employing the Registry’s information will also be encouraged.

2.9. Statistical analysis plan

This is an open-ended Registry, and sample size is not based on statistical considerations. The main objective of the Registry is a descriptive analysis regarding demographic and clinical aspects, disease activity, and safety issues at Registry entry and during the follow-up. Statistical analyses are performed on clinical parameters such as relapse and disability outcomes, included in the minimum dataset. Analyses may also be performed on other parameters included in the uploaded datasets.

3. Discussion and future directions

During the last decade there has been a surge of interest in the epidemiology of MS in LATAM, and several investigations have begun

to provide a reasonable estimate of the burden of disease in the region (Cristiano and Rojas, 2017). This promotes a deeper understanding of how the disease behaves in epidemiological aspects in our region. However, scant information comes from population-based studies, and no ongoing nationwide registry exists in LATAM.

RelevarEM is the first MS nationwide registry in Argentina and in LATAM. Its objective is to provide reliable real-world data of MS in the country. The mission of the Registry is not limited to describing the disease and assuring quality healthcare for patients with MS, but also to promote research projects addressing high-priority issues. We believe that through the collaborative work of the professionals involved in the care of patients with MS, reliable data can be obtained regarding the frequency and distribution of the disease and that a clearer understanding of patient access to healthcare gained with the objective of identifying aspects that can be improved. Likewise, it will also constitute a research base that allows us to better understand how the disease behaves in our country. We believe it is important to mention that much of the effort of the project is dedicated to complying with the necessary and required regulatory aspects as well as to various strategies that aim to increase the quality of the data obtained.

Patient registries gather valuable long-term patient information from the real world which is useful to a wide range of purposes (epidemiology, economic impact, healthcare access, and aspects concerning safety and effectiveness) (Trojano et al., 2018; Flachenecker et al., 2014).

In the near future, a wider use of MS disease registries in the region would be desirable in order to better understand the behavior of the disease in our region. Furthermore, it would be essential that registries include information and outcomes drawn directly from patients and proxies to better understand not only the disease but also how it impacts in the daily life of patients.

Conflict of interest

We wish to confirm that there are no known conflicts of interest associated with this publication and there has been no significant financial support for this work that could have influenced its outcome

Author declaration

We confirm that the manuscript has been read and approved by all named authors and that there are no other persons who satisfied the criteria for authorship but are not listed. We further confirm that the order of authors listed in the manuscript has been approved by all of us. We confirm that we have given due consideration to the protection of intellectual property associated with this work and that there are no impediments to publication, including the timing of publication, with respect to intellectual property. In so doing we confirm that we have followed the regulations of our institutions concerning intellectual property

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