Development and Implementation of a Patient Registry: The Experience of a Multiple Sclerosis Center in Portugal

Desenvolvimento e Implementação de um Registo de Doentes: Experiência de um Centro de Esclerose Múltipla em Portugal

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ABSTRACT

Introduction: Patient registries allow better evaluations of therapeutic outcomes and support personalized health care in several conditions. This study aimed to implement a local registry in a multiple sclerosis center in Portugal, in order to carry out a critical analysis of its development stages, and to perform an initial analysis of the included patients.

Material and Methods: The establishment of the registry was divided in two phases – development (creation of the online platform for data entry) and implementation (recruitment of patients and retrospective and prospective collection of available information). A demographic and clinical analysis of patients was performed.

Results: Neurologists and study coordinators participated in the project, accounting for a total of 1050 hours of work in the implementation phase. Amongst the 498 multiple sclerosis patients included, 72.9% were female and relapsing-remitting multiple sclerosis was the most common subtype of the disease. The most frequently prescribed drugs at diagnosis were beta interferons. Missing data in electronic health records were detected concerning the progression of disability and diagnostic tests.

Conclusion: Despite the amount of data collected within the scope of this study, several difficulties affected the implementation and maintenance of the registry, which could be overcome by improving future strategies.

Keywords: Medical Records; Multiple Sclerosis; Prospective Studies; Registries; Retrospective Studies

RESUMO

Registos de doentes permitem avaliar melhor resultados terapêuticos e suportar a personalização de cuidados de saúde em diversas patologias. Este trabalho teve como objetivos: implementar um registo local num centro de esclerose múltipla em Portugal; proceder a uma análise crítica das suas etapas de desenvolvimento; e realizar uma primeira análise dos doentes incluídos.

Material e Métodos: A criação do registo dividiu-se em duas fases: desenvolvimento (construção da plataforma *online*) e implementação (recrutamento de doentes e recolha retrospetiva e prospetiva da informação disponível). Realizou-se uma análise demográfica e clínica dos doentes incluídos.

Resultados: Especialistas em Neurologia e coordenadores de estudo participaram no projeto, num total de 1050 horas de trabalho na fase de implementação. Dos 498 doentes com esclerose múltipla incluídos no estudo, 72,9% eram do género feminino, tendo sido identificada como subtipo de doença mais comum a esclerose múltipla surto remissão. Os fármacos mais frequentemente prescritos após diagnóstico foram interferões beta. Detetaram-se lacunas no processo clínico dos doentes relativamente à progressão da incapacidade e a exames complementares de diagnóstico.

Conclusão: Apesar do volume de dados recolhidos no âmbito deste estudo, foram encontradas dificuldades que comprometeram a implementação e manutenção do registo, que poderão ser ultrapassadas com a otimização de estratégias futuras.

Palavras-chave: Esclerose Múltipla; Estudos Prospetivos; Estudos Retrospetivos; Processos Clínicos; Registos

INTRODUCTION

Os Patient registries are more than just a database; they are organised and systematic programmes for the compilation, storage, and dissemination of data regarding patients who are identified for a specific aim, which is clearly explained to them.[1]

The integration of high-quality records and databases into comprehensive healthcare quality management systems is a factor in the improvement of the clinical practice and health outcomes.[2]

At a global level, nationwide patient registries allow for better assessment of therapeutic outcomes by physicians, providing more detailed and comprehensive information than small local studies.[3] However, it is worth mentioning that the development of functional and useful registry systems is a gradual process requiring time, prior studies, and accumulation of results.[4]

Multiple sclerosis (MS) is a heterogeneous neurological condition with significant variation in terms of clinical

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phenotypes, laboratory and imaging data, disease course and response to therapy. These characteristics have led to the adoption of the multifactorial approach in the personalisation of care for MS patients that is currently recommended, including the analysis of multiple parameters.[5]

Patient registries provide cross-sectional and longitudinal data that would otherwise be unavailable.[6] In the case of MS, these have the added value of supporting the personalisation of care.[7]

This study was aimed at the creation and maintenance of a local registry in a MS centre in Portugal. In addition, a critical analysis of its implementation and development was carried out. Finally, it was also aimed at describing the demographic and clinical characteristics of the MS patients in the registry, in compared to patients with a more recent first consultation at the same MS centre, as well as to patient groups described in scientific literature.

MATERIAL AND METHODS

This was an observational, longitudinal and unicentric study and was approved by the Ethics Committee of the *Centro Hospitalar de Lisboa Norte, EPE* in July 2017, in compliance with the good practices of clinical and scientific research, as well as the Helsinki Declaration.

Development of the registration platform

The registry consists of an online platform, with a design that was widely discussed by physicians and IT (information technology), aimed at obtaining a platform aligned with the information collected within the clinical practice, as well as making the registration of the required data easier, while allowing for a direct and intuitive data analysis. The development stage included the selection of fields to be completed by the authors of the study, based on previous knowledge of studies in the same area, and on the organisation of the clinical records at *Hospital de Santa Maria* (HSM). This also included a review, testing and final validation by the authors of the study - neurologists (namely by performing validation tests based on the preliminary collection of data from randomised clinical files); the required changes were made, corresponding to three periods of changes in the platform for standardisation and classification.

The fields to be completed in the platform, organised into 11 different sections, are shown in Table 1. The user interface of the platform was developed in HTML/Javascript, the database (DB) in MySQL and the interaction with the DB was programmed in PHP.

The access to the platform was limited to the centre's staff, with password. Each registered patient was assigned a sequential numeric code, with no relation with the patient's clinical file at the hospital, ensuring the anonymisation of data.

In total, around eight months were dedicated to the development process and an estimated 960 working hours were spent.

Table 1 – Collected variables

Section	Field
I. Characterisation	Patient's identification number Age Gender Education, occupational status Weight, height
II. Diagnosis	MS diagnosis date - Symptoms - Testing (MRI, LP, EP tests) - EDSS score Date of first consultation at HSM Date of the first symptoms - Symptoms Subtype
III. Consultation record	Date of consultation Clinical status Adverse events Adherence to therapy EDSS score
IV. Medication	Drug Therapy duration Reason of withdrawal
V. Comorbidities	Pathology Date of diagnosis
VI. Complications	Diagnosis Duration
VII. Pregnancy	Pregnancy intention Previous pregnancies
VIII. Tests	Date of completion MRI - Type of number of lesions - Worsening LP - CSF - IgG EP testing - VEP, AEP, SEP
IX. Outbreaks	Date Type Severity Treatment
X. Laboratory analysis	Lymphocyte count Leukocyte count Albumin level ALT, AST, ALP

MS: multiple sclerosis; MRI: magnetic resonance imaging; LP: lumbar puncture; EP: evoked potentials; EDSS: expanded disability status scale; HSM: Hospital de Santa Maria; CSF: cerebrospinal fluid; IgG: G immunoglobulin; VEP: visual evoked potentials; AEP: auditory evoked potentials; SEP: somatosensory evoked potential; ALT: alanine aminotransferase; AST: aspartate aminotransferase; ALP: alkaline phosphatase

Registry implementation

The implementation stage started in October 2017 and patient recruitment ran for 12 months. All the patients attending the neurology outpatient's clinic at HSM and diagnosed with MS during a routine consultation were invited to participate in the study, during the first stage, between October 2017 and October 2018.

The following inclusion criteria were considered: patients diagnosed with MS – based on the patient's medical record as a diagnosis and using the date of diagnosis obtained from this record - from whom written informed consent was obtained to collect information from their medical record for this study. No exclusion criteria were considered.

All patients who agreed to participate signed an informed consent form that clearly explained the nature and objectives of the registry. Some patient demographic and clinical data were collected at this stage, upon written consent.

The legal representatives of any minor patients (aged under 18) and any patients reaching adulthood (age of 18) throughout the study period were asked to sign an informed consent at that moment and in agreement with the use of any previously collected data.

The second stage of the registry implementation consisted of the systematic and retrospective collection of clinical, imaging and laboratory data from the patient's clinical file at the HSM, namely clinical history, first symptoms, outbreaks, date of diagnosis, EDSS (expanded disability status scale) score, imaging findings and laboratory results.

The third and final stage consisted of the prospective longitudinal collection of outpatients clinical, imaging and laboratory data, specifically including any record of outbreaks and their typologies, laboratory data focusing on lymphocyte count and liver function parameters, in addition to imaging results.

The second and third stages ran between March 2018 and October 2019.

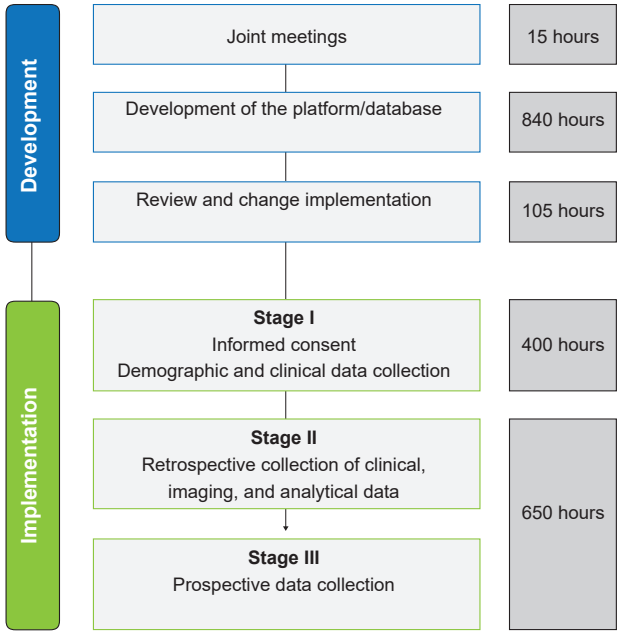

Figure 1 – Stages of the development of the registry

Characterisation of the patients included in the registry

A general analysis of demographic and clinical data of all patients included in the registry was carried out. Considering that patients with a first consultation between 2016 and 2018 could present more complete or divergent information in clinical records, a descriptive and comparative analysis of this subgroup of patients with the general group was also performed.

RESULTS

Resource analysis for the implementation and longitudinal stages of the registry

A total of 498 patients diagnosed with MS and attending the outpatient neurology clinic at the HSM were included in the registry within the implementation stage (stage 1 - recruitment) and the physicians and study coordinators assigned to the project were involved in this stage. It is estimated that a total of 400 working hours were spent (150 hours by researchers and 250 hours by study coordinators), corresponding to about 36 hours per month.

On average, 10 minutes were spent in the presentation of the study and informed consent; 7 minutes were spent in direct questions to patients in the initial assessment and 15 minutes in file review and filling in the platform until completion of the individual record.

In the longitudinal phase, 650 working hours for 20 months were spent in patient follow-up, including the time spent by researchers in completing data in consultation and the collection of retrospective information carried out on a regular basis (4 - 8 hours per week).

The different stages of the registry are shown in Fig. 1.

Global analysis of the characterisation of the patients included in the registry

A total of 498 patients diagnosed with MS were included in the registry, with information gaps in data collected retrospectively from the clinical file.

Sociodemographic characterisation

Mostly female patients were included (72.9%; n = 363), mean age of 45.8 years (SD 11.9); 45% (n = 222) of the patients pursued higher education studies and more than 50% were professionally active at the date of inclusion (53.8%; n = 268). Additionally, 32% of the patients were overweight (BMI > 25 kg/m^2) and 8% were obese (BMI > 30 kg/m^2) (Table 2).

Characterisation of the disease at diagnosis

Patients were aged between 6 and 70 years at diagnosis (mean = 34.1; SD = 10.8). The median time between diagnosis and the patient's first visit to the HSM was 31 months, and 15% of the patients were diagnosed on their first visit to the HSM. Diagnosis was established between 1 June 1971 and 1 December 2018.

Relapsing-remitting MS subtype was mostly found (71.1% of the patients) (Table 3). A median EDSS (expanded disability status scale) score of 0 was found at diagnosis,

Table 2 – Sociodemographic characteristics of the patients in the registry

	Mean	SD
Age, years	34.1	10.8
BMI, kg/m^2	24.2	4.8
	n (%)	
Female	363 (72.9)	
Education		
Basic level – primary education	43 (8.6)	
Intermediate level- primary education	70 (14.1)	
Secondary education	160 (32.1)	
Undergraduate degree	172 (34.5)	
Master's degree	41 (8.2)	
PhD degree	9 (1.8)	
DK/NO	3 (0.6)	
Occupational status		
Active	268 (53.8)	
Unemployed	45 (9.0)	
Retired	162 (32.5)	
Student	17 (3.4)	
Working student	2 (0.4)	
Housekeeper	4 (0.8)	

SD: standard deviation; DK/NO: Don't know / No opinion; BMI: body mass index

with 29% of the patients showing an EDSS ≥ 1 and 19% ≥ 2. This variable was only available in 195 of the patients.

Sensory (45%), visual (36%) and motor symptoms (25%) were the most frequent clinical manifestations before diagnosis.

At the time of diagnosis, 33% of patients had undergone magnetic resonance imaging (MRI), 20% evoked potential (EP) tests and 15% lumbar puncture (LP), based on the clinical records.

The most frequently prescribed drugs at diagnosis included interferon beta-1a (37%), interferon beta-1b (21%) and glatiramer acetate (14%).

Characterisation of the subgroup of patients with first consultation between 2016 and 2018

One hundred and seven patients were assessed at the HSM MS consultation for the first time between January 2016 and December 2018.

The sociodemographic characteristics of this subgroup compared to the total cohort included similar percentage of female patients (68); lower mean age, 40.6 years (SD 12.0), $p < 0.001$; higher education level (59% with undergraduate or higher education, $p < 0.001$); higher percentage of professionally active individuals (61.7%) and similar percentage of overweight or obese patients (30% and 5%, respectively).

At diagnosis, patients were aged between 18 and 70 years, mean 36.2 (SD 11.8), like the total cohort. Two months was the median time between diagnosis and first attendance at HSM (lower than the total cohort, $p < 0.001$), and 26% of the patients were diagnosed at their first attendance.

Relapsing-remitting MS was mostly found (75.7%). The median value of EDSS at diagnosis was 0, with 21% of patients showing EDSS ≥ 1, and 8% ≥ 2. Again, this variable was only obtained from the clinical files of 63 patients.

Sensory (47%), visual (39%) and motor symptoms (13%) were the most frequent clinical manifestations before diagnosis.

At the time of diagnosis, 40% of patients underwent MRI, 25% evoked potential tests and 20% lumbar puncture.

The most frequently prescribed drugs at the time of diagnosis included beta-1a interferon (35%), dimethyl fumarate (25%), glatiramer acetate (17%) and teriflunomide (16).

DISCUSSION

Cross-sectional procedures, including the development of adequate platforms and interfaces, data insertion and validation, in addition to the implementation of monitoring and quality processes are involved in the creation of a registry, regardless of any clinical or geographic scope.[8]

The MS registry was based on the development of a platform requiring interactions between physicians and other professionals in the department, as well as the contribution of an experienced programmer. This dynamic collaboration allowed for the final platform to reflect the professionals' needs and expectations, enhancing their subsequent participation.

The results obtained from the analysis of demographic variables are in line with the epidemiological data found in literature, namely the incidence rate of the disease in female patients.[9,10] When compared to other Portuguese studies, the patients in our group were younger and with a higher level of education than what is described in Portuguese literature.[11] Relapsing-remitting is described in literature as the most frequent subtype, in line with our data.[12,13] However, a higher rate (71.1%) has been found, when compared to studies previously published in Portugal.[11]

Compared to the total cohort, the patients with their first attendance between 2016 and 2018 were younger and with higher education, with shorter time between diagnosis and first attendance, showing an improvement in healthcare provided to MS patients. MRI records were also higher in this population, which may correspond to an improvement in the accuracy of clinical records. Differences were also found as regards the prescription of disease-modifying therapies, namely dimethyl fumarate, reflecting an increased diversity in therapeutic options for the disease,[14] and in the specific indications.

Information gaps were found in data insertion and validation stage, mostly related to retrospectively collected data, namely EDSS score at diagnosis and testing (MRI records were only found in 33% of the patients, the remaining having been omitted from the clinical files), reflecting the heterogeneity of the information recorded in MS patients' clinical files. Since the registry was based on

Table 3 – Characteristics of the disease at diagnosis

	Mean	SD	Median	IQR
Age at diagnosis, years	34.1	10.8	-	
Time between diagnosis and 1st attendance to HSM, months	-	-	31.0	2.0 - 104.5
		n (%)		
Clinical subtype				
RRMS		155 (71.1)		
SPMS		33 (15.1)		
PPMS		26 (11.9)		
CIS		4 (1.8)		
EDSS score				
≥ 0		10 (5.1)		
≥ 1		56 (28.7)		
≥ 2		36 (18.5)		
≥ 3		19 (9.7)		
≥ 4		23 (11.8)		
≥ 5		26 (13.3)		
6 - 8		25 (12.8)		
Clinical manifestations				
Visual symptoms		177 (35.5)		
Brainstem symptoms		16 (3.2)		
Motor symptoms		122 (24.5)		
Balance symptoms		67 (13.5)		
Sensory symptoms		224 (45.0)		
Sphincter abnormalities		8 (1.6)		
Cognitive symptoms		1 (0.2)		
Fatigue		36 (7.2)		
Testing				
MRI		166 (33.3)		
Evoked potentials		99 (19.9)		
Lumbar puncture		74 (14.9)		
DMTs				
Interferon beta-1a		177 (37.2)		
Interferon beta-1b		101 (21.1)		
Peginterferon beta-1a		8 (1.7)		
Glatiramer acetate		67 (14.0)		
Teriflunomide		23 (4.8)		
Fingolimod		8 (1.7)		
Dimethyl fumarate		37 (7.8)		
Natalizumab		19 (4.0)		
Cladribine		2 (0.4)		

SD: standard deviation; IQR: interquartile range; HSM: Hospital de Santa Maria; EDSS: expanded disability status scale; RRMS: relapsing-remitting MS; SPMS: secondary-progressive MS; PPMS: primary-progressive MS; CIS: clinically isolated syndrome; DMTs: disease modifying therapies

retrospective data (underlying its design and implementation stage), there is a significant limitation resulting from missing data in clinical files (with the potential to over or underestimate any information, due to its coexistence with missing information for the same variables under study). We believe that this limitation may be overcome with the definition of mandatory elements to be included in the records of MS patients' files, which will benefit the accuracy of the registry, namely regarding its prospective component.

Constraints in registry maintenance were also found in

Table 4 – Disease progression and current characteristics of the patients

	Mean	SD	Median	IQR
Time since diagnosis, years	12.5	9.0	-	
Time between first and last attendance to HSM, months	85.7	76.3	-	
No. of consultations			13.0	7.0 - 18.0
No. of consultations per year			2.0	1.5 - 2.7
No. of outbreak episodes			1.0	1.0 - 2.0
No. of outbreaks per year			0.2	0.1 - 0.5
No. of MRI	-	-	1.0	1.0 - 2.0
No. of MRI per year	-	-	0.3	0.1 - 0.5
		n (%)		
DMTs				
Interferon beta-1a		82 (16.4)		
Interferon beta-1b		18 (3.6)		
Peginterferon beta-1a		14 (2.8)		
Glatiramer acetate		51 (10.2)		
Teriflunomide		36 (7.2)		
Fingolimod		43 (8.6)		
Dimethyl fumarate		58 (11.6)		
Natalizumab		32 (6.4)		
Cladribine		5 (1.0)		

SD: standard deviation; IQR: interquartile range; DMTs: disease modifying therapies

the prospective data collection. It could be argued that the number and complexity of the fields to be completed had a negative impact on accuracy, thus advocating for more 'minimalist' records to overcome this limitation. However, it should be recognised that reducing the number of data and variables could impact on the quality/utility of the registry.

Apart from the clinical staff, the work team relied on the collaboration of other professionals in the collection of retrospective and prospective data. While the clinical staff was responsible for presenting the study to the patients and collecting the informed consent form, there was a need to involve additional staff in the initial data collection and data entry at the platform level (namely clinical study coordinators and professionals with experience in data entry). This collaboration throughout the study allowed physicians to free up time for other tasks, namely data analysis, and to complete the registry more quickly. Additionally, the presence of other elements to the medical team enhanced the standardisation of the processes, assessed as a team.

However, the cost and efficiency of the integration of additional elements should be discussed, the number of which will depend on the volume of information to be registered, the expected time for data collection and the patient population. The reduction in time spent by physicians with the concomitant increase in time allocated to other professionals would allow for reducing the costs with increased sustainability. The development of more 'minimalist' registries (with lower completion time) could also play a relevant role at this level.

Compliance with good practices in scientific research should be considered in all steps of the implementation of a medical registry, also considering all ethical issues. The anonymisation of data was ensured by assigning a numerical code to each patient and by limiting access to the data entry platform. In addition, the information was stored in secure servers with encrypted access, only accessible to the members of *Keypoint - Consultoria Científica Lda.* responsible for conducting the study.

Therefore, we consider that it would be desirable to establish a balanced approach, through the definition of mandatory data, regular checking of data disparities by internal audits, allocation of data collection and validation to other professionals, in addition to self-reporting of characterisation and follow-up data by patients.

Finally, we consider that the motivation and participation of professionals may be optimised through (i) the use of data to support the follow-up of MS patients, by inserting new elements in the interface, focused on personalised care; (ii) the use of the registry to perform basic statistical evaluation, through a supplementary module; (iii) the inclusion, whenever available, of cohorts and comparative epidemiological data in relation to the theme under study; (iv) the use of simpler applications when assessing patients in emergency or at other settings, for example in case of an outbreak; and (v) the presence of additional elements in collaboration for the collection of information and registry completion.

CONCLUSION

This paper describes the steps for the creation and implementation of a patient registry in a Portuguese multiple sclerosis hospital centre. The implementation of the registry consisted of retrospective and prospective data collection, with global characterisation (demographic and clinical) of the patients included in the study. Even though a large amount of information was obtained from the population of MS patients attending the outpatient clinic at the HSM, the results showed that, (i) the heterogeneity of the information recorded in the clinical files, (ii) the number and complexity of the fields to be completed and (iii) the time spent by the medical team in data entry had an impact on the implementation and maintenance of this registry. The definition of new strategies and improvements in participation may allow overcoming the constraints, laying the foundations for future registries at a national level.

AUTHOR CONTRIBUTION

JS: Significant contribution in study design. Participation in data collection and interpretation. Critical revision of contents and approval of the final version of the manuscript.

JF: Participation in data collection and interpretation. Approval of the final version of the manuscript.

AM: Significant contribution in study design. Participation in data analysis and interpretation. Participation in writing and approval of the final version of the manuscript.

HUMAN AND ANIMAL PROTECTION

The authors declare that this project complied with the regulations that were established by the Ethics and Clinical Research Committee, according to the 2013 update of the Helsinki Declaration of the World Medical Association.

DATA CONFIDENTIALITY

The authors declare that they have followed the protocols of their work centre on the publication of patient data**.**

CONFLICTS OF INTEREST

The authors declare that there were no conflicts of interest in writing this manuscript.

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