MULTIPLE SCLEROSIS JOURNAL | MSJ

Research Paper

Multiple sclerosis registries in Europe – results of a systematic survey

Multiple Sclerosis Journal

2014, Vol. 20(11) 1523–1532

DOI: 10.1177/1352458514528760

Peter Flachenecker, Karoline Buckow, Maura Pugliatti, Vanja Bašić Kes, Mario A Battaglia, Alexey Boyko, Christian Confavreux†, David Ellenberger, Danica Eskic, David Ford, Tim Friede, Jan Fuge, Anna Glaser, Jan Hillert, Edward Holloway, Eva Ioannidou, Ludwig Kappos, Elisabeth Kasilingam, Nils Koch-Henriksen, Jens Kuhle, Vito Lepore, Rod Middleton, Kjell-Morton Myhr, Anastasios Orologas, Susana Otero, Dorothea Pitschnau-Michel Otto Rienhoff, Jaume Sastre-Garriga, Tsveta Schyns-Liharska, Dragana Sutovic, Christoph Thalheim, Maria Trojano, Yan V Vlasov, Özgür Yaldizli, for the EUReMS Consortium*

Abstract

Background: Identification of MS registries and databases that are currently in use in Europe as well as a detailed knowledge of their content and structure is important in order to facilitate comprehensive analysis and comparison of data.

Methods: National MS registries or databases were identified by literature search, from the results of the MS Barometer 2011 and by asking 33 national MS societies. A standardized questionnaire was developed and sent to the registries' leaders, followed by telephone interviews with them.

Results: Twenty registries were identified, with 13 completing the questionnaire and seven being interviewed by telephone. These registries differed widely for objectives, structure, collected data, and for patients and centres included. Despite this heterogeneity, common objectives of the registries were epidemiology (n=10), long-term therapy outcome (n=8), healthcare research (n=9) and support/basis for clinical trials (n=8). While physician-based outcome measures (EDSS) are used in all registries, data from patients' perspectives were only collected in six registries.

Conclusions: The detailed information on a large number of national MS registries in Europe is a prerequisite to facilitating harmonized integration of existing data from MS registries and databases, as well as comprehensive analyses and comparison across European populations.

Keywords: Multiple sclerosis, registries, Europe

Date received: 11 November 2013; revised: 24 February 2014; accepted: 25 February 2014

Correspondence to:
Peter Flachenecker
Neurological Rehabilitation Center Quellenhof, Kuranlagenallee 2, D-75323 Bad Wildbad, Germany.
peter.flachenecker@sana.de

Karoline Buckow
David Ellenberger
Tim Friede
Otto Rienhoff
University Medical Center, University of Göttingen, Germany

Maura Pugliatti
University of Sassari, Italy

Vanja Bašić Kes
University Hospital Sestre milosrdnice, Croatia

Mario A Battaglia
Liguria and Tuscany MS Register, Italy

Christian Confavreux†
University of Lyon, France

Alexey Boyko
Yan V Vlasov
All-Russian MS Society, Russia

Danica Eskic
Association of MS Societies of Croatia, Croatia

David Ford
Institute of Life Sciences, College of Medicine, Swansea University, UK

Jan Fuge
Dorothea Pitschnau-Michel
German MS Society, Germany

Anna Glaser
Jan Hillert
Karolinska Institute, Sweden

Edward Holloway
Rod Middleton
UK MS Society, UK

Eva Ioannidou
Greek MS Society, Greece

Ludwig Kappos
Jens Kuhle
Özgür Yaldizli
University Hospital, Switzerland

Introduction

Multiple Sclerosis (MS) is a chronic inflammatory disease of the central nervous system that has a high impact on both the health-related quality of life (HRQoL) of patients with MS and their families, and on society. In Europe, more than 500,000 people are affected by the disease. However, healthcare for MS patients as well as their socioeconomic conditions differs greatly across the European Union.[1] Although the European Commission intends to tackle those disparities more effectively, its support to the member states is impaired due to the lack of valid data at the European level. MS registries are essential tools for providing such information, and different registries and databases do already exist in various countries, but these systems differ in terms of objectives, time, and resources spent for registration and analytical preferences.[2]

With the general aim of establishing a European-wide platform for systematic analysis and comparison of longitudinally collected MS data in Europe, the European Register for Multiple Sclerosis (EUReMS) project was set up in 2010 by an international consortium. It is co-funded by the European public health program and involves both scientists and patient organizations (Appendix 1). Based on the assumption that a comprehensive approach to and harmonization of MS data collection at a European level is needed, a consensus statement on EUReMS' vision, mission and strategies

Elisabeth Kasilingam
Tsveta Schyns-Liharska
Christoph Thalheim
European MS Platform, Brussels, Belgium

Nils Koch-Henriksen
Danish MS Registry, Copenhagen University Hospital, and Department of Clinical Epidemiology, Clinical Institute Aarhus University, Denmark

Vito Lepore
Consortium Mario Negri Sud, Chieti, Italy

Kjell-Morton Myhr
Norwegian MS Registry and Biobank, Haukeland University Hospital, Norway/ KG Jebsen Centre for MS Research, University of Bergen, Norway/University of Bergen, Norway

Anastasios Orologas
University of Thessaloniki, Greece

Susana Otero
Jaume Sastre-Garriga
MS Centre of Catalonia (Cemcat), Vall d'Hebron University Hospital, Barcelona, Spain

Dragana Sutovic
MS Society of Serbia, Belgrade, Serbia

Maria Trojano
Neurosciences and Sense Organs, University of Bari, Italy

was approved.[3] Four areas of action were defined: (1) MS epidemiological and clinical surveillance; (2) long-term efficacy, safety and cost-effectiveness of MS disease-modifying and symptomatic treatments; (3) provision and quality of healthcare services; and (4) quality of life, the burden of symptoms and socioeconomic aspects from the patient's perspective.[3]

One of EUReMS' principles is that it should build on already existing national or regional MS registries and databases. For this purpose, the identification of MS registries that are currently in use in Europe as well as acquiring a detailed knowledge of their content and structure is of utmost importance in order to enable merging of data and their comparison at a European level. In this paper, we report the results of a survey on MS registries in Europe that was performed between January and April 2012 as part of the EUReMS project.

Methods

Identification of MS registries and databases
The existing registries and databases in Europe were identified from recent reviews,[2,4,5], from records of the European Multiple Sclerosis Platform (EMSP) derived by the MS Barometer in 2011,[1] and from a PubMed search. In addition, the references of relevant publications and abstracts were checked, and the 33 national European MS societies were contacted and asked whether they were aware of systematic data collection in their countries.

Development of the questionnaire
Based on a previous survey on MS registries,[5] and on the experiences with data management in the registry context, a questionnaire was developed by EUReMS Steering Committee (SC) members (Appendix 1, available to view online) using a peer focus group approach (Appendix 2, available to view online) and sent to the registries' leaders. Information on the following domains was collected (see supplementary data online for full list of SC members in Appendix 1):

- Organizational structure
- Background and purposes
- Inclusion criteria and patients
- Documentation process
- Data collected
- Quality control
- Governance
- Current state of the registry (updated to 31 December, 2011)

Along with the questionnaire, a cover letter was enclosed wherein the registry's scientific and technical staff were invited to participate in a one-hour standardized interview with SC members.

Analysis of the results
Frequencies and proportions were reported along with 95% confidence intervals (CI) according to Clopper-Pearson for the proportions. The analysis is descriptive and therefore no hypothesis tests were conducted. With regard to the methodology of data collection and to the items collected, each registry was identified as potentially serving one or more EUReMS missions indicated above.

Results

Literature search and information from the MS Barometer yielded 17 national MS registries. After contacting the European MS societies, three additional registries were identified (Table 1). The survey was thus sent to 20 MS registry contact persons; of these, five did not respond after at least one reminder. In Austria, only registries for MS patients treated with natalizumab or fingolimod exist, and in Iceland, nearly every MS patient has been documented by one neurologist, but these data could not be retrieved. Thus, detailed information was available from 13 (65%) registries. Seven of these agreed to participate in the standardized telephone interview.

Results of the standardized questionnaire
The main purposes of the registries were (multiple answers possible) epidemiological research (n=10; 77%; 95% CI: 46–95%), healthcare research (n=9; 69%; 95% CI: 39–91%), long-term therapy research (n=8; 62%; 95% CI: 32–86%), and support/basis for clinical trials (n=8; 62%; 95% CI: 32–86%). Less frequent registry aims were cost and cost-effectiveness of treatment (n=5), quality management of healthcare (n=5), and gathering data (n=1). Seven to 10 registries met at least one of the EUReMS missions, whereas Greece, Norway and Sweden met all four (Table 2). In Russia, there is a united registry aimed at integrating the registries of 83 regional ministries of health of the Russian Federation, which is run by the Ministry of Health with the purpose of making purchases on their own and providing MS patients with disease-modifying drugs (DMD).

All registries included patients with MS according to the McDonald criteria. In addition, six registries applied Poser criteria, and eight registries also collected data on patients with clinically

Table 1. MS registries in Europe.

Country	Survey	Interview	Website
Literature/MS Barometer			
Austria	no[a]	-	
Bosnia-Herzegovina	no response	-	
Croatia	yes	yes	www.sdmsh.hr/baza
Czech Republic	no response	-	
Denmark	yes	yes	www.ms.research.dk
France	yes	-	www.edmus.org
Germany	yes	yes	www.dmsg.de/msregister/
Greece	yes	-	www.gmss.gr
Iceland	no[b]	-	
Italy	yes	yes	www.imedweb.it
Malta	no response	-	
Netherlands	no response	-	
Norway	yes	yes	www.ms-kompetansesenter.no
Slovenia	no response	-	
Spain (Catalonia)	yes	yes	www.epidemcat.cat/index.php/en/epidemcat—registro
Sweden	yes	-	www.msreg.net
United Kingdom	yes	yes	www.ukmsregister.org www.mssociety.org.uk
MS societies			
Russia	yes	-	
Serbia	yes	-	
Switzerland	yes	-	

Overview of the responses of MS registries as identified by literature search and the MS Barometer (above) and by asking MS societies (below). Indicated is whether the registries responded to the survey (2nd column), and whether interviews could be performed (3rd column).
[a]only treatment registries for natalizumab and fingolimod.
[b]no access to data.

isolated syndromes (CIS). The Catalan registry was specifically designed for CIS patients. The majority of respondents stated that the registry was hospital-based (*n*=10, 77%), and five (38%), that it was population-based, with three registries being hospital- and population-based together. In three registries, patient lists from MS societies were used either exclusively (*n*=1) or in combination with the above-mentioned sources of data collection. Most registries (*n*=9, 69%) intended to capture all MS patients in the country, whereas four registries (31%) attempted to collect data on representative subsets (regions) of patients (Croatia, Italy, Switzerland and United Kingdom).

Some key features of the registries are shown in Table 3. There is a large heterogeneity in organizations running the registries: academic institutions (*n*=5), national MS societies (*n*=4), and ad hoc institutions (*n*=3); in one case (Russia), the registry is kept by the government. More than half of the registries (*n*=7) collected data for more than 10 years, whereas two registries just started in the year before the survey. The number of centres that took part in each registry ranged from five to approximately 150 (median 15.5), and the number of patients from 270 to about 40,000 (median 8,300). In nine registries (69%), regular follow-up was intended, mainly annually or biannually (Table 3).

Registration is mainly performed by neurologists or medical staff (*n*=11, 85%). Data are collected exclusively from patients in Croatia and Serbia, whereas in Italy and UK, both sectors contributed to data collection. Longitudinal data were collected by 11 registries, where different datasets of one patient acquired in one or more centres at different time points can be linked.

The data collected in the registries are shown in Table 4. Mostly, demographic and basic clinical data

Table 2. Coverage of EUReMS' missions by 13 national MS registries.

Country	Mission[a]				Others
	#1	#2	#3	#4	
Croatia		x	x	xxx	clinical research
Denmark	x	x	x		clinical research, quality management
France	x	x			clinical research
Germany	x		x	(planned)	clinical research
Greece	x	x	x	x	
Italy	x	x		x	clinical research
Norway	x	x	x	x	clinical research, quality management
Russia					number of patients to Expensive Pharmaceutical Provision programme
Serbia			x	x	
Spain (Catalonia)	xxx		x		clinical research
Sweden	x	xxx	x	x	quality management
Switzerland	x	x			cohort study on DMD, clinical research
United Kingdom	x		x	x	

[a]EUReMS' missions:
#1: MS epidemiological and clinical surveillance across European countries, including the assessment of the 'MS burden' in Europe.
#2: Assessment of long-term efficacy, safety and cost-effectiveness of MS diseases-modifying and symptomatic treatments across European countries.
#3: Assessment of provision and quality of healthcare services across European countries.
#4: Assessment of quality of life, burden of symptoms and socioeconomic aspects from the patient's perspective across European countries.
x purpose of the registry xxx main purpose,
DMD = disease-modifying drugs.

including data on current DMDs are gathered. Less frequent data were current disease activity (in particular the number of relapses within the last two years) and symptomatic treatment. Only six registries (Croatia, France, Italy, Norway, Sweden and United Kingdom) included patient-reported outcomes (Table 5).

Informed consent from patients is needed in 11 registries; this is done mainly in written form (n=9). In two registries (Denmark and Spain/Catalonia), it is not mandatory to inform patients. Approval from local authorities was obtained in most of the registries (data protection authorities, n=7; ethic committees, n=7).

Results of the interviews

The leaders from seven (54%) registries were interviewed via telephone conferences: Croatia, Denmark, Germany, Italy, Norway, Spain and United Kingdom. The interviews followed the structure of the survey and lasted about one hour. For the SC, PF, KB and MP took part, supported by the EUReMS scientific coordinator (TS). The initials of the registries' representatives are given in brackets:

Croatia (VBK): The registry started in 2007 and is run by the Association of MS Societies of Croatia (AMSSC) including 20 member organizations that contributed to the registry. Its most important purpose is to obtain data on the costs and cost-effectiveness of treatment. Patients with a definite diagnosis of MS (validated with medical records) obtained in one of the 10 Croatian MS centres are included. Documentation is done by patients who fill in the paper-based questionnaire. Different quality control mechanisms ensure correct format and structure of data as well as plausibility and consistency within a dataset. There are regular updates once a year by telephone.

Denmark (NKH): In the Danish MS registry, all incident cases of MS have been registered since 1948. The sources of data collection are broad: all 22 departments of neurology, private practitioners in neurology, the MS rehabilitation clinics in Ry and Haslev, the Danish MS Treatment Registry (established in 1996), the Danish MS Society and neuropathologists. Linkage to other national registries such as the National Patient Registry (containing information on all hospital admissions since 1977), and the National Registry of Causes of Death (wherein all causes of

Table 3. Key features of 13 national MS registries.

Country	Institution	Start	No. of patients[a]	No. of centres	follow-up
Croatia	MS society	2007	2,477	10/21[b]	annually
Denmark	Danish MS registry	1948/1996	12,500	16	no
France	EDMUS Coord. Centre	1976	~ 40,000		yes
Germany	MS society	2001	~ 30,000	~ 150	no
Greece	MS society	2011	3,500		yes
Italy	Network of MS centres	2001	~ 20,000	40	biannually
Norway	University of Bergen	1998	5,100	20	yes
Russia	Healthcare ministry	2006	21,500		unknown
Serbia	MS society	2000	3,500		no
Spain (Catalonia)	Vall d'Hebron University Hospital	2009	616	~ 20	CIS pts only
Sweden	Swedish MS registry	1997	12,900		yes
Switzerland	University of Basel	2012	270	8	bi-/annually
United Kingdom	University of Swansea	2009	8,300	5 (pilot)	yes

[a]as of 31 December 2011,
[b]21 MS societies sending questionnaires, clinical data from 10 MS centres.

death have been registered since 1943) is facilitated by a unique registration number that is assigned to each Danish citizen. The main purpose of the registry is epidemiological investigations. Data collection is done by two neurologists who extract the relevant information from the medical records. A number of quality control mechanisms exist. As of 31 January 2012, 20,000 patients had been registered, of whom 12,500 were still alive (coverage of 90%). In 1996, the Danish MS Treatment Registry was established, and all patients treated with DMDs are obliged to be followed prospectively every six months. Documentation is done online by the neurological clinics. As of January 2012, a total of 6,700 patients and 11,300 datasets had been recorded. A number of papers have been published in recent years using these data, including immunomodulatory treatment, mortality, causes of death and twin studies.[6,7–11]

Germany (JF): The German MS Registry is run by a company aligned to the German MS Society. Since 2001, data from over 30,000 patients have been collected (with over 80,000 datasets) from over 150 clinical centres (university hospitals, neurological clinics, rehabilitation units and neurologists) who are obliged to participate in order to be certified as an MS centre by the MS Society. The main purposes are epidemiological studies, healthcare research, quality management of healthcare and clinical research. Documentation is done locally by neurologists, with transfer of pseudonymized data every three months. A number of quality checks are available. The design and results of the registry have been published.[12–14]

Italy (MT): The registry is kept by the network of 40 MS centres and coordinated by the University of Bari and the Consortium Mario Negri Sud, Chieti. The main purpose is clinical research, with a number of publications arising from the collected data since 2001.[15–18] Co-authorship is the motivating factor for data collection. Thus, most centres are university hospitals (80%); less frequently, neurological clinics (15%) and rehabilitation clinics (5%) participate. Documentation is performed by neurologists, medical assistants and patients (self-reported questionnaires for depression, fatigue and HRQoL), and done locally at the centre level by using the iMed system, with export of anonymous data twice yearly. There are a number of quality control mechanisms. Regular updates are done biannually. In addition to the network, two regional MS registries established by the Italian MS Association (AISM) exist: the Tuscany MS registry which has documented 2,040 patients since 2006, and the Liguria MS registry which started documentation in 2012.

Norway (KMM): The Norwegian MS Registry started data collection in 2001. The initial purpose was research, but it is expanding to include quality control of healthcare provided to MS patients, particularly by means of an electronic platform since 2012. The registry is population-based, with the participation of approximately 20 departments of neurology, rehabilitation clinics and specialized practitioners/neurologists.[19] Up to now, data have been collected on paper forms; electronic documentation is planned that will enable the inclusion of patient-reported outcomes

Table 4. Data collected in the 13 surveyed national MS registries.

Category	Sub-category	Cro	Den	DeT	Fra	Ger	Gre	Italy	Nor	Rus	Ser	Spa	Swe	Swi[a]	UK
Personal data	Date of birth	M	M	M	M	M	Y	M	M	M	M	M	M	M	M
	Gender	M	M	M	M	M	Y	M	M	M	M	M	M	M	M
Disease data	Disease course	M	M	M	auto	O		M	M	M		M	O	M	O
	Time of disease onset	M	M	M	M	O		M	M	M	–	M	M	M	O
	Time of diagnosis	M	M	M	–	O		M	M	M	M	M	O	M	M
	Symptoms at onset	M	M	M	O	O		M	M	M	–	M	O	–	O
	Past disease activity	M	–	M	O	–		M	Y/N	M	–	M	O	M	O
	Diagnostic accuracy (McDonald /Poser)	M	M	M	auto	M		M	M	M	O	M	O	M	O
	Number of relapses in the last 12/24 months	–	–	M	O	–		M	Y/N	M	–	–	O	M	O
	EDSS	–	M	M	M	M		M	O	M	–	–	O	M	O
	MSFC	–	–	–	O	O		O	O	M	–	–	O	O	–
Treatment	Relapse therapy	M	–	M	O	O		M	M	M	–	–	O	M	–
	Past disease-modifying therapies	M	–	M	O	O		M	O	M	–	–	O	M	O
	Current disease-modifying therapies	M	–	M	O	O		M	M	M	M	–	O	M	O
	Drug safety	M	–	M	O	O		M	M	–	–	–	O	M	–
	Current symptomatic therapies (medical)	M	–	–	O	O		M	O	M	–	–	–	M	O
	Current symptomatic therapies (non-medical)	M	–	–	O	O		M	O	–	–	–	–	O	O
	Complementary/alternative therapy	M	–	–	O	O		O	–	–	–	–	–	–	O
Diagnostic tests	Evoked potentials	M	M	–	O	O		M	M	M	–	O	–	O	–
	MRI	M	M	M	O	O		M	M	M	–	M	O	M	O
	CSF	–	M	M	O	O		M	M	–	–	O	O	M	O
	Biopsy	M	O	O	O	–		O	–	–	–	–	–	–	O
	Linkage to brain/tissue bank	–	O	O	O	–		–	Y	–	–	–	–	–	–
Co-morbidities	Chronic diseases	M	Link	Link	O	O		M	O	M	O	–	O	M	O
	Co-medication	M	–	–	O	–		M	O	M	–	–	–	M	O
Socioeconomic data	Education	M	Link	Link	O	–		O	O	–	M	–	–	–	–
	Employment	M	-	M	O	O		M	O	–	M	–	O	–	O
	Care/support due to MS	M	–	–	O	O		O	–	M	M	–	–	–	O
	Provision of aids (i. e. walking sticks, wheelchair, etc.)	M	–	–	O	O	Y	O	–	M	–	–	–	–	–
Patient-derived outcomes	Health-related quality of life	–	–	–	O	–		O	O	–	O	–	O	–	O
	Patient-derived disease steps (PDDS)	–	–	–	–	–		–	–	O	–	–	–	–	–
	Depression	M	–	–	O	–		M	–	–	–	–	–	–	O
	Fatigue	–	–	–	O	–		M	O	–	–	–	O	–	O
	Socioeconomic data	M	Link	Link	O	–		O	–	–	–	–	–	–	O

M: documentation of data is mandatory; O: documentation of data is optional, Y: yes (data are collected, but it is not stated whether mandatory or optional); "–": data are not documented, auto: automatically generated; Link: due to link with other national registries.
Cro: Croatia; Den: Denmark (Danish MS Registry); DeT: Danish MS Treatment Registry; Fra: France (EDMUS); Ger: Germany; Gre: Greece; Nor: Norway; Rus: Russia; Ser: Serbia; Spa: Spain (Catalonia); Swe: Sweden; Swi: Switzerland; UK: United Kingdom.
CSF: cerebrospinal fluid; EDSS: Expanded Disability Status Scale; MRI: magnetic resonance imaging; MSFC: Multiple Sclerosis Functional Composite Score.
[a]mandatory bi/-annual biobanking of serum, plasma, whole blood samples and CSF (if lumbar puncture is clinically indicated).

Table 5. Patient-reported outcomes.

Country	HRQoL	Depression	Fatigue	Disability
Croatia	–	not specified	–	–
Denmark	–	–	–	–
France	not specified	not specified	not specified	
Germany	–	–	–	–
Greece	–	–	–	–
Italy	FAMS/MSQoL-54	BDI/Hamilton	FSS	-
Norway	MSIS-29/EQ5d[a]	–	FSS	–
Russia	–	–	–	PDDS
Serbia	–	–	–	–
Spain (Catalonia)	–	–	–	–
Sweden	MSIS-29/EQ5d	-	-	-
Switzerland	–	–	–	–
United Kingdom	MSIS-29/EQ5d	HADS	–	–

BDI: Beck Depression Inventory; FAMS: Functional Assessment of MS; FSS: Fatigue Severity Scale; HADS: Hospital Anxiety and Depression Scale; MSIS-29: Multiple Sclerosis Impact Scale 29; PDDS: Patient-derived Disease Steps.
[a]planned.

such as HRQoL (MSIS-29, EQ-5d) and fatigue (FSS). Different quality check routines are implemented at the time of data collection as well as within the database. Regular follow-up is supported: one year for patients without DMDs, and six months for patients with DMDs. As of January 2012, 5,100 patients have been documented (approximately 60% coverage).

Spain/Catalonia (JSG, SO): The main purpose of the Catalan MS registry is epidemiological investigations, particularly incidence studies. Newly diagnosed patients with MS according to McDonald criteria and those with possible MS/CIS have been included since 2009.[20] Prospective follow-up is only performed until the diagnosis of MS is confirmed. Ninety percent of centres in Catalonia take part (six academic centres and 15 neurological clinics). Documentation is web-based and done by neurologists, and multiple quality control routines are performed. The registry is run by the University Hospital Barcelona, and owned by the Department of Health of Catalonia. Up to 2012, 616 incidence cases had been recorded.

United Kingdom (RM): The registry is funded by the UK MS Society and has just finished the pilot phase started in 2009. It has three data sources: (1) clinical data that are recorded in five hospitals by medical staff using two systems (iMed and a modified open source program called OpenEMR); (2) an online portal with patient questionnaires including HRQoL (MSIS-29, EQ-5d) and depression (Hospital Anxiety and Depression Scale); and (3) routine data collected anonymously on all inpatient and outpatient attendances within Wales during the last 20 years. Datasets can be linked. Access to the web portal is open to all MS patients in the UK. Quality control mechanisms check the plausibility and consistency of both datasets. At the end of the pilot phase, approximately 1,200 clinical datasets and 8,300 patient-reported datasets had been collected.

Discussion

The present survey on MS registries in Europe yielded several important results: (1) in many European countries, national MS registries do exist; (2) these registries differ widely from country to country; and (3) despite this heterogeneity, a considerable number of registries have common objectives and cover at least some of the missions of the EUReMS project.

Number of MS registries: By using various sources we were able to identify 20 MS registries on a national level that are currently in use in Europe. This number is higher than expected and higher than found previously.[2,3,5] The majority of the registries responded to the standardized survey and provided detailed information on structure and content. Moreover, leaders from seven registries participated in telephone interviews, which made it easier to obtain more and detailed insights and to validate the data from the survey. The increasingly recognized importance of MS registries in providing data that cannot be captured in any other way[21] is underlined by the fact that nearly

one third of registries studied herein started in the five years before the survey.

Heterogeneity of MS registries: As in previous reports,[2,4,5] the registries evaluated in this study varied considerably from country to country. Mainly, they were intended for epidemiological, healthcare and long-term therapy research and to support clinical trials, whereas HRQoL from the patients' perspective and particularly the cost and cost-effectiveness of treatment and quality management of healthcare were less frequent aims. There is also a huge variety in terms of data collection (e.g. hospital-based vs. population-based), coverage, involvement of national MS societies, documentation (paper forms vs. electronically, neurologist vs. patients), quality control mechanisms and governance.

Compliance to EUReMS missions: Although background and purposes differ between national MS registries, many of them cover at least some of the EUReMS' missions. Only six registries collect data from the patients' perspective, and only five of them use standardized instruments such as the MSIS-29, the Functional Assessment of Multiple Sclerosis (FAMS), and the EQ-5d, while physician-based outcome measures such as the Expanded Disability Status Scale (EDSS) are used in all registries. This underrepresentation of patient-reported outcomes is also found in clinical trials, which are heavily weighted towards physician-based instruments. However, it is increasingly acknowledged that these standard clinical endpoints do not fully reflect the patient's experience of the disease, and particularly employment status, social and family relationships, bladder/bowel dysfunction, fatigue, visual disturbances, cognitive dysfunction and affective disorders may have an enormous impact on patients with MS.[22] Patient-reported outcomes are thus advocated to be routinely used in clinical trials for assessing HRQoL.[22,23] In this regard, the UK MS registry is unique in that it combines clinical data that are recorded from neurologists or medical assistants (physician-oriented) and HRQoL data that are collected directly from the patients via an online portal (patient-reported). Based on the UK experience, incorporating HRQoL measures into a European-wide platform for data collection seems feasible. Therefore, by considering the patients' perspective in large-scale registries over long periods, the EUReMS project will provide additional value beyond that of the existing data collection systems.[24] The next steps for EUReMS are to provide a platform for harmonized and standardized integration of data from existing MS registries, and to set up a data architecture and appropriate methods to collect and combine MS data from different sectors and different European regions.[3] These data may provide new insights into the disease burden, causes and natural history of the disease, the long-term effectiveness of disease-modifying therapies, the provision of healthcare services, and the impact of the disease on HRQoL in patients with MS across Europe.

Acknowledgements

The EUReMS project is a three-year project initiated and led by the European Multiple Sclerosis Platform (EMSP) in partnership with the following organizations: Association of Multiple Sclerosis Societies of Croatia (AMSSC), Croatia; Deutsche Multiple Sklerose Gesellschaft, Bundesverband e.V., Germany; Università degli Studi di Sassari, Italy; Universitetet i Bergen, UiB, Norway; Fundació Institut de Recerca Hospital Universitari Vall d'Hebron, Spain; Polskie Towarzystwo Stwardnienia Rozsianego, Poland; Societatea de Scleroza Multipla din Romania, Romania; UK MS Society, United Kingdom; Universitätsmedizin der Georg-August Universität Göttingen, Germany; Karolinska Institute Stockholm, Sweden; Neurologisches Rehabilitationszentrum Quellenhof in Bad Wildbad, Germany.

Conflicts of interest

Peter Flachenecker has received speaker's fees and honoraria for attending advisory boards from Almirall, Bayer Schering, Biogen Idec, Genzyme, Novartis, Merck-Serono, Sanofi-Aventis and/or Teva. He has participated in pharmaceutical company-sponsored clinical trials by Almirall, Biogen Idec and Novartis. None resulted in a conflict of interest.

Maura Pugliatti has received honoraria for advisory board membership from EMSP, speaker's fee from Aventis, participation in pharmaceutical company-sponsored trials and travel support from Biogen Idec, Merck-Serono, Novartis, Sanofi-Aventis and/or Teval. None result in a conflict of interest.

Tim Friede is a consultant to Novartis and Biogen Idec. This did not result in a conflict of interest.

Jan Hillert has received honoraria for serving on advisory boards for Biogen Idec and speaker's fees from Biogen Idec, Merck-Serono, Bayer Schering, Sanofi-Aventis and/or Teva. He has served as principal investigator for projects sponsored by, or received unrestricted research support from Biogen Idec, Merck-Serono, Teva, Novartis and Bayer Schering. His MS research is funded by the Swedish Research Council.

Ludwig Kappos has participated in the last 24 months as principal investigator, member or chair of planning and steering committees or advisory boards in corporate-sponsored clinical trials in multiple sclerosis and other neurological diseases. The sponsoring pharmaceutical companies for these trials include Actelion, Advancell,

Allozyne, BaroFold, Bayer Health Care Pharmaceuticals, Bayer Schering Pharma, Bayhill, Biogen Idec, Biotica, CLC Behring, Elan, Genmab, GeNeuro SA, Genmark, GlaxoSmithKline, Genzyme, Johnson & Johnson, Lilly, Mitsubishi Pharma, Merck-Serono, Novartis, Novonordisk, Octapharma, Peptimmune, Roche, Sanofi-Aventis, Santhera, Teva, UCB, Xenoport and Wyeth. He has lectured at medical conferences or in public on various aspects of the diagnosis and management of multiple sclerosis. In many cases these talks have been sponsored by non-restricted educational grants to his institution from one or another of the above-listed companies. Honoraria and other payments for all these activities have been exclusively used for funding the research of his department. Research and the clinical operations (nursing and patient care services) of the MS Center in Basel have been supported by non-restricted grants from one or more of these companies and by grants from the Swiss MS Society, the Swiss National Research Foundation, the European Union, the Gianni Rubatto, Novartis and Roche Research Foundations.
Vanja Bašić Kes, Mario A Battaglie, Alexey Boyko, Karoline Buckow, David Ellenberger, Danica Eskic, David Ford, Jan Fuge, Anna Glaser, Edward Holloway, Eva Ioannidou, declare no conflicts of interest.

Funding
This publication arises from the EUReMS project which has received: (1) co-funding from the European Union, in the framework of the Second Health Programme 2008–2013, Priority Area: 3.3.2 Promote health – promote healthier ways of life and reduce major diseases and injuries – Action 3.3.2.7 Prevention of major and chronic diseases and rare diseases; and (2) from the following sponsors: Almirall, Bayer Pharma AG, Biogen Idec, ECTRIMS, GSK, F. Hoffmann La Roche, Genzyme, Medtronic Foundation, Merck-Serono, Coloplast, Novartis, Teva. The sole responsibility lies with the author, and the Executive Agency for Health and Consumers is not responsible for any use that may be made of the information contained herein.

References

1. European Multiple Sclerosis Platform (EMSP). Multiple Sclerosis Information Dividend (MS-ID). MS Barometer 2011. www.emsp.org/attachments/article/160/MS-Barometer_2011.pdf date accessed 29 October 2013.
2. Flachenecker P and Stuke K. National MS registries. *J Neurol* 2008; 255: 102–108.
3. Pugliatti M, Eskic D, Mikolcic T, et al. Assess, compare and enhance the status of persons with multiple sclerosis (MS) in Europe: A European Register for MS. *Acta Neurol Scand* 2012; 126 (Suppl 195): 24–30.
4. Hurwitz BJ. Registry studies of long-term multiple sclerosis outcomes: Description of key registries. *Neurology* 2011; 76(suppl 1): S3-S6.
5. Pugliatti M and Sanna PS. Multiple sclerosis databasing and registries in Europe: Methodological issues. Teching course n. 3 on "MS registries and natural course of multiple sclerosis". 26th Congress of the European Committee for Treatment and Research in Multiple Sclerosis (ECTRIMS) & 15th Annual Conference of Rehabilitation in MS (RIMS), Gothenburg, Sweden 2010.
6. Hansen T, Skytthe A, Stenager E, et al. Risk for multiple sclerosis in dizygotic and monozygotic twins. *Mult Scler* 2005; 11: 500–503.
7. Bronnum-Hansen H, Stenager E, Hansen T, et al. Survival and mortality rates among Danes with MS. *Int MS J* 2006; 13: 66–71.
8. Bronnum-Hansen H, Hansen T, Koch-Henriksen N, et al. Fatal accidents among Danes with multiple sclerosis. *Mult Scler* 2006; 12: 329–332
9. Sorensen PS, Koch-Henriksen N, Ravnborg M, et al. Immunomodulatory treatment of multiple sclerosis in Denmark: A prospective nationwide survey. *Mult Scler* 2006; 12: 253–264.
10. Koch-Henriksen N. The Danish Multiple Sclerosis Registry: A 50-year follow-up. *Mult Scler* 1999; 5: 293–296.
11. Bronnum-Hansen H, Stenager E, Nylev SE, et al. Suicide among Danes with multiple sclerosis. *J Neurol Neurosurg Psychiatry* 2005; 76: 1457–1459.
12. Flachenecker P, Zettl UK, Götze U, et al. MS Register in Deutschland – Design und erste Ergebnisse der Pilotphase. *Nervenarzt* 2005; 76: 967–975.
13. Stuke K, Flachenecker P, Zettl UK, et al. Symptomatology of MS: Results from the German MS Registry. *J Neurol* 2009; 256:1932–1935.
14. Flachenecker P, Stuke K, Elias W, et al. Multiple-Sklerose-Register in Deutschland. Ausweitung des Projektes 2005/2006. *Dt Ärztebl* 2008; 105: 113–119.
15. Trojano M, Paolicelli D, Lepore V, et al. Italian Multiple Sclerosis Database Network. *Neurol Sci* 2006; 27(Suppl 5): S358–61.
16. Trojano M, Pellegrini F, Fuiani A, et al. New natural history of interferon-beta-treated relapsing multiple sclerosis. *Ann Neurol* 2007; 61: 300–306
17. Trojano M, Pellegrini F, Paolicelli D, et al. Real-life impact of early interferon beta therapy in relapsing multiple sclerosis. *Ann Neurol* 2009; 66: 513–520.

18. Trojano M, Pellegrini F, Paolicelli D, et al. Post-marketing of disease modifying drugs in multiple sclerosis: An exploratory analysis of gender effect in interferon beta treatment. *J Neurol Sci* 2009; 286: 109–113.

19. Myhr KM, Grytten N, Aarseth JH, et al. The Norwegian Multiple Sclerosis National Competence Centre and National Multiple Sclerosis registry – a resource for clinical practice and research. *Acta Neurol Scand* 2006; 183(Suppl): 37–40.

20. Otero S, Batlle J, Bonaventura I, et al. Situación epidemiológica actual de la esclerosis múltiple: Pertinencia y puesta en marcha de un registro poblacional de nuevos casos en Cataluna. *Rev Neurol* 2010; 50: 623–633.

21. Hurwitz BJ. Analysis of current multiple sclerosis registries. *Neurology* 2011; 76(suppl 1): S7–13.

22. Miller D, Rudick RA and Hutchinson M. Patient-centered outcomes: Translating clinical efficacy into benefits on health-related quality of life. *Neurology* 2010; 74: S24-S35.

23. Riazi A. Patient-reported outcome measures in multiple sclerosis. *Int MS J* 2006; 13: 92–99.

24. The Lancet Neurology. Making EUReMS count for people with multiple sclerosis. *Lancet Neurol*. 2011; 10: 865.