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## Report on Multiple Sclerosis Registries - Workshop 7 July 2017

Patient Registry Initiative

### 1. Executive summary

The EMA [Initiative for Patient Registries](#) aims to optimise and facilitate the use of patient registries for benefit-risk evaluations of medicinal products in the European Economic Area. Following a workshop in October 2016 that explored barriers and challenges to collaboration between stakeholders including registry holders, patients, regulators, reimbursement bodies, marketing authorisation holders and health technology assessment (HTA) bodies, the EMA hosted a workshop on multiple-sclerosis (MS) registries in July 2017.

This explored in detail the factors needing to be addressed across MS registries to ensure their data are adequate, in terms of content, quality and representativeness, to support benefit-risk evaluations of MS treatments. The aim of the workshop was to reach agreement on implementable recommendations to achieve the objectives. The factors discussed included registry governance, patient consents, data sharing, data quality, registry interoperability, and core common data elements needed by the different stakeholders.

Participants comprised representatives from the European MS Platform (EMSP) and its EUREMS group and "Big MS Data" group, marketing authorisation holders and applicants (MAHs, MAAs), patients, HTA and reimbursement bodies, National Competent Authorities (NCAs) and the European Medicines Agency (EMA). Prior to the workshop, participants considered questions relating to the objectives and provided information that formed the basis of discussions during the workshop. This report includes participant observations on the current situation at national and European level in respect of the factors discussed, and in each case, makes recommendations for advancing the systematic use of registries to support regulatory evaluations.

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The MS registry landscape in Europe comprises regional and national registries that are broadly affiliated with one of two main collaborations, the European MS Platform (EMSP) and the Big MS Data group. To ensure that interested MS registries may contribute optimally to regulatory evaluations throughout product lifecycles, it is necessary for registry holders to agree on core common data elements with standardised terminologies and definitions to be collected in all registries, to establish robust quality assurance procedures, and to establish procedures for data sharing with stakeholders.

Table 1 summarises the main recommendations made by workshop participants and the actions needed to ensure they are achieved.

**Table 1: Summary of the main recommendations**

Topic	Participants' Recommendations	Agreed Actions	Owners
<b>Governance</b>	Regulators and MAHs to be aware of the data that can feasibly be collected systematically by registries and to inform registries on their data needs	Improve registry holder, MAH and regulator collaboration so that registry holders understand the nature and quality of data needed for regulatory purposes and MAHs and regulators understand what information may feasibly be collected	Registry holders Regulators MAHs Registry Task Force
	Registry holders should establish a centralised data application process with a template for requests	Set up a standard process for MAHs and regulatory requests for registry data	
	Communicate to patients and the public the benefits and uses of patient registry data	Raise patient and public awareness about the importance of registry data for benefit-risk evaluations	Registry holders Regulators
<b>Informed consents, data protection and data sharing</b>	Ensure all registry patients have provided consent	Registries to undertake audits of patient consents at appropriate intervals ensuring they are current and that any restrictions on data use and consent withdrawals are recorded	Registry holders Registry Task Force
	Review whether registries' current consents are broad enough for possible future situations taking into account EU General Data Protection Regulation	Review current consents and issue guidance on any amendments needed in consents for new patients joining registries	
	Develop a policy on data sharing to include summary data, pseudo-anonymised data, and patient-level data	Draft a data-sharing policy	
<b>Data Quality</b>	Develop an agreed set of data quality indicators to be applied to all regional and national registries and to include source data verification procedures	Data quality to be audited annually in national registries and reported in their annual reports	Registry holders Regulators Registry Task Force
<b>Processes for Data upload</b>	Explore options to minimise the number of (manual) steps and duplications in registry data entry	Map and review the current processes at national level to determine if steps could be removed or simplified	Registry holders
<b>Common Data elements</b>	Agree on core common data elements to be collected by all registries as a basis for regulatory evaluations	Agree on the core common data set, including associated definitions and data dictionaries	Registry holders

Table 2 summarises the actions required from the stakeholder groups to deliver the workshop recommendations.

**Table 2: Summary of actions for the main stakeholder groups**

Group	Actions
<b>Regulators</b>	<ul style="list-style-type: none"> <li>✓ Promote the potential value of data from patient registries to relevant stakeholders</li> <li>✓ Facilitate communications between registry holders and MAHs/MAAs</li> <li>✓ Support registry holders to establish robust measures for data quality assurance and provide guidance on mechanisms for accreditation of registries using existing platforms, e.g. a qualification procedure</li> <li>✓ Include patient registry data where appropriate in regulatory processes throughout product lifecycles</li> <li>✓ Engage with relevant initiatives that are also exploring the potential of registry data for healthcare evaluations, e.g., the European Network for Health Technology Assessment (EUnetHTA) Joint Action 3</li> </ul>
<b>Registry Holders</b>	<ul style="list-style-type: none"> <li>✓ Agree on the core common data elements, including their definitions, to be collected by registries as a basis for regulatory evaluations</li> <li>✓ Ensure that harmonised processes for quality assurance of data, including source data verification, are applied systematically across CF registries</li> <li>✓ Obtain accreditation for data quality and registry standards</li> <li>✓ Develop a policy on sharing summary, pseudo-anonymised, and individual patient data</li> <li>✓ Develop a process for handling MAH/MAA and regulatory requests for registry data</li> <li>✓ Inform patients on the benefits and uses of registry data including appropriate data sharing with relevant stakeholders.</li> <li>✓ Inform MAHs/MAAs and regulators of the type and detail of data that may feasibly be collected by registries and shared within consent and governance parameters</li> </ul>
<b>MAHs / MAAs</b>	<ul style="list-style-type: none"> <li>✓ Understand the regulatory data requests that are likely to arise in the event of a successful marketing authorisation application, especially for post marketing surveillance</li> <li>✓ Consider early in new product development if appropriate registry data would have a place in the regulatory evaluations</li> <li>✓ Identify if a suitable patient registry exists</li> <li>✓ Develop a preliminary study protocol and explore with the registry holder/s and the regulator if the registry could fulfil the data needs</li> </ul>
<b>Patient Representatives</b>	<ul style="list-style-type: none"> <li>✓ Engage with registry holders in order to understand and communicate to patients the potential uses and associated benefits and risks of sharing patient registry data to assist in medicines evaluations</li> <li>✓ Advise on appropriate patient reported outcomes that might feasibly be collected and included in registries.</li> </ul>
<b>HTAs and Reimbursement Bodies</b>	<ul style="list-style-type: none"> <li>✓ Learn about the nature and purpose of the data included in patient registries</li> <li>✓ Engage with registry holders to adapt registry data collection where feasible to support information needs</li> <li>✓ Continue engagement with stakeholders through current initiatives, e.g., EUnetHTA Joint Action 3</li> </ul>

In the next step, the MS stakeholder groups need to develop implementation plans. They will be facilitated in this by the EMA Registries Task Force.

## 2. Background

The EMA is exploring the use of real world data in supporting medicines authorisation. Its [Initiative for Patient Registries](#) launched in September 2015, aims to optimise and facilitate the use of existing patient registries for the benefit-risk monitoring of medicinal products throughout their lifecycles. Regulators and marketing authorisation holders face multiple challenges currently in using registry information to support benefit-risk evaluations of new treatments. These include poor coordination between ongoing initiatives at national and international level, absence of harmonised protocols, scientific methods and data structures for undertaking registry-based studies, limited transparency and capacity for data sharing and in some cases, doubtful sustainability of the registries.

At the Patient Registries Workshop in October 2016, stakeholders including registry holders, patient groups, marketing authorisation holders, regulators and health technology and payer representatives made recommendations on optimising the use of registry data – Report of the Registries Workshop. The EMA undertook to deliver on a number of the activities arising including bringing together stakeholders in certain disease areas to help implement particular recommendations and to act as exemplars for later recommendations generalizable to registries more broadly. The Multiple-Sclerosis (MS) Registries Workshop was among the first of these. It aimed to come to agreements on factors that will help to assure the quality and interoperability of MS registry data for supporting regulatory evaluations while ensuring also that appropriate governance arrangements are in place.

The MS landscape in Europe is evolving. There are many local and regional registries and considerable heterogeneity in terms of their organisation, purposes, core data elements collected, and data platforms. There are two main collaborations, the European MS Platform (EMSP) and Big MS Data. EMSP represents 39 MS societies from 34 European countries and through its European Register for MS (EUReMS) initiative of 2011-2014, established a network of registries to facilitate epidemiological and clinical evaluations and research in MS. The Big MS Data group represents a network of national registries from Denmark, France, Italy, Sweden and MSBase, an international online registry established to facilitate research in MS. Some registries are affiliated with both collaborations. There is no single agreed core data set that is collected systematically nor are there standard data definitions or dictionaries that apply across all MS registries. These impediments have been overcome on a case-by-case basis when registries have collaborated on academic studies although this is time-consuming and work-intensive and substantially limits the potential for MS registry data to contribute to regulatory decision-making.

## **3. Workshop objectives and methodology**

### **3.1. Objectives**

The primary objectives of the workshop were to agree on:

- ❖ Implementable recommendations on core data elements to be collected in MS registries, common procedures, consents, governance, data quality, and registry interoperability
- ❖ Actions to be taken for the further development and finalisation of recommendations.

### **3.2. Participants**

All of the workshop participants had involvement with MS from a scientific, clinical or regulatory perspective. They included representatives from national and regional registries as well as from the EMSP and Big MS Data collaboratives, national competent authority (NCA) MS medicines assessors, EMA assessors, HTA and reimbursement representatives, a patient representative, marketing authorisation applicants (MAAs) with MS products in development and MAHs with MS products on the European market. The Workshop Agenda and Participant List are available in Appendix 1.

### **3.3. Methods**

Participants selected one of three topics for group work:

- Group 1 – Common data elements needed by all stakeholders; data validation
- Group 2 – Informed consents, governance, data protection, data access: patient level data versus aggregated data; custodianship of data
- Group 3 – Common procedures, registry interoperability, quality assurance to support regulatory evaluations and data analysis.

Each group included participants representing registry holders, regulatory assessors, and MAAs/MAHs. Five weeks before the workshop, participants were sent a group-specific pre-work package that sought their views, experiences, and needs in relation to their group topic (Available in Appendix 2). The EMA Patient Registries Initiative team collated the responses and provided these as background information for each group during the week prior to the workshop. The intention was that participants had a good understanding of each other's perspectives in advance of the workshop in order to facilitate productive group work on the day.

At the workshop, following introductions, each group worked together with two moderators to discuss their topic, agree their recommendations, and then present these to the whole group who further discussed and refined them and agreed on the main recommendations and next steps. Throughout the discussions, the moderators made detailed notes of participants' observations in order to provide

context for the final report and to explain factors that facilitated or limited the scope of the recommendations.

Following the workshop, the Patient Registries Initiative team drafted the observations and recommendations made by each of the three groups and circulated these to the group members for review and amending (Summaries by Group available in Appendix 3). These were then collated into the eight sub-sections that are contained in Section 4 and are followed in Section 5 by an outline of the actions arising and their owners. The Patient Registries Taskforce will facilitate implementation of the recommendations by working with the owners in each case to establish task and finish work groups to deliver on the actions. The taskforce will also publish an implementation plan.

## **4. Workshop observations and recommendations**

In this section, participants' detailed observations and recommendations relating to the use of MS patient registry data to support medicines evaluations are set out.

### ***4.1. Utility of registries for regulators and marketing authorisation holders***

#### **Observations**

- European MS registries are heterogeneous in terms of their organisation and the data collected.
- The availability of registry data in aggregate form to third parties such as regulators and MAHs would be of great value potentially for post-authorisation studies of safety and effectiveness.
- While registries may be useful for safety signal evaluation, they are limited for real time safety signal detection and do not routinely collect all of the data needed for pharmacovigilance purposes.
- Retrospective use of registry data for safety evaluations is considered as secondary use thereby falling under good vigilance practice (GVP) rules for safety data reporting (GVP Module VI: Management and reporting of adverse reactions to medicinal products).
- For MAHs, registries should fulfil the following criteria: availability of appropriate, verifiable data, adequate sample size, timeliness of response and of interactions between the MAH and registry holders.
- For regulators, the geographical spread of the registry network (i.e. wide range of EU countries) is a key factor for understanding treatment practices and outcomes across the EU and data need to be of appropriate quality.

## **Recommendations:**

- MAHs, regulators and registry holders, plus other stakeholders where relevant (for example, reimbursement bodies), should engage in discussions early during the regulatory processes for approval of new treatments to consider data needs and scientific / study protocols and to understand the range and nature of data that registries could provide, especially for post-authorisation studies.
- Registry holders should agree on core common data elements to be collected systematically by all registries (See detail in section 4.8.2).
- While acknowledged that registries are not the best source for identifying adverse events in real time, automated flagging of designated events may help identify certain serious events and alert physicians to report them through normal routes but should not replace spontaneous reporting by physicians.
- For a specific post-authorisation study or adverse event signal validation, registries could participate in targeted, time-limited, monitoring following a protocol agreed with the requesting stakeholders. Post-authorisation studies should be registered into the EU PAS register.
- For a prospective post-authorisation safety study (PASS) to be set up within a registry, the study protocol should ensure that data collection is in accordance with GVP requirements (GVP Module VIII, PASS).

## **4.2. Governance and timelines for data requests from registries**

### **Observations**

- A key principle of registry governance is the protection of the patient (and site as necessary) anonymity.
- Each registry has its own governance framework that generally reflects a commitment to the registry contributors, is seen to work well in its own context, and currently is preferred over a harmonised governance framework.
- Timeliness is an important consideration when data are needed to inform safety evaluations and providing recent data within short deadlines is a challenge for many registries taking into account the time needed to review and accept a request, to undertake the study, and to prepare a report. When several registries collaborate to conduct a study, a longer time is needed.
- Currently, requests for registry data are managed by individual registries (Big MS Data network members) or groups of registries (EMSP) on a case-by-case basis. Individual registries collaborate in combining their data to create a large dataset where this is needed in individual studies. Seeking access and approvals to run multi-country studies is done on a registry-by-registry basis – the organisation is challenging and time consuming.

- Registries would like to establish a structured framework for collaboration with MAHs and regulators and agree that a single point of contact for data requests could be useful. As the governance of each registry is different, such a single point of contact would not control or grant data access but could evaluate requests and provide a recommendation for registries on participation in the study. Individual registries would then decide on participation and collaborate with the stakeholders to plan and undertake the study.
- From the MAH and regulator perspectives, it would also be desirable for registry holders to collaborate to establish a single point of contact to evaluate requests and provide recommendations to registries on participation thereby facilitating timely access to adequate data for a safety or effectiveness study.
- Currently for registry-based studies, data analysis is undertaken internally or through an independent third party (e.g. academic institution). The capacity for internal statistical analyses varies across registries. When results are shared with regulators or MAHs, independent third-party analyses are preferred by regulators if there is no adequate capacity to perform analyses internally, taking into account that potential conflicts of interest must be managed appropriately.
- National registries holders have limited capacity (and funding) to upload clinical information more frequently than once a year (usually at the end of the year).
- Funding may be obtained for services that registries provide.

### **Recommendations**

- Registry holders should explore mechanisms whereby data requests could be evaluated in a co-ordinated fashion via a single point of contact.
- To assess data / study requests from MAHs or regulators and ensure consistency of responses, the process should include standardised operating procedures (SOPs) for requesting data and outlining the types of data that can be provided by registries and in what form they will be provided.
- Standing agreements between MAHs and registry holders could facilitate provision of data for regulatory procedures, either routine (e.g., periodic safety update reports (PSURs), or exceptional (e.g., during a referral procedure).
- Regulators should establish communications with Registry holders with the following objectives:
  - To be informed of the data that are available or can be collected by registries at the time when post-authorisation information is being requested from MAHs
  - To support Registry holders' understanding of regulators' requests to MAHs and of the data elements and the quality standards required
- Registry holders should communicate to patients and health care providers regarding the post authorisation studies to which they contribute, informing them about the goals of the studies, and the benefits for public health.



### **4.3. Informed consents**

#### **Observations**

- The current framework of informed consents is not harmonised across MS registries. As each registry's approach to consent complies with research governance in the country/countries involved, a single Europe-wide consent was not deemed feasible.
- As it is not desirable / possible to standardise consents, requests for registry data must be managed within the current framework of consents.
- Some national registries (for example, Sweden) do not take formal consent from patients while others obtain consent through a signature or through the clinician ticking a box confirming the information has been provided to the patients. In general, registry holders do not systematically audit their patient consents.
- Consents are largely paper-based. Patients may withdraw consent or restrict the use of their data at any time. An electronic system would facilitate keeping track of consents, restrictions and withdrawals.
- Some studies require specific consents to be obtained from participating patients – this can be burdensome.

#### **Recommendations**

- Registries should maintain records, ideally in electronic form, of patient consents obtained, any restrictions on consents, and withdrawals, and should audit the records at appropriate intervals to ensure completeness.
- At the time of their inclusion in a registry, patients should be fully informed about the purpose of the registry, why it was created, who will be included, and with whom summary or patient level data might be shared, and should have the option to put restrictions on the use of their information.
- Future development of informed consents should ensure they are broad enough to cover all potential uses of registry data in line with the applicable legislation including the option for data sharing/ pooling between registries and across country borders and with other stakeholders including regulators and MAHs.

### **4.4. Data sharing**

#### **Observations**

- Registry holders are willing to share data in keeping with their governance and consent frameworks and currently make agreements for sharing data on a project by project basis. Individual patient data always remain in the ownership of the registry.
- Registry holders are keen to collaborate with regulators and MAHs on clearly-defined questions or projects.

- Currently, when a MAH needs to provide registry data to regulators in the context of a post-authorisation study, communications are typically between the registry holders and the MAH but do not include the regulator.
- The consent framework permits sharing of aggregated/ summary data and results with MAHs and regulators but does not permit sharing of patient level data with MAHs.
- In rare circumstances (urgent safety or efficacy issues/signals), regulators may request patient level data. Such requests would be reviewed on a case by case basis by the registries.
- As indicated (Governance, 4.2. ), registry holders are already broadly agreeable for data analyses to be undertaken by an independent /academic third party.

### **Recommendations**

- All registry holders should provide information for regulators and MAHs on situations where sharing of data is acceptable within their governance and consent frameworks and on the form in which data may be shared.
- Registry holders should consider amending their governance procedures to allow data sharing
- As noted (Governance, 4.2. ), clear process information and SOPs from registry holders would facilitate consistency in data requests as well as in provision of data from the registries.
- Regulators need to consider how they could better engage with registry holders to encourage the provision of appropriate data of acceptable quality for regulatory purposes. Scientific advice could be an entry point for involving registry holders as well as MAHs in considerations of data needs for supporting regulatory evaluations.
- The impact on MS registries of the forthcoming General Data Protection Regulation ([GDPR regulation](#)) needs to be assessed, including its impact on the anonymisation and pseudo-anonymisation of patient level data to facilitate data sharing and on circumstances where data sharing can be allowed (e.g. in the interest of public health – see Appendix 4).

## **4.5. Processes for data upload - two national registry examples**

### **Observations**

In general, local/regional MS registries have individual structures and processes for data upload to national registries and contribute data at agreed intervals, for example, quarterly or annually. Data are generally entered manually. Two national registries, Germany and Italy, provided detailed information on their processes. This is available in Appendix 5.

- The **German Registry** is composed of a network of approximately 170 centres and has a harmonised common data set. Data are uploaded from centres at least once per year. Quality assurance is predominantly software driven. An audit trail records any changes made to individual datasets. There is limited source data verification and audit.

- The **Italian Registry** is composed of 138 clinical centres, 62 of which have been authorised (Ethics Committee approval) to contribute an agreed minimum data set that is uploaded quarterly to a dedicated centralised platform. Quality assurance includes software checks. There are also mandatory data fields.

### **Recommendations**

- Registries should explore options to minimise the number of (manual) steps and duplications of data entry into the national registries in order to minimise errors and decrease the time needed for the national data to be available.
- National registries should agree on a core common data set and establish common quality assurance parameters to apply to individual data fields.

## **4.6. Data quality**

### **Potential enablers to ensure registry data are of appropriate quality for supporting regulatory evaluations**

- Recognition by all stakeholders of the need for reliable, valid data representative of the MS patient populations at both local and national level
- Recognition by stakeholders that to ensure data are reliable, valid and representative, there is a need to be able to systematically verify source data and to ensure registry data are of acceptable quality.
- Some data quality checks are already embedded in national registries (Germany and Italy examples noted above).

### **Potential barriers to data quality**

- The absence of an agreed minimum core data set and agreed data quality standards that apply to all MS registries.
- Lack of knowledge among registry holders of the quality requirements of stakeholders using data to inform population-level treatment decisions for MS.
- Inability to systematically link registries with external data sources; Linkages are desirable because they can help to inform on mortality, co-morbidities, health care resource utilisation, safety, and effectiveness of treatments.
- Lack of support to maintain registries including their quality assurance activities.

### **Recommendations**

- Agree a common core data set for MS registries and define the associated quality measures.

- Quality check / audits: Agree on acceptable data standards and establish a common system for quality assurance to be applied consistently across registries at agreed time points, for example, annually.
- Use software to facilitate data quality control, for example, data entry tracking and flags and blocks on data entry if mandatory information is missing.
- Registry holders need to provide support at the individual registry level for training on data entry and quality assurance.
- Establish registry linkages with external data sources whenever feasible.
- Regulators should provide registry holders and MAHs with information on legal provisions and procedures for reporting requirements and access to data quality standards.
- Explore sustainable options for registry support.

#### 4.7. Developing an agreed set of data quality indicators

##### Observations

- Table 3 includes suggestions from the stakeholder group on Data Quality, its measurement using harmonised standard indicators and solutions to help ensure consistent quality:

**Table 3: Data quality indicators**

Role	Name	Indicators of quality	Solutions
Consistency	Uniformity of core data elements entered over time	<p>Minimum data entry frequency – eg, 6 months in first year, then annually.</p> <p>Patient attrition rates</p> <p>Completeness of core data field completion</p>	<p>- Training of personnel</p> <p>- Benchmarking of data entry completeness</p> <p>- Assess patient attrition rates.</p> <p>- Linkage to external data sources</p> <p>- Standard Terminology, Coding SOPs, user guides</p> <p>- Drop down menus, alerts, text prompts</p> <p>- Help screens/desk</p>
Accuracy	How well are the data entered? (errors, contradictions or value impossibilities, duplicates)	Frequency of errors, duplicated / wrong data	<p>- Common dictionaries, terminology and definitions e.g. Harmonise MRI reporting parameters</p> <p>- Validate against source data</p>

Role	Name	Indicators of quality	Solutions
			<ul style="list-style-type: none"> <li>- Data Audits / Inspections</li> <li>- Training, software checks</li> </ul>
Completeness	How much data is missing?	<p>Eg, 90-95% complete in the mandatory fields</p> <p>Proportions lost to follow-up / Patient attrition annually</p>	<ul style="list-style-type: none"> <li>- Data source verification: eg, research assistants check at local registry level</li> <li>- Annual audits on patient attrition and on numbers of unknown/not entered values</li> </ul>
Representative	How well /accurately is the exposed population reflected by the registry data?	% of patients covered (compared to national social security systems)	<ul style="list-style-type: none"> <li>- Linkage between registries and with external systems</li> <li>- Communication to patients to encourage enrolment</li> </ul>

### Recommendations

- Raise awareness of all stakeholders on data needs, acceptable standards and the need to assure data quality
- Agree on indicators and standards of data quality, terminologies/coding and reporting requirements to apply to local and national registries, train participating healthcare professionals accordingly, and provide performance feedback to registry holders.
- Establish processes for systematic audits of registry data with feedback to registry holders.
- Establish an independent formal accreditation process for registries that will signify appropriate operating processes and data quality.
- Communicate the value of registries, their limitations, and the importance of consistent data quality to all participating healthcare professionals and to those using the data including MAHs, regulators, health technology assessment (HTA) groups and reimbursement bodies.
- Provide feedback for clinicians and patients so that their contributions are recognised.

### 4.8. Common data elements needed by all stakeholders

Stakeholders at the EMA's registry workshop in October 2016 agreed that patient registries are to be preferred over product registries owing to the limitations of the latter. Currently no single registry platform or software is used by all MS registries in Europe but it has been possible to combine data from registries in both the EMSP and Big MS groups. Agreement on the data elements to be collected in MS registries would facilitate treatment evaluations and comparisons of safety and effectiveness outcomes between different MS populations and across multiple countries.

In some cases, data entry to the registry is encounter-based at each clinic visit. In others, data are uploaded at intervals from local registries to a national registry (See Section 4.6. ). In discussing the common data elements desired in registries, it was clear that the list would be extensive. It was therefore agreed by workgroup participants to consider data collection in terms of a “**core data set**” comprised of the elements agreed by the whole group and a “**data wish list**” that included elements considered important but not key to the design of a registry or that were not agreed by all the group members.

## **4.8.1. Core data set - Observations**

### **4.8.1.1. Patient specific data**

- Dates of birth/death, gender and country of residence are relevant for demographics and for identifying MS incidence and prevalence patterns.
- It is important to record information about employment status and how the disease affects patients’ social functioning including working environment, employment opportunities, and income.

### **4.8.1.2. Disease specific data**

- Patients commonly have already had symptoms on several occasions prior to being diagnosed with MS so the dates of MS onset and diagnosis are generally different and both should be recorded. MS type should be recorded so that progression over time may be determined.
- The Expanded Disability Status Scale (EDSS) is an established measure of disability and its progression over time and is feasible to collect at each clinic visit. Evaluation of other functional scales, for example, MS Functional Composite sub-domain scores, was considered unlikely to be done at every clinic visit.
- Relapses, the severity of the relapses (reflected in need for steroid treatment or change in EDSS) and the frequency of their occurrence were considered important to be recorded.
- Hospitalisations due to MS progression and/or complications were considered key for the evaluation of the effect of the disease on the patient and society.
- For quality of life measurements, there is no standardised tool/scale used by all physicians, and most reported that they do not collect these data routinely. Regardless, it was concluded that this information crucial for multiple stakeholders, and a standardised tool/scale should be agreed to facilitate assessment and between-group comparisons.

### **4.8.1.3. Para-clinical investigations**

- There was discussion on whether volumetric parameters should be evaluated in MRIs rather than counting the number of lesions since this is not a reliable measure of

disease progression in some forms of MS. It was considered desirable to collect information on MRIs performed (with agreement needed on the result measures to be recorded), frequency (dates), method and parameters used (gadolinium +/-, resolution).

- Considering laboratory tests, it would not be feasible to include all results because manual upload is needed in most registries. However, as lymphopenia is one of the most common adverse events associated with MS drugs and of itself may be a risk factor for some adverse events, it was suggested that a threshold defining lymphopenia should be established so that a Yes or No response could be entered rather than recording the actual lymphocyte count (time consuming, transcription error risk).
- Following the same rationale, data on liver enzymes need to be collected based on threshold measure agreement.
- Cerebro-spinal fluid (CSF) oligo-clonal bands are an important diagnostic test and should be included.

#### **4.8.1.4. Co-Morbidities**

- It was agreed that co-morbidities should be recorded.

#### **4.8.1.5. Treatment**

- It was decided to group treatments as follows: MS therapy (disease modifying and immunotherapy); MS symptomatic therapy, and Other therapy including treatments for co-morbidities.
- Treatment-related information considered relevant included name, indication, dose, route, frequency, and start/stop dates (as precisely as possible). It was also desirable to know reasons for stopping MS therapies. There was a wish to record consecutive doses in cases of titration but the feasibility of this was not discussed.

#### **4.8.1.6. Serious suspected adverse events and adverse events of special interest**

- It was agreed that there was a desire by regulators and industry for a standardised way to collect information on adverse events for MS therapies, categorised into groups using MedDRA terms and recording the date of onset, the therapy associated with the event, the nature, severity and outcome of the event.
- The feasibility of such detailed recording, especially if an event occurred at a time distant from the patient's clinic attendance was not discussed but needs to be considered. Typically, registries are of value in follow-up evaluation of serious adverse event signals or new/potential safety issues but are not suitable for identifying adverse events in real time.

#### **4.8.1.7. Pregnancy**

- It was unclear if registries consistently include a field for pregnancy but it was agreed that relevant information included MS course during the pregnancy, outcome of the pregnancy, delivery date, live birth, birth weight, spontaneous abortion, complications and adverse events.
- More information about child development would need a different consent to what is obtained already and would not be feasible for all registries.

#### **4.8.1.8. Patient Reported Outcomes**

##### **Observations**

- It was agreed that would be of value to capture PROs in the registries. This is not currently done.
- Certain PRO information is of particular interest to HTA and reimbursement stakeholders.

##### **Recommendation**

- Patient, clinical, and registry groups to determine what is possible in relation to inclusion of PROs in registries and how these might be standardised and inclusion operationalised.

#### **4.8.1.9. Data wish list**

As part of the **data wish list** (See 4.8.3 below) (i.e. items that were regarded important, but for different reasons were not accepted by consensus), elements considered relevant included the race and ethnicity of the patient, the level of education, MS diagnostic criteria used, other functional (besides EDSS) and composite scores (the Multiple Sclerosis Functional Composite (MSFC), swapping the Paced Auditory Serial Addition Test (PASAT) for the Symbol digit modalities test, since it is regarded as a more reliable tool to measure cognition); family history of MS; other lab results such as the John Cunningham Virus (JCV) antibody index (given the importance of the risk of Progressive Multifocal Leukoencephalopathy (PML)) and the Varicella Zoster antibody level; patient reported outcomes additional to relapses and Quality of Life measures; clinical trial participation.

It was agreed that a core data set for paediatric patients is needed but this was not discussed.

#### **4.8.1.10. Registry platform and software**

In order for data elements to be captured systematically and in a standard form, a common platform and software are desirable. Appropriate tools to measure disease progression as well as quality of life data should be agreed, along with a standardised way to register comorbidities and adverse events.



## **4.8.2. Recommendations: Core Data Set Items**

### **4.8.2.1. Patient specific data**

- Date of Birth
- Date of Death
- Gender
- Country of Residence
- Employment Status

### **4.8.2.2. Disease Specific Information**

- Date of Diagnosis
- Date of Onset
- MS Type
  - Relapsing remitting
  - Secondary progressive
  - Primary progressive
  - Benign
  - Clinically Isolated Syndrome
  - Radiologically Isolated Syndrome
- Expanded Disability Status Scale (*EDSS*) Score
- Relapses
  - Severity (Steroids (dose, route, duration) needed; *EDSS* change)
  - Frequency (number in past year)
- Quality of Life measure (most recently recorded for the year)
- Hospitalisation (number in past year)

### **4.8.2.3. Para-clinical Investigations**

- MRI:
  - Yes/ No
  - Date
  - Report – *information measures to be agreed*

- Lymphopenia ( $< n\text{-count}$  (agree on a cut-off measure)): Yes/No
- Liver Enzyme (ALT, AST, GGT, LDH) elevation ( $>3X$  upper limit of laboratory range): Yes/No
- Cerebro-Spinal Fluid Oligoclonal Bands: Yes/No

#### **4.8.2.4. Co-Morbidities**

- None
- Cardiovascular
- Respiratory
- Gastrointestinal
- Psychiatric
- Metabolic
- Malignancies
- Musculo-Skeletal
- Auto-Immune conditions other than MS
- Other

#### **4.8.2.5. Treatment**

- **MS Therapy**
  - Name
  - Start date
  - Stop date & reason (for medications ceased)
  - Dose, Route, Frequency/Schedule
- **MS Symptomatic Therapy**
  - Indication
  - Start date
  - Stop date & reason (for medications ceased)
  - Dose, Route, Frequency/Schedule
- **Other Therapy**
  - Indication
  - Start date, Stop date & reason (for medications ceased)
  - Dose, Route, Frequency/Schedule

#### **4.8.2.6. Serious Suspected Adverse Events**

- No adverse events
- Serious adverse event occurred (*consider use of MedRA terms*)
  - Treatment/s associated with event
  - Nature of event [Psychiatric; Cardiovascular; Haematological; Urinary Tract; Opportunistic Infection; Neoplasm; Other]
  - Outcome (*use Adverse Event reporting descriptor terminology*)

#### **4.8.2.7. Pregnancy**

- Registries should include a field for pregnancy. Information to be included would include the MS course during the pregnancy, treatment changes as a consequence of pregnancy, outcome of the pregnancy, delivery date, live birth, birth weight, spontaneous abortion, complications and adverse events.

#### **4.8.3. Recommendations - Data Wish List**

- Clinical trial participation (Yes / No)
- Education Level
- Family history of MS
- Functional scores other than EDSS
  - 25 Foot Walk Velocity test (25FWT)
  - Symbol Digit Modalities Test (SDMT)
  - 9-Hole Peg Test (9HPT)
  - Low contrast visual acuity
- JCV Antibody Titre
- MS Diagnostic criteria used
- Patient Reported Outcomes (PROs)
- Race / Ethnicity
- *Varicella zoster* Antibody levels

#### **4.9. Summary of the main recommendations**

A summary of the main recommendation is presented in Table 1 of the Executive Summary section of the report.

## **5. Next steps and Actions**

### ***5.1. Role of the Patient Registries Task Force in guiding implementation of recommendations***

The Patient Registries Task Force will work with MS stakeholders where possible to assist in developing plans to facilitate implementation of the Workshop recommendations. This will prioritise the recommendations for which actions were agreed (Table 1) and assist in ensuring that actions are completed by each owner to an agreed timeline (Table 2 and Appendix 3).

### ***5.2. Actions for Regulators***

Regulators need to support MS stakeholders broadly by:

- Promoting the potential value of data from patient registries to MAHs, HTAs, reimbursement bodies and patient groups
- Considering if appropriate registry data would have a place in evaluations of new products.
- Facilitating communications between registry holders and MAHs
- Supporting registry holders to establish robust measures for assuring the quality of registry data and providing guidance on mechanisms for formal accreditation of registries using existing platforms, for example, a qualification procedure with HTA / reimbursement body involvement.
- Including patient registry data where appropriate in regulatory processes throughout product lifecycles.
- Engaging with relevant initiatives that are also exploring the potential of registry data to contribute to healthcare evaluations, for example, the work of EUnetHTA in its Joint Action 3 (Work package 5B) and the European Platform on Rare Diseases Registration.

### ***5.3. Actions for Registry Holders***

Registry holders should agree on a core common data set that would be collected by all registries contributing data for regulatory evaluations of new medicines. The core data set recommended by MS workshop participants is a starting point. The associated definitions and data dictionaries also need to be clearly established and applied. Registries need to prioritise measures to assure the quality of registry data and its reliability by:

- Ensuring that processes for quality assurance of registry data, including source data verification, are harmonised and applied systematically across MS registries.

- Gaining independent certification of the data quality and the standards applying in the patient registry.
- Developing a policy on sharing summary, pseudo-anonymised, and individual patient data with stakeholders.
- Developing a standard process for MAH and regulatory requests for registry data.

In addition, Registry holders need to optimise communications with patients, MAHs, and regulators by:

- Informing patients on the benefits and uses of patient registry data including appropriate sharing with relevant stakeholders.
- Informing MAHs and regulators of the type and detail of registry data that may feasibly be shared within consent and governance parameters.

#### **5.4. Actions for MAHs**

Marketing Authorisation Holders and Applicants need to have discussions with regulators early in the clinical development of new medicines in order to:

- Understand the regulatory data requests that are likely to arise in the event of a successful application, especially for post marketing surveillance.
- Consider if appropriate registry data would have a place in the regulatory evaluations.
- Identify if a suitable patient registry exists and make early contact to explore data availability and access.
- Develop a preliminary study protocol and explore with the registry holder/s and the regulator if the registry could fulfil the data needs.

#### **5.5. Actions for patient groups**

Patient representatives need to engage pro-actively with registry holders in order to:

- Ensure they understand and can communicate to patients the potential uses and associated benefits and risks of using patient registry data to assist in medicines evaluations, including appropriate sharing with relevant stakeholders.
- Provide insight on patient reported outcomes that might feasibly be collected in registries.

## **5.6. Actions for HTAs and reimbursement bodies**

HTAs and reimbursement bodies need to develop their understanding of the possible roles for patient registries in supporting technology assessments and informing reimbursement decisions by:

- Learning about the nature and purpose of the data collected in patient registries.
- Engaging with registry holders to adapt or optimise data collection in order to support their information needs where feasible.

Ongoing work by the European Network for Health Technology Assessment in its Joint Action 3 (Work package 5B) is highly relevant in this respect bringing together multiple groups to focus on registries in health technology assessment.

## **5.7. Summary of the main actions**

A summary of the main actions is presented in Table 2 in the Executive Summary section of the report.

# **6. Conclusions**

The MS patient registry landscape in Europe is heterogeneous. While all stakeholders are keen to optimise the use of MS registry data for supporting regulatory evaluations, there is considerable work needed to agree on a core common data set collected by all registries and to establish systematic processes to verify source data and assure registry quality. Once established, this could be accompanied by an independent certification process through existing platforms thereby helping to assure users that the data are of acceptable quality for regulatory purposes. An early priority is to improve communications between registry holders, regulators and MAHs/MAAs and to create a centralised process for requesting and obtaining data. The ultimate objective is that relevant data from registries will be incorporated in benefit-risk evaluations throughout medical product lifecycles.

# **7. Glossary**

- Anonymised Data: Data 'rendered anonymous in such a way that the data subject is not or no longer identifiable' (Recital 26, GDPR)
- Big MS Data: a network of national registries from Denmark, France, Italy, Sweden and MSBase
- EMSP: European Multiple Sclerosis Platform <http://www.emsp.org/about-emsp/>
- EUnetHTA: European Network for Health Technology Assessment

- EUReMS : European Register for Multiple Sclerosis <http://www.emsp.org/projects/eurems/>
- Encounter-based data entry: patient data entered directly to the registry during the clinical encounter, for example, an out-patient visit
- GDPR: Generalised Data Protection Regulation - Refer Appendix 4
- GVP: good vigilance practice
- HTA: Health Technology Assessment
- Individual patient data - Data separately recorded for each participant in a clinical study [http://www.ema.europa.eu/docs/en\\_GB/document\\_library/Other/2014/10/WC500174796.pdf](http://www.ema.europa.eu/docs/en_GB/document_library/Other/2014/10/WC500174796.pdf)
- Informed consent: The process by which a patient learns about and understands the purpose, benefits, and potential risks of a medical or surgical intervention, including clinical trials, and then agrees to receive the treatment or participate in the trial (medicinenet.com)
- MAA: marketing authorisation applicant
- MAH: marketing authorisation holder
- MSBase: an international online registry <https://www.msbase.org/>
- NCA: national competent authority
- Patient Registry: An organised system that uses observational methods to collect uniform data on a population defined by a particular disease, condition, or exposure, and that is followed over time  
[http://www.ema.europa.eu/ema/index.jsp?curl=pages/regulation/general/general\\_content\\_000658.jsp](http://www.ema.europa.eu/ema/index.jsp?curl=pages/regulation/general/general_content_000658.jsp)
- Pseudo-anonymised Data: data processed 'in such a way that the data can no longer be attributed to a specific data subject without the use of additional information.' (Appendix 4; GDPR Article 4 (5))
- SOP: Standard Operating Procedure

## 8. Appendices

Appendix 1 - Workshop Agenda and Participant List

Appendix 2 – Pre-work for participants (slides)

Appendix 3 - Tables of recommendations made by each of the three work groups

Appendix 4 - Generalised Data Protection Regulation, [GDPR regulation](#)

Appendix 5 - Details of the German and Italian national registries

**Link to reach Appendices 1-3 and 5**

[http://www.ema.europa.eu/ema/index.jsp?curl=pages/news\\_and\\_events/events/2017/10/event\\_detail\\_001523.jsp&mid=WC0b01ac058004d5c3](http://www.ema.europa.eu/ema/index.jsp?curl=pages/news_and_events/events/2017/10/event_detail_001523.jsp&mid=WC0b01ac058004d5c3)