



MSDA Stakeholder Engagement Meeting

Wednesday 20 November 2019

Grand Hotel Dino, Baveno, Italy





Table of Contents

Table of Contents	2
Summary	3
Abbreviations	4
1 Introduction	5
1.1 The MSDA History	5
1.2 MSDA Strategic Objectives	6
1.3 Participants MSDA Stakeholder Meeting	6
2 The multi-stakeholder's perspective on the value of scaling up real-world MS data	8
2.1 A Patient's Perspective	8
2.2 An Industry Perspective	8
2.3 A Researcher's Perspective	10
2.4 A Regulator's perspective	11
2.4.1 European Medicines Agency (EMA)	11
2.4.2 Health Technology Assessment (HTA)	12
3 Success stories of scaling up real-world MS data	14
3.1 Observational Data in MS – an overview	14
3.2 MSDA Catalogue – our approach	15
4 Data harmonization – why is it necessary and how can it be done?	18
4.1 Big MS Data Network (BMSD)	18
4.2 Patient Reported Outcomes for MS (PROMS) – a joint global initiative	18
4.3 Large-scale federated analytics in Europe through the use of OMOP common data model	19
4.4 MSDA Switchbox – our approach	20
5 Patient engagement and health data research	22
6 Data sharing – codes of practices	24
7 MSDA next steps	26
Acknowledgment	27
References	28



Summary

The Multiple Sclerosis Data Alliance (MSDA) is a global multi-stakeholder collaboration working to accelerate research insights for innovative care and treatments for people with Multiple Sclerosis (MS). Scaling-up real-world MS data is necessary to transform the care of people with MS and MSDA envisions a patient-centric data ecosystem in which all stakeholders contribute and use big data to co-create the innovations needed to advance timely treatment and care of people with MS. MSDA implements a dual approach and combines the MSDA Academy with the MSDA Toolbox. The MSDA Academy focuses on awareness raising, community building and education, while the MSDA Toolbox aims to reduce the time needed to find and assess data registries and cohorts.

The MSDA Stakeholders include MS patient (societies), MS researchers, industry, regulatory decision makers, MS data custodians and MS umbrella organizations. One of the major strategic focus areas of the MSDA is to build a multi-stakeholder data community, because there is a need to improve communication and collaboration between different stakeholders and to raise community awareness about the importance of MS data for different purposes. To accomplish this, a first stakeholder engagement meeting was hosted in Baveno in November 2019.

This meeting aimed to (1) inform all stakeholders about the mission, vision and strategic objectives of the MSDA and (2) to facilitate a multi-stakeholder discussion about how real-world data (RWD)/real-world evidence (RWE) can become the co-driver of (regulatory) decisions.

RWE generated from RWD has the potential to close the gaps between evidence and practice. Some examples include:

- expand our knowledge on MS disease behavior and effects on disease behavior of comorbidities or other factors;
- enable innovation through a better understanding of treatment outcomes;
- identify and assess potential for safety issues;
- evaluate effectiveness and patient relevance of existing therapies;
- enlarge/enrich the database for the European Medicines Agency (EMA) and/or payer decision makers;
- optimize the use of medicines through ongoing monitoring;
- complement the data from randomized clinical trials, especially in the case of long-term data, capturing a more holistic picture of the patient, providing novel insights and offering data on medicines used in secondary/tertiary care.

The perspectives of people with MS are central to establishing a trustworthy ecosystem for reusing health data for research and for learning health systems and that they need to be engage people with MS in decisions about the use of their data. The MSDA will collaborate closely with the European Patient Forum (EPF) and their [“Data Saves Lives”](#) initiative to accomplish this goal

An informed and engaged patient community will lead to: increased compliance to data collection procedures (more specifically when it comes to patient-reported outcome measures); increased patient-driven advocacy for the inclusion of patient relevant RWD in (regulatory) decision making.

A growing number of data collection efforts are underway. These efforts differ, among others, in their genesis, population criteria, types of data collected and duration of follow-up. Every dataset has its own weaknesses and strengths. Strategic oversight and direction are needed to streamline and leverage existing and future efforts. Improved awareness of existing and planned cohorts and registries is needed to better coordinate these efforts and maximize the impact of the limited resources available to support them. The MSDA is working on this by cataloguing MS data initiatives and developed a web-based catalogue that provides strategic oversight and allows end-users to browse meta-data of MS data cohorts and registries.

Next to this, reusability of MS registries/cohort data should be increased by harmonizing structure and variables by developing and promoting the adoption of a common data model (CDM). CDM can be defined as a mechanism by which raw data are standardised to a common structure, format and terminology independent from any particular study in order to allow combined analysis across several MS cohorts. The MSDA TransForMS SwitchBox (in short: SwitchBox) is a tool to harmonize different data formats to a MS specific CDM.

Finally, it is clear that data sharing needs to be done using trustworthy and transparent practices. The MSDA aims to support greater understanding within the community about reuse of RWD through MSDA educational sessions.



Abbreviations

AAN	American Academy of Neurology
AISM	Italian Multiple Sclerosis Society
BMSD	Big Multiple Sclerosis Data network
CDM	common data model
CHMP	Committee for Medicinal Products for Human Use
DMT	disease-modifying therapy
EAN	European Academy of Neurology
ECF	European Charcot Foundation
ECTRIMS	European Committee for Treatment and Research in Multiple Sclerosis
EFPIA	European Federation of Pharmaceutical Industries and Associations
EHDEN	European Health Data & Evidence Network
EMA	European Medicines Agency
EMIF	European Medical Information Framework
EMSP	European Multiple Sclerosis Platform
EPF	European Patients Forum
EUReMS	European Register for Multiple Sclerosis
EUROCAT	European Surveillance of Congenital Anomalies
GDPR	general data protection regulation
HCP	healthcare practitioner
HTA	Health Technology Assessment
i~HD	European Institute For Innovation Through Health Data
IHSI	International Horizon Scanning Initiative
IMI	Innovative Medicines Initiative
INNI	Italian Neuroimaging Network Initiative
MedDRA	Medical Dictionary for Regulatory Activities
MS	multiple sclerosis
MSDA	Multiple Sclerosis Data Alliance
MS PATHS	Multiple Sclerosis Partners Advancing Technology and Health Solutions
NARCOMS	North American Research Committee on Multiple Sclerosis
NIHDI	National Institute for Health and Disability Insurance
OFSEP	Observatoire Français de la Sclérose en Plaques
OHDSI	Observational Health Data Sciences and Informatics
OMOP	Observational Medical Outcomes Partnership
PASS	post-authorization safety study
PRO(M)	patient-reported outcome (measure)
PROMS	Patient Reported Outcomes for MS
PROMOPRO-MS	new functional PROfile to MONitor the PROgression of disability in MS
QoL	Quality of Life
RRMS	relapsing-remitting MS
RWD	real-world data
RWE	real-world evidence
SME	small to medium-sized enterprise



1 Introduction

Dr Liesbet Peeters

The first Multiple Sclerosis Data Alliance (MSDA) Stakeholder Engagement Meeting was a true success. Its purpose was to inform different stakeholders about their mission, vision and strategic focus, and to further engage the stakeholders to be involved in the MSDA (<https://msdataalliance.com/>).

As there is an incredible evolution in collection of data, MSDA was brought alive to accelerate research insights for innovative care and individualize treatment for multiple sclerosis (MS) patients. MSDA is based on global collaborative research, inspired by the patient and empowered by different stakeholders which were well represented at this meeting (i.e. researches, clinicians, industry, regulatory decision makers, data custodians and last but not least patient societies).

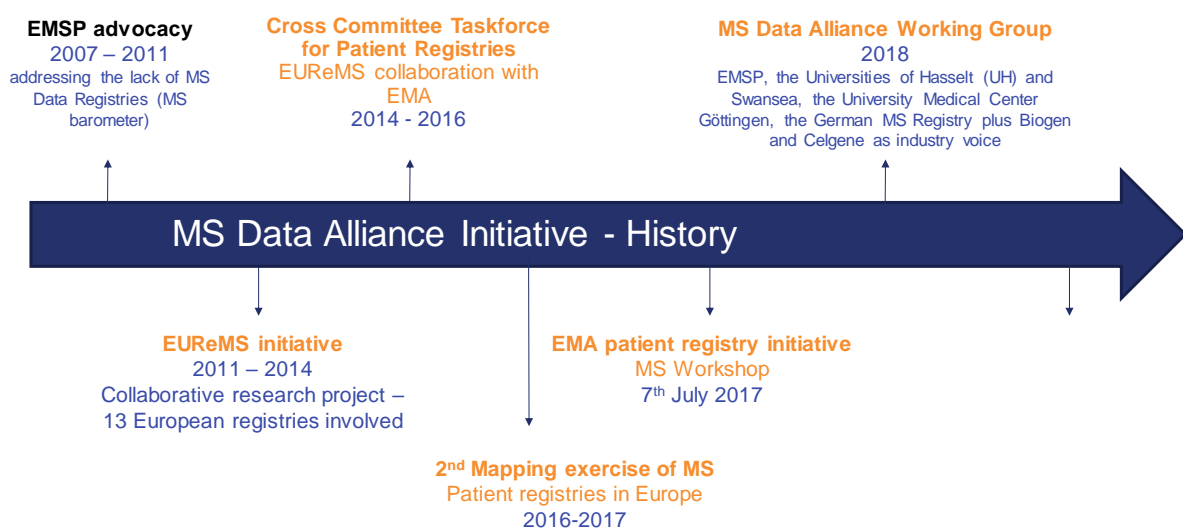
1.1 The MSDA History

Figure 1 summarizes the history of the MSDA. The MSDA initiative arises from the passionate and successful advocacy work for better use of real-world data (RWD) performed by the European Multiple Sclerosis Platform (EMSP). EMSP is a pan-European umbrella of MS societies with 30 years of experience in raising awareness, in collecting and sharing knowledge and patient-driven RWD collection.

The European Register for Multiple Sclerosis (EUREMS) has proved that cross-border MS data collection is possible and can lead to better outcomes for those living with MS in Europe. EUREMS addressed the lack of data at EU and national level on treatment and care for people with MS. The project ran between 2011 and 2014 under the coordination of a consortium of academic institutions and non-governmental organizations. In 2017, the European Medicine Agency Patient Registry initiative selected MS as one of their pilot projects and an MS-specific workshop was organized in 2017. The [report](#) of this meeting was one of the major inspirations for the discussions of the first MSDA working group brought together by EMSP in 2017. Several brainstorm sessions of the working group during 2018 resulted in a concrete kick-off year in 2019. At that time, the MSDA initiative was a joint initiative of Hasselt University (UHasselt) and EMSP.

Today, the MSDA is independent multi-stakeholder initiative under the umbrella of the European Charcot Foundation (ECF) with ECF acting as the legal entity. 6 core partners drive the initiative forward: EMSP, ECF, the European Institute For Innovation Through Health Data [i~HD], and the universities UHasselt, KU Leuven and Universitätsmedizin Göttingen. The MSDA is supported by 9 sponsors: Novartis, Celgene, icometrix, Quanterix, Biogen, Mylan, Spectrum Therapeutics, Merck, and QMENTA.

Figure 1: MSDA history





1.2 MSDA Strategic Objectives

MSDA aims to realize its 2019-2021 strategic objectives sociologically, through the MSDA Academy, as well as technically, through the MSDA Toolbox:

MSDA Academy

- Raise awareness about the importance of research using real-world MS data
- Build a multi-stakeholder MS data community
- Promote trustworthy and transparent practices in the use of real-world MS data

MSDA Toolbox

- Develop tools to reduce the time and efforts needed to find and assess real world MS datasets. Currently, we are focusing on the development and implementation of following tools:
 - **Catalogue:** A web-based catalogue that provides a strategic oversight and allows end-users to browse metadata of MS data cohorts and registries. The first version of the MSDA Catalogue digitalizes the questionnaire used in the most recent European Mapping Exercise (hosted by the European Medical Information Framework, EMIF).¹
 - **SwitchBox:** MSDA aims to maximize reusability of MS registries/cohort data supporting local harmonizing efforts by developing and promoting the adoption of a common data model (CDM).
 - **Cohort Explorer:** A “federated data network”, which allows local querying of different cohorts or registries, respecting the autonomy and ownership of data sources.

1.3 Participants MSDA Stakeholder Meeting

The MSDA Stakeholders include MS patient (societies), MS researchers, industry, regulatory decision makers, MS data custodians and MS umbrella organizations. A limited number of representatives for every stakeholder were invited to the meeting. Figure 2 and Figure 3 visualize the participating organizations that were represented during the meeting as well as their geographical distribution.

Figure 2: Schematic high-level overview of the organizations that participated in the stakeholder meeting

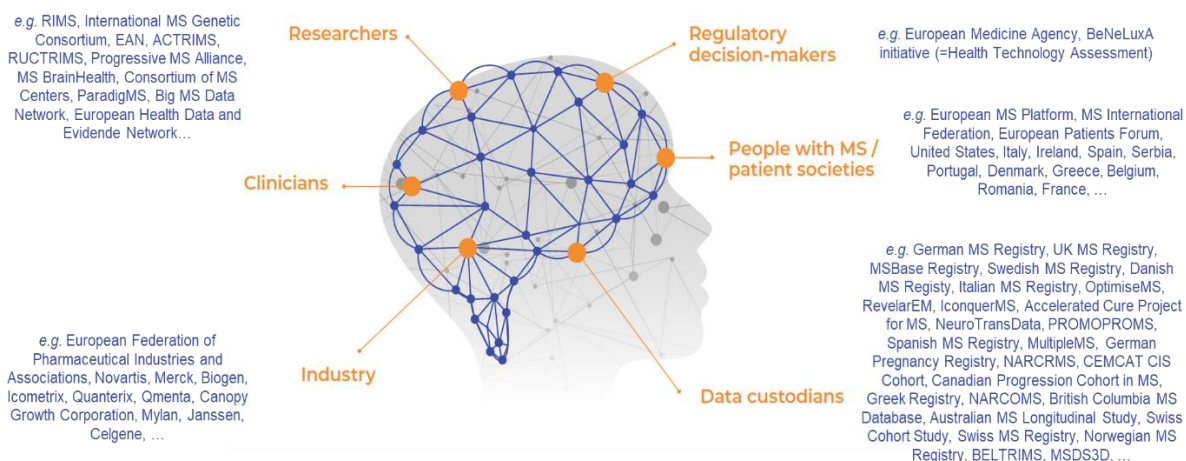
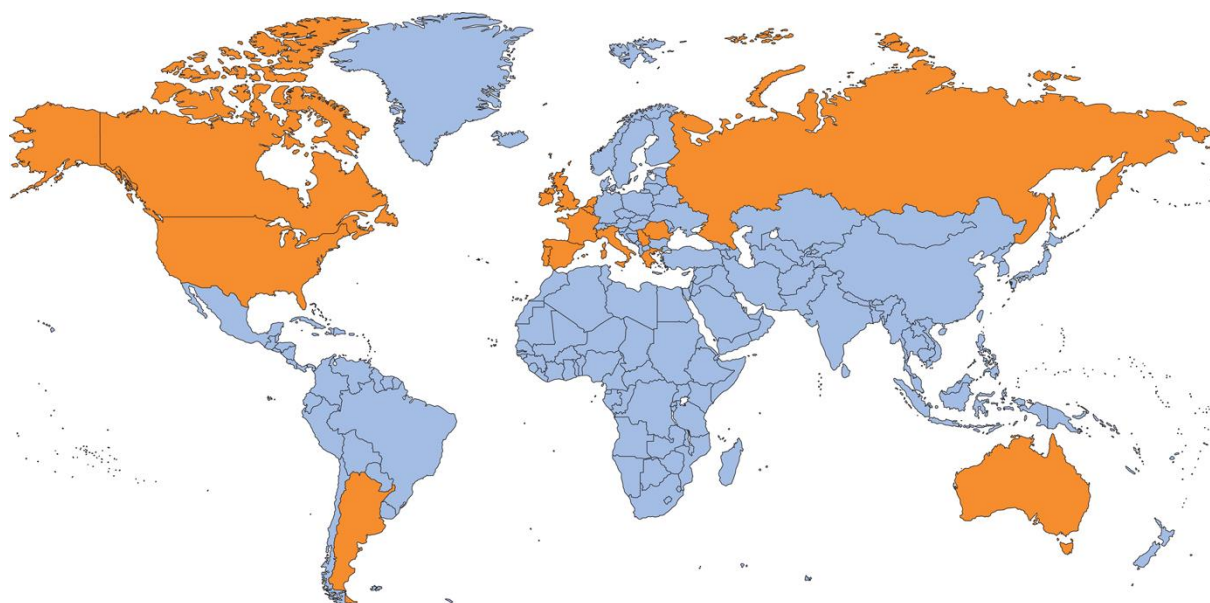




Figure 3: Geographical overview of the nationalities of the participants of the stakeholder meeting





2 The multi-stakeholder's perspective on the value of scaling up real-world MS data

CHAIRS: Giancarlo Comi & Piet Stinissen

With this session, we aimed to inspire our audience about the value of scaling-up RWD. We did this by addressing the questions "how does/would/could/should Big Data benefit different stakeholders". A combination of invited speakers addressed the perspectives of different stakeholders.

2.1 A Patient's Perspective

Jana Hlaváčová, diagnosed with MS in 2012, is a member of the EMSP executive committee and currently employed at the Ministry of Health of the Czech Republic. She raises the voice of the patient. Patient empowerment and involvement in scaling up real world MS data is very useful to her as providing decision-makers with real-world evidence (RWE) can fill the gaps currently seen in randomized clinical trials. This will in turn advance timely access to safer and more efficient treatments meeting the needs of MS patients. Equity in healthcare should be the ultimate goal.



"Patients today are more than willing to contribute with their data, not only to help themselves but also other patients. It is important to involve patients from the very beginning, to better understand their priorities. Making them partners of the process increases their engagement, willingness and trust in the registry. In addition, patients should be well informed on safety, data privacy and data protection. This in turn increases compliance with data collection procedures"

Jana Hlaváčová

Jana briefly brought up the example of ReMuS. The Czech Registry ReMuS has been collecting data from 15 MS centers in the Czech Republic since 2013, covering the whole territory of the state. So far, the registry has reached 70% coverage of patients with MS. The evidence collected has been used by decision-makers for pricing and reimbursement of MS treatments.

2.2 An Industry Perspective

Brendan Barnes from the European Federation of Pharmaceutical Industries and Associations (EFPIA) recognizes the potential benefits of reusing health data specifically for the pharmaceutical industry.

RWD can be used to support decision-making at various time points in a lifecycle of a drug if centered on the patient. For example, at discovery and development stage, RWD could be of interest to better understand a disease and its impact on the health and well-being of the patient while at post-authorization stage, RWD could contribute to improved pharmacovigilance. A complete list is shown in Table 1.



Table 1: Use of real-world data throughout the lifecycle of a drug

At the discovery and drug development stage, RWD are used
<ul style="list-style-type: none"> • To identify diseases or indications of a significant burden to a wider population. • To better understand a disease, e.g. the impacts of a disease on the wider health and well-being of patients, risk factors associated with a disease or disease progression. • To understand the prevalence of a disease or condition. • To provide new insights into disease associations or comorbidities and therefore to target new populations and indications for future research. • To develop targeted and personalized therapies and drugs. • To develop new analytical methods
At the clinical research stage, RWD are used
<ul style="list-style-type: none"> • To inform clinical trial design, e.g. to improve the study population selection for clinical trials, to predict the number of potential patients or to assess the efficacy of a new drug. • To create new approaches to patient stratification. • In feasibility studies. • Alongside or instead of control groups for trials to reduce the need to enroll patients as controls.
At the marketing authorization and market access stage, health data are used
<ul style="list-style-type: none"> • For medicine authorization and regulatory purposes. • To support market access discussions, e.g. to conduct health technology assessments, identify how competitive drugs are used on the market and to support pricing discussions. • To conduct cost-effectiveness analyses.
At the post-authorization stage, health data are used
<ul style="list-style-type: none"> • To support pharmacovigilance, i.e. to identify safety issues and adverse reactions. • For pharmacoepidemiology, i.e. to understand treatment effects across patient populations, to identify patient groups resistant to drugs, as well as get insights into patient adherence. • To add to the medical evidence base and inform changes in practice guidelines. • To support effectiveness comparisons between new and existing drugs. • To inform drug repurposing, i.e. the identification of diseases and conditions that could be treated with an existing drug.

A study by RAND Europe, commissioned by the EFPIA, explored current practices in relation to reusing health data.² The study identified several barriers and enablers to reusing health data. These included the need for continued research and development of analytic tools and for promoting the adoption of standards and interoperability across datasets. Building public confidence and trust in the pharmaceutical industry to reuse health



data and creating a greater collaboration between industry and other key stakeholders also appeared to be of significant importance.

The [Data Saves Lives](#) initiative from the European Patients Forum (EPF) aims to address these challenges and opportunities relating to health data. On one hand the initiative will create a health data community, a “safe space” where stakeholders can openly discuss their views and ideas on data and data policy at European and national level. On the other, the core of the initiative is at the same time the development of an informative web platform that will provide lay language information for patients and citizens who need transparent, understandable and comprehensive information on the topic of health data.

2.3 A Researcher's Perspective

Although evidence from randomized controlled clinical trials is considered the highest level of hierarchy, according to [Jeffery A Cohen](#) from the Cleveland Clinic there is renewed interest in RWD because of:

- the accelerating increase in readily accessible real-world clinical data;
- the development of statistical methods that improve validity;
- the growing interest in comparative effectiveness research among clinicians;
- the increasing demand from other healthcare stakeholders for post-approval evidence concerning new therapies in order to inform reviews of pricing, reimbursement, licensing, and utilization in practice.

RWD sources may be classified as primary or secondary.³ Primary data are collected for direct purposes of the registry (clinician-assessed outcomes, patient-reported outcomes [PROs], imaging and non-imaging biomarkers). Secondary data are comprised of information that has been collected for purposes other than the registry, and they may not be uniformly structured or validated with the same rigor as primary data (medical records, institutional or organizational databases, administrative health insurance claims data, death and birth records, census databases).

RWD could thus address several MS-related questions beyond those addressed by randomized controlled trials, but face methodological challenges:

- Study design and statistical strategies to minimize biases and limitations of real-world observational studies, thereby optimizing their validity and reliability⁴, e.g.
 - **propensity analysis:** method for reducing imbalance in non-randomized studies
 - **pragmatic (point-of-care) studies:** registry-based randomized controlled trials that use registries as a platform for case records, data collection, randomization, and follow-up.⁵ TREAT-MS (NCT03500328) and DELIVER-MS (NCT03535298) are recent pragmatic trials in MS.
- Collection and integration of PROs, imaging, and non-imaging biomarkers; integration of data collection into clinical care.
 - Use of advances in technology to generate and collect standardized patient data (Multiple Sclerosis Partners Advancing Technology and Health Solutions: [MS PATHS](#), iPad-based app MS performance test⁶) combined with quantitative imaging and biospecimen collection.
- Quality, completeness, and standardization of data within a dataset
- Storing and sharing of data which meet security, privacy, and confidentiality requirements across jurisdictions
- Integration and harmonization of data from diverse sources



2.4 A Regulator's perspective

2.4.1 European Medicines Agency (EMA)

Xavier Kurz, head of Surveillance & Epidemiology Service of the EMA, expressed the need for disease registries in the evaluation of medicines. Disease registries can be used for expanding the knowledge of the disease or for guiding product development and monitoring (Table 2).

Availability of data from disease registries offers the possibility of supplementing clinical trials, capturing a more holistic picture of the patient, providing novel insights and offering data on medicines used in secondary/tertiary care."

Xavier Kurz

Table 2: Need for disease registries

Knowledge of the disease	Product development and monitoring
<ul style="list-style-type: none"> • Unmet medical needs • Natural course of the disease following standard of care • Disease incidence/prevalence • Differences in clinical practice • Comparison of surrogate and clinical outcomes • Measurement of background rate of events (for assessment of drug safety) • Characterization /representativeness of patients in clinical practice 	<ul style="list-style-type: none"> • Planning of clinical trials • Source of historical/external control data for contextualization or comparison of clinical trial data – clinical trial data vs. clinical practice • Pragmatic clinical trials • Development/validation of clinical predictor model for treatment response • (Comparative) effectiveness • Extrapolation of adult data to children • Drug utilization – use in different age groups (children) –off label use • Safety monitoring and evaluation • Planning and conduct of post-authorization studies

The use of registries is often requested in the context of risk management plans and other regulatory requirements, e.g. for advanced therapies, medicinal products for pediatric use and orphan drugs. In the context of the measurement of the impact of regulatory decisions, the EMA performed an evaluation of all registries imposed as a legal obligation to companies by the Committee for Medicinal Products for Human Use (CHMP) from 2005 and 2013. The study found that a registry was imposed for 31 of 335 products authorized, or 9%.⁷ Some problems were however observed: 9 registries had not been started and among the other ones 9 had started later than planned, 13 had a low accrual rate and for 9 of them the protocol needed to be amended. Low data quality was also mentioned by the Rapporteur for some registries. It is important to highlight that 65% of registries initiated were product-specific registries and 80% were newly established registries.

There are several opportunities during the development process and during the authorization procedure to discuss use of registries for post-authorization monitoring of a product. The first opportunity is generally the business pipeline meeting between a company and the EMA. Scientific advice procedure may also be initiated at pre-authorization application. Discussions will also take place during the pre-submission meeting and during the



authorization procedure. The discussion between company and regulators should be initiated by the company at the earliest possible stage in order to be proactive in the identification of appropriate registries if needed and to have the time to address different options for the choice of data sources for post-authorization monitoring of the product.

Some considerations in assessing the usefulness of disease registries:

- To supplement efficacy from randomized controlled trials (or in case a randomized controlled trial is not feasible, to increase effect size, unmet medical need);
- Representativeness and validity of data collected;
- Data analytical plan (appropriate methods for controlling bias [e.g. use of propensity score], handling of missing data, ...);
- Automated data quality checks, source data verification, audit system;
- Pregnancy follow-up.

Approach to registries is suboptimal; existing disease registries are not fully exploited leading to duplication of efforts and inefficiency. Use of registries face challenges on recruitment, data quality, lack of quality control and sustainability (funding). Uncertainty about data quality is one of the reasons why companies often prefer to establish individual product registries rather than using existing patient registries.

The [EMA Patient Registry Initiative](#) promotes dialogue between regulators, companies and registry holders to support the use of existing data and creation of new registries, if needed. The initiative provides guidance and workshops to clarify methodological concepts and regulatory requirements (Figure 4).

Figure 4: The EMA patient registry initiative

Common core data elements

- To supplement efficacy from randomized controlled trials (or in case a randomized controlled trial is not feasible, to increase effect size, unmet medical need);
- Representativeness and validity of data collected;
- Data analytical plan (appropriate methods for controlling bias [e.g. use of propensity score], handling of missing data, ...);

Common core data elements

- To supplement efficacy from randomized controlled trials (or in case a randomized controlled trial is not feasible, to increase effect size, unmet medical need);
- Representativeness and validity of data collected;
- Data analytical plan (appropriate methods for controlling bias [e.g. use of propensity score], handling of missing data, ...);

Common core data elements

- To supplement efficacy from randomized controlled trials (or in case a randomized controlled trial is not feasible, to increase effect size, unmet medical need);
- Representativeness and validity of data collected;
- Data analytical plan (appropriate methods for controlling bias [e.g. use of propensity score], handling of missing data, ...);



2.4.2 Health Technology Assessment (HTA)

[Francis Aricxk](#), from the National Institute for Health and Disability Insurance (NIHDI) Belgium, noted that the 3 steps in the process to reimbursement (assessment, appraisal and ministerial decision) are primarily based on data from clinical trials. Chapter IV (in Belgium) relates to reimbursement conditions, meaning that patients have to meet certain criteria (such as disease status, target population) in order to get the medicine reimbursed. Conditional reimbursement is however shifting from a controlled mechanism (quality and budget) towards collection of RWE, in real registries but also virtual registries. Virtual registries come from electronic health records (IT harvests) for which both the patient and physician should be accountable. RWE can be useful for Health Technology Assessment (HTA) to make recommendations and for policy development/adjustment.

[Beneluxa](#) is a collaborative initiative in 5 countries (Ireland, Belgium, the Netherlands, the Grand Duchy of Luxembourg and Austria) on the reimbursement of medicines. Information on drug consumption, disease burden, best practices in health budget management, post-marketing evidence and policy expertise is shared between the collaborating countries. Horizon Scanning aims to highlight important pharmaceutical and medical technology innovations before they reach the market by continuously gathering data and analyzing research and literature. This improves insight in expected costs and enables timely decision making and (joint) price negotiations. One of the Beneluxa goals is to set up a systematic approach on horizon scanning for pharmaceutical products through the International Horizon Scanning Initiative (IHSI).



3 Success stories of scaling up real-world MS data

CHAIR: Bart Van Wijmeersch

With this session, we hoped to inspire our audience with past, recent and future scientific insights that were achieved using real-world MS data and hereby showcasing the value of real-world MS data.

3.1 Observational Data in MS – an overview

Maria Trojano from the University of Bari (Department of Basic Medical Sciences, Neurosciences and Sense Organs) pointed out the difference in terminology of using real-world data (RWD) and real-world evidence (RWE).⁸ RWE is the clinical evidence regarding the use and potential benefits or risks of a drug generated from the analysis of RWD by different study designs. In recent years, the growing recognition of the potential benefits of RWE studies has led to a proliferation of RW studies in MS research, the main drivers being: the accelerating increase in readily accessible RW clinical data, the development of advanced statistical methods that can improve validity and increasing demand from other healthcare stakeholders for supporting regulatory decisions and post-approval evidence concerning new therapies.



“The health care system generates an enormous amount of real-world data every day. To collect real-world data offers the scientific community and the patients many benefits. Many research questions can be addressed by studies based on real-world data”

Maria Trojano

Large MS registries such as the North American Research Committee on MS ([NARCOMS](#)), [MSBase](#)⁹, [Italian MS](#), Observatoire Français de la Sclérose en Plaques ([OFSEP](#)), have grown exponentially. Over 500,000 persons are currently available in these registries! Other RWD sources such as imaging databanks, biobanks (e.g. Italian Neuroimaging Network Initiative, [INNI](#)), PRO (e.g. [MS PATHS](#)), patient self-generated data (wearable biosensor devices) and administrative databases are gradually emerging. Linking data from these emerging sources with data from MS registries may offer improved granularity and important insights into outcomes achieved with new MS therapies.

The EUREMS project, ran between 2011-2014, merged RWD from different European MS registries.¹⁰ The pan-European project focused on epidemiology, long-term treatment outcomes, healthcare and quality of life (QoL) of patients with MS. The European Commission under the Health Programme co-funded this project. EUREMS proved that cross-border MS data collection is possible and can lead to better outcomes for those living with MS in Europe.

Practice guidelines from European (European Committee for Treatment and Research in Multiple Sclerosis,ECTRIMS/European Academy of Neurology, EAN)¹¹ and American (American Academy of Neurology; AAN)¹² associations have been really helpful to provide neurologists with high-quality recommendations based on data from randomized controlled clinical trials. Limitations to answer some crucial questions are however the paucity of head-to-head trials and long-term data.

Below some scientific highlights that have been achieved using RWE:

- Long-term observational studies showing effectiveness of disease-modifying therapies (DMTs; IFN-beta and glatiramer acetate) on long-term disability outcomes in relapsing-remitting MS (RRMS)¹³⁻¹⁵
- DMT comparative effectiveness studies providing recommendations on treatment choices at different MS stages¹⁶⁻¹⁹
- Post-marketing pharmacovigilance:
 - The [EMA initiative for patient registries](#) aims to optimize and facilitate the use of existing data for the benefit-risk monitoring of new drugs, and promoting dialogue between regulators companies and registry holders to understand barriers and opportunities.
 - A Joint protocol has been developed for European post-authorization safety studies (PASS). The EMA has agreed to a core protocol which uses patient data from the Big MS Data (BMSD) group. This core protocol includes specific primary and secondary variables, serious adverse events (coded by Medical Dictionary for Regulatory Activities, MedDRA) and pregnancy outcomes (classified by European Surveillance of Congenital Anomalies, EUROCAT).²⁰

3.2 [MSDA Catalogue – our approach](#)

[Liesbet M. Peeters](#) from Hasselt University enthusiastically shared today MSDA's activities on cataloguing and publishing descriptions of different data sources.



"There is already so much data out there. I am a data geek and therefore I love to search the web and read about existing and emerging data initiatives. And still, every time I go to a conference, I learn that there are promising initiatives that I didn't even know about. We need to know which data is out there and have strategic oversight, so we can optimally use it."

Liesbet M. Peeters

Real-World Datasets are highly heterogeneous. They differ in differing in maturity (years of follow-up), size (number of patients) and depth (number of variables). Next to this, they are designed for different purposes. To visualize this, table 2 pragmatically categorizes some RWD initiatives in 6 categories: (1) regional/national longitudinal follow-up data, (2) deep phenotyping/biobanking, (3) research collaborations, (4) patient-centered data, (5) special target populations and (6) improve care path concept ²¹.

Table 3: Examples of real-world data sharing initiatives pragmatically categorized in 6 categories



Regional- or National Longitudinal follow-up

British Columbia MS Database, Danish MS Registry, Italian MS Registry, New York State MS Consortium, OFSEP, Swedish MS Registry

Many other existing and emerging (Canadian Progression Cohort in MS, Corona MS Registry, Czech MS registry, German MS registries (>3), MS Clinical Database and Registry Health Sciences Centre Winnipeg, SJ MS Center Face to Face Registry, Sonya Slifka Longitudinal MS Study, United Kingdom MS Registry, ...)



Deep phenotyping/Biobanking

Accelerated Cure Project Registry, CEMCAT CIS Cohort, CLIMB Study, John Hopkins Precision Medicine Center of Excellence for MS, MS EPIC Study, MS Partners Advancing Technology and Health Solutions (MSPaths), MS Sunshine Study, NARCRMS, Norwegian MS Registry & biobank, Swiss MS Cohort, ...



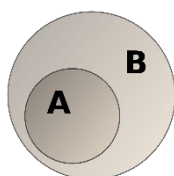
Research Collaborations

BMSD, IMMSG, MSBase Neuro-Immunology Registry, MultipleMS, RADAR-CNS, SUMMIT, ...



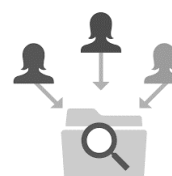
Patient-centered

Australian MS Longitudinal Study, iConquerMSTM People-Powered Research Network, NARCOMS, PatientsLikeMe, PROMOPRO-MS, ...



Special target population

MS in the Hispanic Population (USC Registry), PeMSDD, Sylvia Lawry Centre for MS Research, Veterans Health Administration MS Surveillance Registry (MSSR), ...



Improve care path concept

Cleveland Clinic Knowledge program, MS Documentation System, OptimiseMS, ...

Abbreviations: **BMSD**: Big MS Data Network; **CEMCAT**: Centre D'esclerosi Multiple De Catalunya ; **CIS**: clinically isolated syndrome; **CLIMB** : Comprehensive Longitudinal Investigation of MS ; **EPIC** : MS genetics-, expression, proteomics, imaging clinical ; **IMSG**: International MS Genetic Consortium; **MS**: multiple sclerosis; **MSPaths** : Multiple Sclerosis Partners Advancing Technology and Health Solutions; **NARCOMS**: North American Research Committee on Multiple Sclerosis; **NARCRMS**: North American Registry for Care and Research in Multiple Sclerosis; **OFSEP**: Observatoire Français de la Sclérose en Plaques; **PeMSDD**: Pediatric MS and Other Demyelinating Diseases; **PROMOPRO-MS**: new functional PROfile to MONitor the PROgression of disability in MS; **RADAR-CNS**: Remote Assessment of Disease and Relapse; **SUMMIT**: Serially Unified Multicenter Multiple Sclerosis Investigation



We need a tool that captures this heterogeneity in all its complexity, because “data quality” is in the *eyes of the beholder*. Indeed, if you are looking for a large dataset with a limited list of variables, you are looking for a completely different dataset as compared to someone searching for data to meet a research question that requires deep phenotyping. MSDA developed a web-based catalogue that provides a strategic oversight and allows end-users to browse metadata of MS data cohorts and registries. The first version of the MSDA Catalogue digitalizes the questionnaire used in the most recent European Mapping Exercise, i.e. the EMIF-Catalogue.¹ Liesbet encouraged to check out and provide feedback on the EMIF Catalogue which is made publicly available to the research community (from 2013-2018) and is one of the largest and most cited innovative medicines initiative (IMI) projects (57 partners in 14 countries). The [EMIF Data Catalogue](#) is a text-book example of EMIF's mission to improve identification, access and assessment, and bona fide (re)use of health data within the EU.



4 Data harmonization – why is it necessary and how can it be done?

CHAIR: Patrick Vermersch

Observational databases differ in both purpose and design. Each database is situated in different organizational setting and uses different terminologies or parameter denotations for describing their content. With this session, we hope to inspire our audience with **why data harmonisation strategies are relevant** and showcasing the initiatives that are already doing it.

4.1 Big MS Data Network (BMSD)

Jan Hillert from Karonlinska Institutet in Sweden introduced the **Big MS Data Network (BMSD)**, which is a collaborative harmonization effort between 5 mature MS registries (Danish and Swedish MS registries, OFSEP in France, Italian MS Registry, and the international database network MSBase). The registries were initially designed as tools for patient monitoring and used different platforms allowing to follow-up and visualize clinical information for each patient. Even with differences in the amount of data collected, there is some degree of harmonization on core data elements leading to a CDM (or minimal data set) in MS for further analysis. With the larger pooled data set, new opportunities arise, but also some challenges for data sharing, like ethical and legal constraints, data compatibility and funding. Nevertheless, each registry can retain its governance structure at all times, and collaboration so far is on a project-to-project and opt-out base. New registries are very welcomed.

Using BMSD, 3 demonstrator projects have been conducted to validate the feasibility of pooling data:

- Impact of early treatment on long term disability accumulation in RRMS patients;13
- Treatment discontinuation in the Big Multiple Sclerosis Data Network: a descriptive analysis;22
- Use of DMTs in the progressive phase (H. Butzkueven, Ongoing).

Through the initiative for patient registries, EMA aims to facilitate interactions between registry coordinators and potential users of registry data both at an early stage of the development, during the marketing authorization evaluation procedure and post-authorization. Disease-specific workshops are organized to bring together multiple stakeholders including registry owners, industry, representatives of HTA bodies and regulators to discuss the challenges and barriers to collaboration and identify specific solutions.²³ The discussions will focus on identifying the challenges and opportunities for collaboration between stakeholders, understanding the technical challenges preventing greater use from existing registries and identifying concrete solutions to facilitate collaboration and better use data from existing registries.

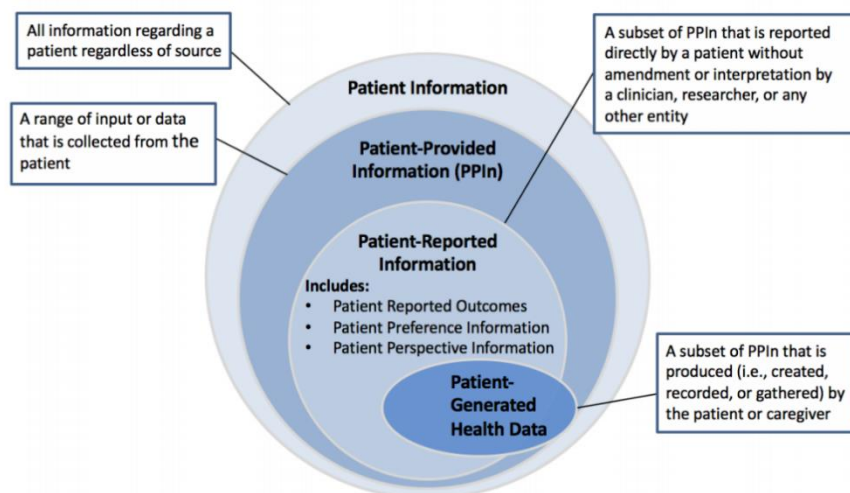
A BMSD PAAS core study protocol has been developed by BMSD wherein registries can analyze own data with aggregated results made available to pharmaceutical industries and authorities for merge and customized secondary data analysis. The protocol specifies primary and secondary variables, emphasizes improved capture of adverse events (MedDRA-coded) and EUROCAT codes for pregnancy outcomes. The protocol specifies principles for quality control and data handling.²⁰

4.2 Patient Reported Outcomes for MS (PROMS) – a joint global initiative

Paola Zaratin, Director of Scientific Research from the Italian MS Society (AISM), elaborated on a new global data harmonization project, Patient Reported Outcomes Initiative for Multiple Sclerosis (PROMS). PROMS is a joint initiative led and also coordinated by ECF and the Multiple Sclerosis International Foundation (MSIF), with AISM acting as lead agency. PROMS' ultimate aim is to understand and incorporate patient needs and perspectives into the process of developing, regulating and delivering new therapies as well as improved care. Although clinicians acknowledge the importance of PROs to facilitate understanding of treatment effects or compare treatment options, patients are frustrated that functional domains that matter most to them are often not addressed.²⁴

Patient-provided information broadly encompasses the entirety of information that can be collected from an interaction with a patient. This includes, but is not limited to, patient views on their disease(s)/condition(s), desired attributes for treatments, benefit-risk preferences and desired goals and outcomes, as well as their experience with the disease and its management (including diagnosis, treatment, and unmet needs) (see Figure 5).²⁵

Figure 5: Types of Patient Information



MSIF is a unique global network of MS organizations, people affected by MS, volunteers and staff from around the world. This movement is made up of 48 MS organizations with links to many others. One of the MSIF strategy 2017-2021 objectives is to advance systems and processes for enabling data sharing and explore the need for and feasibility of global collaborations for registries or databases in relation to PROs. The multi-stakeholder meeting in Lerici in July 2018 also highlighted that PROs have not reached their fully potential of delivering benefits to patients. As a response, PROMS was launched in September 2019, under the lead of AISM. AISM is currently working on an international project to standardize and harmonize outcomes in their own PROMOPRO-MS database and [iConquerMS network](#) (launched by Accelerate Cure Project).

PROMS will advocate for a set of standardized PROs to be used in development of new therapies and promote research to develop new PROs to meet the needs of all relevant stakeholders. PROMS very well recognizes the crucial importance of a framework to guide effective multi-stakeholder engagement. As such, it decides to learn from best practices of other relevant initiatives such as ECF Multistakeholder Initiative, Progressive MS Alliance and the-MULTI-ACT project. The latter, MULTI-ACT, launched in 2018, is facilitating a collaborative approach to develop new tools to assess the value of research in neurology from a patient's perspective, the impact of research in MS being assessed as a first case.

4.3 Large-scale federated analytics in Europe through the use of OMOP common data model

Peter Rijnbeek, Associate Professor Health Data Science Department of Medical Informatics (Erasmus MC Rotterdam), introduced the European Health Data & Evidence ([EHDEN](#)) Project, funded by the Innovative Medicines Initiative (IMI2) with 22 partners which will operate in Europe for the coming five years, 2018 – 2024. EHDEN aims to build a large-scale, federated network of data sources standardized to a CDM, and aspires to be a trusted observational research ecosystem to enable better health decisions, outcomes and care.

A complex health data research landscape is currently observed across Europe. To create a large-scale federated network, EHDEN requires



- Data interoperability: harmonization of the different structures, terminologies and languages
- Standardized analytical pipelines
- Data network services to build an active data network that answers clinically important questions in a timely manner
- A strong community mindset covering all of Europe that collaboratively will improve patient care

Mapping of healthcare data to the Observational Medical Outcomes Partnership (OMOP)-CDM will facilitate the re-use for a variety of purposes, enhancing and accelerating research and healthcare decision-making for global benefit. Type of evidence generated could be classified as such: clinical characterization (what happened to them?), patient-level predictions (what will happen to me?) and population-level effect estimations (what are the causal effects?).

EHDEN is a strong partner of the Observational Health Data Sciences and Informatics (OHDSI, pronounced "Odyssey"). This program is a multi-stakeholder, interdisciplinary collaborative to bring out the value of health data through large-scale analytics. All solutions are open-source. OHDSI has established an international network of researchers and observational health databases with a central coordinating center housed at Columbia University. The program concerns more than 200 collaborators from 25 different countries, currently compassing records on approximately 500 million unique patients in more than 100 databases.

The EHDEN Consortium invites all data custodians to participate in this endeavor by becoming a data partner in the EHDEN community. Data custodians can benefit from seed funding that will be made available via a €17 million "Harmonization Fund" that subsidizes conversions to the OMOP-CDM performed by EHDEN-certified small to medium-sized enterprises (SMEs). So far, 28 eligible SME applications are submitted.

The EHDEN Academy is an e-learning environment that is being developed by EHDEN. Its aim is 3-fold:

- Firstly, to train all stakeholders in the project in the use of the tools and processes that are being adopted in EHDEN.
- Secondly, to provide course development on the OMOP-CDM and the rich set of tools developed in the OHDSI project that have been developed in collaboration with that community.
- And lastly, the Academy is being developed in Moodle and is hosted in the Amazon Web Services cloud.

4.4 MSDA Switchbox – our approach

Tina Meißner from the University Medical Center Göttingen further elaborated on the need for reducing efforts and time needed to find and assess real world MS datasets. The MSDA Switchbox aims to maximize reusability of MS registry/cohort data by harmonizing structure and variables by adopting to a CDM and developing a standardized data dictionary of commonly used MS data concepts.

CDM can be defined as a mechanism by which raw data are standardized to a common structure, format and terminology independent from any particular study in order to pool analyses across different MS cohorts. MSDA SwitchBox builds on top of the OMOP-CDM, a CDM originating from OMOP which is now being implemented and updated by OHDSI. It is being used within the 2 large IMI projects (EMIF/EHDEN) which are the models for the MSDA infrastructure. So far, the following has been set up with the MSDA SwitchBox:

- Started the documentation (MSDA SwitchBox concept) for the transformation of heterogeneous MS registry data to the OMOP-CDM;
- Preparation of a MSDA data dictionary for the minimal dataset translation into OMOP-CDM;
- Analysis of the overall data structure of the 2 pilot registries: German MS registry and UK MS registry;
- Preparation a mapping dictionary of the relevant German and UK MS registry variables for the MSDA minimal dataset;
- Start of data harmonization within the data integration environment.

In the upcoming years, MSDA will focus on:



- Mapping all interested registries/cohorts to the OMOP-CDM formatted minimal dataset;
- Continuously improving the user-friendliness and decrease the workload of our mapping procedures;
- Expanding (or adapting) the minimal dataset based on the strategic input provided in the discussions and by the feedback. A first formal evaluation on data harmonization is planned during one of the stakeholder focus groups.



5 Patient engagement and health data research

CHAIR: Peer Baneke

With this session, we touched upon following question “How can we engage and serve patients through co-creation of value from their data, and grow their trust and confidence”?

Pieter van Galen, from EMSP, is a big promotor of a health ecosystem in which patients are central to decisions.

The current challenges are the lack of data to understand MS and the needs of patients. The notion of patient centricity is recognized but the implementation still needs to be worked out (better connection with the patients are needed). Reliable and accurate data collection systems are not available and/or not sustainable and the gap between patients and healthcare practitioners (HCPs) is still too large.

MS data collection systems across Europe have been evolving over the last years and new registries were created (38% of European countries currently do not collect MS data at national level²⁶). There are no more doubts on the potential outcomes and benefits of standardized data collection systems: they would support better MS research, PROs would allow the emergence of better treatments and therapies for people with MS and would enable improved decision-making based on RWE.



“A patient-centered health ecosystem is only possible if patients are included from the start in defining their needs, working hand in hand with the different stakeholders, keep patient’s needs in mind and readjust the processes accordingly. This will ensure patients adherence and uptake at the end of the process.”

Pieter van Galen

MS societies should act as a multiplier towards patients with regular updates on interim and final results of MSDA and PROMS activities and actively pursue their feedback. As previously said, better trained and informed patients, involved at the early stage in the development of registries, ensure that the indicators are defined with the patients, promoting the importance of the RWE. Ultimately, the data is going to support the key priority area for all patients across Europe to have better and timely access to treatments.

The [Data Saves Lives](#) initiative from EPF aims to address these challenges and opportunities relating to health data.

PANEL DEBATE: Pieter Van Galen (EMSP), Gözde Susuzlu (European Patient’s Forum, Data Saves Lives), Dipak Kalra (European Institute for innovation trough health data), Ruth Bentley (MS Brain health), Stephanie Ribbe (Novartis), Rod Middleton (United Kingdom MS Register)



It was all of the panel members’ conviction that the patient should remain central to the source of information, collect the best of information to provide the best of treatment, keeping the patient informed at all steps of the process.



Patient self-generated data (e.g. through wearables) can fill in the gaps, so patients need to be on board from the beginning and well-educated. An informed consent form with the goal of data sharing, should be transparent, covering safety and security of personal data, and be truly understandable.



6 Data sharing – codes of practices

CHAIR: Maria Pia Sormani

Examples of good practice of collaborative research and data sharing principles were discussed by [Dipak Kalra](#), President of i-HD.

Bona fide (societally acceptable) research is one of the components enabling trustworthy reuse of RWD. A bona fide research organization is one that is appointed or accredited or funded to undertake bona fide research, and/or has made public its commitment to adhere to recognized research governance principles:

- research need not be the primary business of that organization;
- not all of the research undertaken by that organization has to be published;
- the organization does not need to be publicly funded.

The **FAIR** principles can be used for transparency in the data:

- To be **F**indable: a searchable method to discover resources, with standardized metadata and a repository identifier;
- To be **A**ccessible: retrievable metadata, and potentially retrievable data via appropriate controls;
- To be **I**nteroperable: metadata is standardized, data conforms to relevant published standards;
- To be **R**eusable: there is transparency about the terms under which the data may be reused.

The EMIF charter for example states that the EMIF platform only can be used for assessing the feasibility of a study and for conducting research by bona fide research organizations and for bona fide research. Data sources always have autonomy, and should be processed lawfully, fairly and transparently. Data users must adhere to the ethical rules and privacy protection policies of each data source, can only use the data for specific agreed research purposes and must acknowledge the sources of the data they have used.

Data sharing should thus be societally acceptable meaning that data protection regulations should prioritize the rights of the individual to privacy. Many surveys indicate that patients are in favor of their data being re-used for research, but we need to balance the rights of the individual and benefits for society. The public needs and deserves better information on why and how health data are used, safeguarded and the benefits.

Through MSDA educational sessions, MSDA aims to support greater understanding within the community about reuse of RWD. Data custodians will be informed on the importance and mechanism for safety and respectfully sharing data. Examples of educational topics are:

- Data Protection, General data protection regulation (GDPR), legal basis and the appropriate role of consent;
- Data quality assessment and improvement;
- Interoperability standards and CDMs;
- Federated architectures, distributed querying, information security;
- Patient engagement in care and research;
- Data sharing practices and FAIR principles (= Findable, Accessible, Interoperable and Re-Usable).



PANEL DEBATE: Jan Hillert (Swedish MS Registry, Big MS Data Network), Orla Gray (MSBase Registry, Big MS Data Network), Alexander Stahmann (German MS Registry), Robert McBurney (iConquerMS, Accelerated Cure Project), Maria Trojana (Italian MS Registry, Big MS Data Network), Dipak Kalra (European Institute for Innovation through Health Data) Jeffrey Cohen (MSPaths)



In the panel debate, the following questions were central to discussion:

We are moving towards a remote-control world; how can we guarantee we are heading to the right direction?

One of the big challenges – according to different stakeholders – is the fragmented EU legal framework governing data. Ideally, data should be harmonized at EU level, not nationally. Although many scientific communities share the same spirit, money and national legislation lead to fragmentation of several registries across the EU. Disease registries rather than product registries are preferred to avoid further fragmentation. Access to data should be at low cost, and preferably a third party should be involved. GDPR is another issue and is interpreted differently across countries/institutions. The under-resourcing of legal departments makes it even more difficult to get everyone aligned.

A greater collaboration between industry and other key stakeholders, encouraging members to share data, could help, although there always exists a risk for sharing own data with competitors. Industries should share their data, placebo data from clinical studies for example could be very useful.

It was all of the stakeholders' conviction that the patient should be central to the source of information, collect the best of information to provide the best of treatment, keeping the patient informed at all steps of the process. An informed consent form with the goal of data sharing, should be transparent, covering safety and security of personal data, and be truly understandable.



7 MSDA next steps

Liesbet Peeters ended the meeting with an overview of the achievements of MSDA in 2019 and future plans:

MSDA Academy

- Achievements
 - **Raise awareness:** logo developed, website online, project presentations, flyers and posters, conference participation, DataSavesLives kick-off (core group)
 - **Build a multi-stakeholder MS data community:** large stakeholder engagement meeting, stakeholder focus group meetings
 - **Promote trustworthy and transparent practices: future strategic plans available**
- Future plans
 - **Raise awareness:** patient society reach-out, DataSavesLives active participation
 - **Build a multi-stakeholder MS data community:** large stakeholder engagement meeting, stakeholder focus group meetings
 - **Promote trustworthy and transparent practices:** educational sessions supported with online material

MSDA Toolbox

- Achievements
 - **Catalogue:** e-questionnaire fingerprint, MSDA community, registry recruitment started
 - **SwitchBox:** list of variables, harmonization strategy, proof-of-concept
 - **Cohort Explorer:** Demo version
- Future plans
 - **Catalogue:** continue registry recruitment, evaluate and adapt questionnaire, regular updates
 - **SwitchBox:** extend list of variables, improve harmonization strategy, continue registry harmonization
 - **Cohort Explorer:** statutes Cohort Explorer, proof-of-concept



Acknowledgment

We would like to thank all participants for their active and constructive contribution to the first large scale MSDA stakeholder engagement meeting. This event was made possible with the kind support of Novartis, Celgene, Icometrix, Quanterix, Biogen, Mylan, Canopy Growth Company, Merck and QMenta.



References

1. Glaser A, Stahmann A, Meissner T, et al. Multiple sclerosis registries in Europe – An updated mapping survey. *Multiple Sclerosis and Related Disorders*. 2018; 27.
2. Hocking, Lucy, Sarah Parks, Marlene Altenhofer, and Salil Gunashekar, Reuse of health data by the European pharmaceutical industry: Current practice and implications for the future. European Federation of Pharmaceutical Industries and Associations (EFPIA), 2019. Available at: https://www.rand.org/pubs/research_reports/RR3247.html. Accessed: December 2019.
3. Cohen JA, Trojano M, Mowry EM, Uitdehaag BMJ, Marrie RA. Leveraging real world data to investigate multiple sclerosis disease behavior, prognosis, and treatment. *Mult Scler J* (in press).
4. Trojano M, Tintore M, Montalban X, et al. Treatment decisions in multiple sclerosis - insights from real-world observational studies. *Nature reviews Neurology*. 2017; 13: 105-18.
5. Li G, Sajobi TT, Menon BK, et al. Registry-based randomized controlled trials- what are the advantages, challenges, and areas for future research? *Journal of clinical epidemiology*. 2016; 80: 16-24.
6. Rudick RA, Miller D, Bethoux F, et al. The Multiple Sclerosis Performance Test (MSPT): an iPad-based disability assessment tool. *J Vis Exp*. 2014: e51318-e.
7. Bouvy JC, Blake K, Slaterry J, De Bruin ML, Arlett P and Kurz X. Registries in European post-marketing surveillance: a retrospective analysis of centrally approved products, 2005-2013. *Pharmacoepidemiology and drug safety*. 2017; 26: 1442-50.
8. US FDA. Real-World Evidence. Available from: <https://www.fda.gov/science-research/science-and-research-special-topics/real-world-evidence>. Accessed: November 2019.
9. Kalincik T and Butzkueven H. The MSBase registry: Informing clinical practice. *Multiple sclerosis (Houndmills, Basingstoke, England)*. 2019: 1352458519848965.
10. Flachenecker P. Multiple sclerosis databases: present and future. *European neurology*. 2014; 72 Suppl 1: 29-31.
11. Montalban X, Gold R, Thompson AJ, et al. ECTRIMS/EAN guideline on the pharmacological treatment of people with multiple sclerosis. *European journal of neurology*. 2018; 25: 215-37.
12. Rae-Grant A, Day GS, Marrie RA, et al. Practice guideline recommendations summary: Disease-modifying therapies for adults with multiple sclerosis: Report of the Guideline Development, Dissemination, and Implementation Subcommittee of the American Academy of Neurology. *Neurology*. 2018; 90: 777-88.
13. Laffaldano P. et al. submitted
14. Big multiple sclerosis data network: marginal structural models confirm the long-term impact of DMTs on disability progression. ECTRIMS Online Library. Lucisano G. Sep 11, 2019; 279417; 94.
15. Lorscheider J, Kuhle J, Izquierdo G, et al. Anti-inflammatory disease-modifying treatment and disability progression in primary progressive multiple sclerosis: a cohort study. *European journal of neurology*. 2019; 26: 363-70.
16. Granqvist M, Borelmalm M, Poorghobad A, et al. Comparative Effectiveness of Rituximab and Other Initial Treatment Choices for Multiple Sclerosis. *JAMA neurology*. 2018; 75: 320-7.
17. Lorscheider J, Benkert P, Lienert C, et al. Comparative analysis of natalizumab versus fingolimod as second-line treatment in relapsing-remitting multiple sclerosis. *Multiple sclerosis (Houndmills, Basingstoke, England)*. 2018; 24: 777-85.
18. Alping P, Frisell T, Novakova L, et al. Rituximab versus fingolimod after natalizumab in multiple sclerosis patients. *Annals of neurology*. 2016; 79: 950-8.
19. Brown JWL, Coles A, Horakova D, et al. Association of Initial Disease-Modifying Therapy With Later Conversion to Secondary Progressive Multiple Sclerosis. *Jama*. 2019; 321: 175-87.



20. Big Multiple Sclerosis Data - A registry basis for post authorization safety studies (PASS) for multiple sclerosis by Jan Hillert. ECTRIMS Online Library; Sep 13 2019. Available at: <https://onlinelibrary.ectrims-congress.eu/ectrims/2019/stockholm/278582/jan.hillert.big.multiple.sclerosis.data-.a.registry.basis.for.post.html>. Accessed: December 2019.
21. Bebo BF, Jr., Fox RJ, Lee K, Utz U and Thompson AJ. Landscape of MS patient cohorts and registries: Recommendations for maximizing impact. *Multiple sclerosis (Houndmills, Basingstoke, England)*. 2018; 24: 579-86.
22. Treatment discontinuation in the Big Multiple Sclerosis Data Network: a descriptive analysis by Tim Spelman ECTRIMS Online Library; Oct 12 2018. Available at: https://onlinelibrary.ectrims-congress.eu/ectrims/2018/ectrims-2018/229035/tim.spelman.treatment.discontinuation.in.the.big.multiple.sclerosis.data.html?f=menu=14*browseby=8*sortby=2*media=3*speaker=440992. Accessed: December 2019.
23. Report on Multiple Sclerosis Registries - Workshop 7 July 2017. Patient Registry Initiative. EMA/548474/2017. Available at: https://www.ema.europa.eu/en/documents/report/report-multiple-sclerosis-registries_en.pdf. Accessed: December 2019.
24. The Lancet N. Patient-reported outcomes in the spotlight. *The Lancet Neurology*. 2019; 18: 981.
25. National Health Council. The National Health Council Rubric to Capture the Patient Voice: A Guide to Incorporating the Patient Voice into the Health Ecosystem. June 2019. Washington, DC. Available from: <https://www.nationalhealthcouncil.org/Patient-Engagement-Rubric>. Accessed: November 2019.
26. MS Barometer 2015. Raising the voice of people with MS. Available at: www.emsp.org/wp-content/uploads/2017/02/BAROMETER-2015-Final-10.05.2017.pdf. Accessed: December 2019.