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Draft Qualification Opinion for the Big Multiple Sclerosis Data (BMSD) network

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Qualification Opinion

Based on the evidence presented, CHMP considers that the Big Multiple Sclerosis Data Network (BMSD) can be used as a data source for post-authorisation safety studies (PASS) regarding Disease Modifying Therapies (DMTs) for Multiple Sclerosis intended to inform regulatory decision-making.

Agreed Context of Use (CoU):

Post-authorisation safety studies (PASS) conducted based on data from the Big Multiple Sclerosis Data Network (BMSD) applying the common data model (CDM). The selection of BMSD registries (one single registry, a sub-set of registries, or all registries) as data sources for a given PASS will be based on a mandatory study-specific feasibility assessment to ensure relevance for a given research question.

EMA/CHMP qualification opinions or qualification advice of novel methodologies for medicinal product development are provided without prejudice to any potential requirements related to other applicable legislation (e.g. MDR/IVDR and AI Act).

Executive Summary

Background

Multiple Sclerosis (MS) is a chronic, inflammatory, and demyelinating disease of the central nervous system that affects approximately 2.3 million people worldwide. Although there is currently no cure for MS, the development of disease modifying therapies (DMTs) has been very successful in the past 30 years and there are currently several different treatment options available for MS patients.

There is a continuous development of new DMTs for MS. To characterise further the safety profile of these medicinal products in real world clinical practice, post-authorisation safety studies (PASS) may be requested by the EMA to be conducted by the marketing authorisation holders (MAHs). To address adequately the objectives of a PASS, there is a need for high-quality data regarding the characteristics of the MS population under study, as well as follow-up information on drug exposure, safety outcomes of interest, and relevant covariates. MS registries can represent an important data source for such studies, as they systematically collect longitudinal clinical and treatment data in large populations of patients treated in routine care.

The Big Multiple Sclerosis Data (BMSD) Network brings together leading MS registries and databases to allow joint analyses of structured clinical data. The BMSD's effort to align a core set of data elements and data quality standards across different registries offers the possibility to conduct PASS to address the knowledge gaps on real-world use of DMTs, to inform regulatory decision-making.

This is a qualification opinion for the BMSD network and its individual MS registries in the context of use (CoU) of PASS. The BMSD Network, coordinated by the Applicant, Karolinska Institutet, consists of 6 different MS registries:

- The Czech Registry of Patients with MS (ReMuS)
- The Danish Multiple Sclerosis Registry (DMSR)
- The French Multiple Sclerosis Registry (OFSEP)
- The Italian Multiple Sclerosis Register (RISM)
- The Swedish Multiple Sclerosis Registry (SMSR)
- The International MSBase Registry (MSBase)

The clinical data systematically collected in these registries is considered a valuable source of safety data regarding the use of DMTs. At this point, an estimated 360,000 patients are included in the BMSD; almost 168,000 MS patients are on active DMTs.

The EMA issued an initial Qualification Advice (QA) for performing PASS in the BMSD network in 2021 (EMA/SA/0000050512) and issued a letter of support.[1] Two main issues that prevented qualification at that point were identified:

1) Uncertainties about the extent to which data elements crucial for conduct of PASS can be collected

2) A concrete set of minimum quality requirements for the registries

The Applicant considers that these issues are now resolved and has requested a QO.

Data relevance for PASS

PASS can address various research questions related to the safety of medicinal products, and the relevance of a given data source depends on the availability of data elements needed to address the specific question of interest. One of the main scopes of this procedure was therefore to assess the availability of data elements in the BMSD registries to answer research questions typical for PASS.

In cooperation with six MAHs of DMTs, the Applicant developed a core protocol for PASS which provides a framework for future PASS involving the BMSD registries. While the specific research question and study methodology would be a matter of assessment by the EMA, the principles proposed in the core protocol are overall in agreement with plausible regulatory needs with regards to risk characterisation in a real-world context.

The core data set collected in all BMSD registries is overall aligned with the recommendations of the EMA Report on Multiple Sclerosis Registries Workshop (EMA/548474/2017).[2] The collection of certain key variables is mandatory across the individual registries and high completeness is documented for these. Overall, there is high completeness of key variables with regards to demographics, MS diagnosis and disease, DMT treatment and prespecified serious adverse events (SAEs). However, the completeness of other relevant data elements is overall lower (e.g. medical history, co-morbidities and concomitant medications). Importantly, variables not collected as part of follow-up visits can be obtained via linkage in some of the registries and this is considered highly valuable. The quality and completeness of data obtained via linkage is less clear based on the submitted data and the consistency varies across the registries and the nature of the databases to be linked. Nevertheless, it is acknowledged that linkage efforts are evolving and that a higher level of data capture and/or completeness can be anticipated in the future.

The individual registries have previously shown the capability to adjust the data inclusion in a coherent fashion (e.g. for COVID-19), and this indicates that future needs of amendments are also feasible to be included. The timeliness of such adjustments varies between registries but is overall acceptable.

At the core of many PASS is the estimation of incidence of SAEs, and the Applicant conducted a feasibility study to demonstrate actual availability of relevant safety outcome data such as malignancies and serious infections based on two ongoing PASS. SAE collection procedures in the BMSD registries are based on the patient-physician dialogue as part of scheduled follow-up visits. This form of data collection was associated with a high degree of underreporting for DMSR and SMSR.

[1] Letter of Support for performing registry-based post authorisation safety studies (PASS) in Multiple Sclerosis (MS) usingdataof the Big MS Data Network (BMSD)
[2] https://www.ema.europa.eu/en/documents/report/report-multiple-sclerosis-registries_en.pdf

Therefore, person-level linkage to national databases will be used for the ascertainment of outcome data in these two registries.

In PASS with inferential study objectives, valid comparative analyses depend on the availability of relevant covariates to control adequately for confounding and support exchangeability between exposure groups. This was not assessed in the feasibility study but results of ongoing or finalised PASS utilising BMSD registries provide proof-of-concept evidence regarding the possibility to collect data needed for adequate confounding control methodologies. The completeness of confounders is variable across registries (e.g. smoking status). However, such limitations are considered somewhat inherent to secondary use of real-world data (RWD). Moreover, improvement efforts such as a higher degree of linkage as well as the adaptability of the registries to collect additional elements if needed are anticipated to keep these issues at an acceptable level. Linkage capabilities and data completeness differ between registries. This can be acceptable, given the fact that feasibility assessment, before the PASS is allocated, will ultimately identify whether data are sufficiently complete.

Other relevant study objectives of PASS pertain to risk characterisation and evaluation of effectiveness of risk minimization measures (RMM). In the context of a descriptive study, not only incidence rates of SAEs can be of interest, but also descriptive analyses regarding event severity, latency, clinical course, treatment of the event, and risk factors may be required to inform adequate risk minimisation. Moreover, evaluation of effectiveness of RMM studies typically addresses questions relevant to understand whether specific clinical measures are adhered to in clinical practice such as e.g. liver function monitoring, contraindications, pregnancy testing or immunizations. While there is some proof-of-concept evidence regarding availability of these elements (e.g. all registries collect data on JC-virus antibody status), the level of capture seems variable across BMSD registries. Therefore, if collection of such information is a primary study aim, feasibility assessments are needed to confirm specific data availability in the individual registries.

Pregnancy data elements can be collected by all BMSD registries, but the completeness is not validated and there is currently no proof-of-concept pregnancy PASS. In some of the registries, complete data can be obtained via linkage (DMSR and SMSR), but linkage possibilities vary across BMSD registries. Without linkage to e.g. birth registries, the data collected only at the MS registry may not be sufficient to assess adequately pregnancy outcomes of interest. As such, it can be concluded that the BMSD network can be a valuable data source for a pregnancy study, but not all the individual registries can currently be considered fit-for-use in this context. Therefore, a feasibility assessment will be needed to determine which of the BMSD registries are most suitable.

The national BMSD registries demonstrate high coverage of MS patients, especially for patients on DMTs, which supports adequate generalisability of findings from PASS based on BMSD registries to a European target population.

Given the uniqueness of each individual registry and the difference in specific events collected, for each PASS there is the need for a study-specific assessment of fitness-for-purpose for of each of the registries before the PASS is allocated to the BMSD network. Qualification of the BMSD network does not replace this need, which is intrinsic to the qualification.

Data quality

Data quality is influenced at the level of individual MS centres, at the level of individual MS registries responsible for national data management, and at the level of the BMSD, which supports data analysis overall. Each registry has its own governance tradition, technical details and constraints, and national legislation to follow, which has formed the data collection process and initial data management. Despite heterogeneity between registries, the overall process is similar and is found acceptable with

built-in elements to ensure data quality. Furthermore, implementation of a common data model (CDM) supports registry interoperability crucial in multi-country studies based on large datasets.

The CDM is developed for the harmonisation of MS patient data from various registries based on a common data dictionary, scripts for conversion of data into the CDM format and scripts for validation. Examples of quality reports in relation to e.g., consistency, completeness and accuracy have been presented by the Applicant and the CDM initiative is highly welcomed to facilitate sufficient data quality.

For combining the data of the individual registries into a common analysis, the CDM facilitates meta-analysis with aggregated data or federated data analysis. For meta-analyses, aggregated results from the individual registries are shared with the coordinator responsible for the respective PASS and then combined centrally, and these have been applied in finalised and ongoing PASS. In the federated approach, one universal script of CDM data format is disseminated across the contributing data sources generating individual data results which are then shared with the BMSD. While there is also the possibility of pooling of individual-level data, the Applicant discussed that sharing of data has become increasingly difficult due to national data protection legislations. Therefore, the BMSD favours an approach where datasets can be established, managed and analysed locally for the results to then be shared within a coordinating centre managing the common project.

All registries comply with the General Data Protection Regulation (GDPR) in its present wording.

Life-cycle management

With regards to life-cycle management (LCM), the BMSD plans to publish annual PASS reports in which the continued performance of the registry in the context of PASS is assessed. These will cover: 1) key overall statistics for each registry, 2) an assessment of key data quality elements for the population eligible to participate in a PASS, 3) data on adverse events and key confounding factors, and 4) a development status update of the CDM.

In addition, the Applicant proposed a set of requirements for new registries to join the BMSD, which include adoption of the CDM and successful data transformation, demonstration of similar data quality characteristics and AE reporting as established BMSD registries.

The BMSD's LCM strategy is overall supported. The Applicant is encouraged to notify EMA about the addition of a new registry and to update the entry of the network in the HMA-EMA Catalogue of RWD sources. However, in case it is not obvious that requirements based on data for existing registries are met, the applicant is expected proactively to submit the relevant documentation to EMA for review. In addition, the BMSD should proactively contact EMA when they notice a risk of decline in the quality of the data / availability of variables compared to the metrics of previous years, together with proposed actions on how to mitigate the risks. Provided adherence to these elements by the applicant, regular re-assessments of annual reports or other LCM related data by the EMA are not considered warranted.

Overall conclusion

The six registries included in the BMSD network collect rich clinical information relevant for the conduct of PASS for DMT products. A major strength of the BMSD is its multi-country setting covering a large number of MS patients on active DMTs. For the context of PASS requested in the EU risk management plan (RMP), the possibility to include a broad study population from multiple European countries is an important advantage. Each registry has a relatively high national coverage, which supports the generalisability of findings from the BMSD to a European target population. Moreover, large sample sizes enable the study of rare adverse events. Similar data collection processes, alignment between individual registries for some aspects of data management, and implementation of a common data model (CDM) support registry interoperability crucial in multi-country studies based on large datasets.

Furthermore, the individual registries have previously shown the capability to adjust the data inclusion in a coherent fashion (e.g. for COVID-19), and this indicates that future needs of amendments are also feasible to be included.

The BMSD network demonstrates a high completeness of core variables crucial for the conduct of PASS, and actual availability of SAE data is demonstrated, which was a key outstanding issue in the initial QA. In addition, there is adequate demonstration of data availability of non-core variables important for confounding control methodologies. The availability of data elements to address other potential research questions relevant for PASS, such as those related to pregnancy outcomes, descriptive risk characterisation purposes, or evaluation of effectiveness of RMM is variable and context dependent across the individual registries. This is acceptable, given that a feasibility assessment will be needed prior to the allocation of the BMSD to conduct any PASS. This is mandatory, to determine fitness-for-use of the individual registries for a specific research question, based on the principles laid out in the ICH M14 guideline and the EMA Reflection paper on use of RWD in non-interventional studies to generate RWE for regulatory purposes.[3,4] Moreover, these limitations are not fixed considering ongoing developments of the BMSD registries with regards to linkage to external sources as well as further development of the CDM and the demonstrated adaptability of the registries to collect additional elements if needed. Overall, the BMSD network as well as the six individual registries are qualified within the specified context of use.

[3] ICH_M14_Step4_Final_Guideline_2025_0905.pdf
[4] https://www.ema.europa.eu/en/documents/other/reflection-paper-use-real-world-data-non-interventional-studies-generate-real-world-evidence-regulatory-purposes_en.pdf

Abbreviations:

AE	Adverse Event
BMSD	Big MS Data network
CDM	Common Data Model
CoU	Context of Use
CHMP	Committee for Medicinal Products for Human Use
DMSR	The Danish Multiple Sclerosis Registry
DMT	Disease Modifying Therapy
EDSS	Expanded Disability Status Scale
EMA	European Medicine Agency
GDPR	General Data Protection Regulation
ICD	International Classification of Diseases
JCV	John Cunningham Virus
LCM	Life Cycle Management
MAH	Marketing Authorisation Holder
MedDRA	Medical Dictionary for Regulatory Activities
MRI	Magnetic Resonance Imaging
MS	Multiple Sclerosis
MSBase	The International MSBase Registry
OFSEP	The French Multiple Sclerosis Registry
PASS	Post Authorisation Safety Study
PRAC	Pharmacovigilance Risk Assessment Committee
PS	Propensity Score
ReMuS	The Czech Registry of Patients with MS
RISM	The Italian Multiple Sclerosis Register
RWD	Real World Data
SAE	Serious Adverse Event
SAWP	Scientific Advice Working Party
SMSR	The Swedish Multiple Sclerosis Registry
SOP	Standard Operating Procedure

Qualification Opinion – detailed assessment

Based on the evidence presented in the qualification opinion request and in a discussion meeting, CHMP considers that the Big Multiple Sclerosis Data Network (BMSD) can be used as data source for post-authorisation safety studies (PASS) regarding Disease Modifying Therapies (DMTs) for Multiple Sclerosis intended to inform regulatory decision-making.

Agreed Context of Use (CoU):

Post-authorisation safety studies (PASS) conducted based on data from the Big Multiple Sclerosis Data Network (BMSD) applying the common data model (CDM). The selection of BMSD registries (one single registry, a sub-set of registries, or all registries) as data sources for a given PASS will be based on a mandatory study-specific feasibility assessment to ensure relevance for a given research question.

Rationale for the BMSD and the individual participating registries

Multiple Sclerosis (MS) is a chronic, inflammatory, and demyelinating disease of the central nervous system that affects approximately 2.3 million people worldwide. Although there is currently no cure for MS, the development of disease modifying therapies (DMTs) has been very successful in the past 30 years and there is currently a number of different treatment options available for MS patients.

There is a continuous development of new DMTs for MS. To characterise further the safety profile of these medicinal products in real world clinical practice, post-authorisation safety studies (PASS) may be requested by the EMA to be conducted by the marketing authorisation holders (MAHs). To address adequately the objectives of a PASS, there is a need for high-quality data regarding the characteristics of the MS population under study, as well as follow-up information on drug exposure, safety outcomes of interest, and relevant covariates. MS registries can represent an important data source for such studies, as they systematically collect longitudinal clinical and treatment data in large populations of patients treated in routine care.

The BMSD brings together leading MS registries and databases to allow joint analyses of structured clinical data. The BMSD's effort to align a core set of data elements and data quality standards across different registries offers a unique possibility to conduct PASS to address the knowledge gaps on real-world use of DMTs to inform regulatory decision-making.

Description of the BMSD Network

The Big Multiple Sclerosis Data (BMSD) Network, coordinated by the Applicant, Karolinska Institutet, consists of 6 different multiple sclerosis (MS) registries:

- The Czech Registry of Patients with MS (ReMuS)
- The Danish Multiple Sclerosis Registry (DMSR)
- The French Multiple Sclerosis Registry (OFSEP)
- The Italian Multiple Sclerosis Register (RISM)
- The Swedish Multiple Sclerosis Registry (SMSR – also referred to as SMSreg)
- The International MSBase Registry (MSBase)

At this point, an estimated 360,000 patients are included in the BMSD; almost 168,000 MS patients are on active DMTs (see Table 1).

Table 1: An overview of the key characteristics of the registries in the BMSD network. The numbers are correct as of June 2024.

Registry	Launch date	Estimated number of patients	Total MS patients on active DMT treatments	Added patients per year	Coverage % *) Number of MS patients in the registry compared to estimated prevalent MS population in the corresponding country	Number of publications
ReMus (Czech Republic)	2013	22,500	17,133	800-1000	70	20
DMSR (Denmark)	1956	34,000	10,340	900	95	190
OFSEP (France)	1980	82,500	37,381	4000-5000	~65	155
RISM (Italy)	2001	93,802 (2025-0430)	51,760	3500-4500	~72	60
SMSreg (Sweden)	2000	24,000	12,684	800	85	300
MSBase (International)	2001	109,000 (82,000 unique pts)	48,808		Variable, depending on the contributing registries	120
BMSD (currently six MS registries)	2014	359,000	167,917	NA	NA	<800

(table from Annex 1)

Currently (2025), all the BMSD registries are participating in ongoing EMA mandated PASS and several of them take part in the same studies. A BMSD core protocol has been developed and describes the principles of how to perform a PASS involving the BMSD registries (Annex 2).

The EMA issued an initial Qualification Advice (QA) for performing PASS in the BMSD network in 2021 (EMA/SA/0000050512). Two main issues that prevented qualification at that point were identified:

1) Uncertainties about the extent to which data elements crucial for conduct of PASS can be collected

2) A concrete set of minimum quality requirements for the registries.

Therefore, the Applicant was advised to conduct a formal feasibility study for each of the individual registries to obtain data demonstrating that the registries are fit for purpose, and to introduce a harmonised approach to quality assurance.

Description of the individual registries

Each registry has its own governance tradition, technical details and constraints, and national legislation to follow. This has also formed the data collection process in each of the registries. Despite heterogeneity between registries, the overall process is similar and can be summarized as follows:

At each MS patient visit to the MS center, the neurologist is required to ask the patient regarding details related to treatment and adverse events since the last visit. The reply will be recorded by the neurologist/dedicated health care professional in a dedicated software/web-based system with various built-in mechanism to increase data quality such as drop-down menus, no free text fields, logical blocks and checks to minimize risk of errors, reminders, and pop-ups in relation to missing information. Standardised routines for data export and cleaning are implemented.

Data elements

The core (mandatory) variables that are collected are grouped into the following categories: Registry information, patient information, visits, medical conditions, treatments, diagnostic results, relapses, CSF, MRI, pregnancy, patient extra (optional). Some registries collect additional data either in relation to the mandatory categories or in relation to other optional categories (e.g. cognitive scores).

Some registries receive information about a patient from other health care providers in relation to a health problem outside the scope of the MS center. This will increase completeness and robustness of the data collected.

Linkages

Various registries do linkages to other registries to retrieve additional information in relation to e.g. pregnancy, co-morbidity, (co)medication, death/loss to follow-up. This approach is welcomed to increase completeness and enrichment of data. To increase further the value of the BMSD and the associated registries, data linkages are encouraged to be pursued. This would broaden the possible scope of potential research questions to be addressed and for completeness of data in the individual registries.

Linkage capabilities and data completeness are expected to differ between registries. Since there will be a feasibility assessment before the PASS is allocated, this will identify whether data from external sources is sufficiently complete to meet the purpose of a planned PASS.

Survival analysis and registration of dates

Dates of exposure, diagnoses, and follow-up information are either captured by the individual MS centres or obtained by linkages to registries. In survival analyses, patients are typically censored at the time of the last documented contact, to account for potential loss to follow-up. Given the nature of the data collection process, this is found acceptable.

Coding (AEs)

Terminology for medical events is based on existing international/European standardized formats such as MedDRA, ICD, SNOMED, EDSS, and EUROCAT. For SAE coding, four registries use MedDRA coding; SMSR and DMSR use ICD-10 which, by the CDM methodology, is translated into MedDRA based on the Observational Health Data Sciences and Informatics (OHDSI) methodology. This translation model is updated on a regular basis to be more complete with a current 96.4% success rate in translation, which is found sufficient.

GDPR/Audits

The individual registries are all GDPR compliant, have quality assured data storage with back-ups, and traceability of logins and entry of data.

Audit practices are implemented in all individual registries, albeit heterogeneously. These auditing procedures include mainly IT / software solutions, but semi-manual audits can also be performed. Audits can be performed on a regular routine basis or in connection with potential specific issues or projects. It can be related to participating MS centres or conducted at national level by comparison of monthly data extracts.

The potential commitments of monitoring and reporting of adverse events that already pertain to the data collection are independent of the present qualification opinion.

Inspections

Regarding PASS conducted in BMSD, all partners will have to agree to the conditions specified in the study agreements. Conditions for inspections should be contractually specified.

Timeliness

In addition to the core data elements, the BMSD network has demonstrated that additional variables can be included depending on complexity, needs, and approvals from the government boards. For the specific situation around COVID-19 pandemic the Applicant informed (as an example) that COVID-19 related information was adopted by all BMSD registries by April 2020.

For the approvals of specific PASS, the timeframes also vary between the registries (6 weeks – 9 months), depending on application type and approval from data protection agencies. Given the individual governance structures this is found acceptable. If the need for fast track PASS results should emerge, some registries will likely be found more suitable than others.

Representitiveness

The national BMSD registries demonstrate high coverage of MS patients (Table 1). For patients on DMTs, coverage is even higher, which supports adequate generalisability of findings from the BMSD to a European target population. The variability in treatment patterns between European countries and the extent to which BMSD registries are representative in this regard was addressed in the assessment. The Applicant demonstrated that the treatment patterns of the countries represented in the BMSD overall align well with the European region.

Core protocol for PASS

In cooperation with six MAHs of DMTs, the Applicant developed a core protocol for PASS which provides a framework for future PASS involving the BMSD registries (**Error! Reference source not found.**). While the specific research question and study methodology would be a matter of assessment by the EMA, the principles proposed in the core protocol are overall in agreement with plausible regulatory needs with regards to risk characterization in a real-world context.

Important research objectives such as the estimation of incidence/event rates of serious adverse events (SAEs) as well as comparison of these between different DMTs are proposed. To address this, the methodology for a non-interventional observational cohort study based on secondary use of data from the MS registries part of the BMSD Network is laid out.

The study population includes patients with MS who are either untreated but eligible for treatment or have initiated treatment with DMTs in routine clinical practice and covered by the BMSD network registries. Exposure to the DMT of interest as well as to potential comparator drugs will be captured in the registries. The primary outcomes are SAEs and specifically malignancies, non-melanoma skin cancers, treatment-related infections, and all-cause mortality and cause of death. Pregnancy outcomes and drug utilization variables are defined as secondary outcomes. Covariates such as patient characteristics and disease-specific information are collected and considered for inclusion in the analytical models. Analyses will be tailored to the specific objective of a PASS, but the principles for descriptive measures of occurrence of SAEs or drug utilization and/or comparative measures of association are presented. For the latter, a target trial approach may be adopted in the design of the analysis. If the study populations included in each registry meet requirements for homogeneity, techniques will be used to pool the aggregate data from the different registries to produce overall effect estimates.

These core methodology elements for PASS based on data from the BMSD network provide a useful framework in support of the proposed context of use and are overall supported. Given the limitations

of clinical trials, there is indeed often a need for further characterization of safety concerns via descriptive measures of occurrence such as estimation of an incidence rate of an already identified risk. Moreover, the proposed comparative analyses can provide a basis for causal inference, which often is desired when characterizing potential risks of a medicinal product. However, PASS addressing additional aspects which are not reflected in the core protocol may be required. In the context of a descriptive study, not only incidence rates of SAEs can be of interest, but also information on severity, latency, clinical course, treatment and risk factors. Moreover, PASS with an evaluation of effectiveness of risk minimization measures (RMM) scope are sometimes required. In addition to drug utilization, such studies typically address questions relevant to understand if specific clinical measures are adhered to in clinical practice such as e.g. liver function monitoring prior to and during treatment, contraindications, pregnancy testing or immunizations. However, based on the assessment of data elements (see below), these types of research questions can likely be addressed using BMSD registries to an acceptable degree. If the core protocol is used as a framework for an actual PASS, the Applicant is advised to incorporate the above-mentioned study objectives into the core protocol for future use.

Data elements

The core data set collected in all BMSD registries is overall aligned with the recommendations of the EMA Report on Multiple Sclerosis Registries Workshop (EMA/548474/2017). [5] Variables on patient characteristics (e.g. date of birth, BMI), MS disease specific information (e.g. date of diagnosis, MS type, MS course), treatment (e.g. DMT product, start date of DMT) and outcomes (e.g. SAEs, time to onset) are collected. The collection of certain key variables is mandatory across the individual registries and high completeness is documented for these variables (

Table **2**).

Table 2: Characteristics and data density of registry populations relevant for the performance of PASS, defined as patients on treatment with data recorded from a visit within the past 36 months (data by the end of 2024): Seen & treated past 36 months

	SMSreg	DMSR	REMUS	OFSEP	RISM	MSBase
N	11181	10903	17093	25597	34232	40790
Female %	69.10%	68.8 %	70.5 %	72.2 %	66.9 %	71.0 %
Mean age {SD)	45.64 {11.79)	47.9 {11.8)	45.5 {11.2)	46.6 {12.1)	47.3 {12.35)	46.0 {12.2)
Documented age	100.00 %	100.0 %	100.0 %	100.0 %	100 %	100.0 %
Documented sex	100.00 %	100.0 %	100.0 %	100.0 %	100 %	100.0 %
Documented MS onset date	98.07 %	100.0 %	100.0 %	100.0 %	98.3 %	98. 5%
Documented diagnosis date	97.76 %	99.2 %	84.1 %	83.2 %	96.3 %	77. 0%
Documented MS course	99.69 %	100.0 %	98.8 %	100 %	95.3 %	96.1 %
Ever recorded relapses	60.41 %	77.8 %	98.6 %	100 %	79.2 %	80.8 %
>= one MRI	93.39 %	99.5 %	75.1 %	97.5 %	93.1 %	87.2 %
>= two MRI	88.95 %	97.3 %	68.0 %	95.7 %	90.9 %	75.7 %

[5] https://www.ema.europa.eu/en/documents/report/report-multiple-sclerosis-registries_en.pdf

>= one EDSS	94.99 %	99.9 %	100.0 %	100.0 %	100 %	98.9 %

Not all variables recommended in the Multiple Sclerosis Registries Workshop (EMA/548474/2017)[6] as core data set items are collected on a mandatory basis across registries. For example, the expanded disability status scale (EDSS) score is an optional variable for the SMSR; nevertheless, a high completeness is reported for this variable (75% - 90%). Overall, there is high completeness of key variables with regards to demographics, MS diagnosis and disease, DMT treatment and prespecified SAEs (as demonstrated in the feasibility study (Annex 4)). However, the completeness of other relevant data elements is overall lower (e.g. medical history, co-morbidities and concomitant medications). Importantly, variables not collected as part follow-up visits can be obtained via linkage in some of the registries (Table 3).

Table 3: Overview of linkage possibilities for the individual registries

Registry	Linkage	Description
SMSR	National health registries	Nationwide population-based health registries covering healthcare contacts, linkable via a unique personal identifier
DMSR	National health registries	Nationwide population-based health registries covering healthcare contacts, linkable via a unique personal identifier.
ReMuS	ÚZIS	National administrative healthcare data including ICD-10 coded diagnoses from all healthcare encounters.
OFSEP	SYSTÈME NATIONAL DES DONNÉES DE SANTÉ (SNDS)	Medico-administrative database. Consulting, drug dispensing, biological exams, issuance of technical aids, long-term disease, hospitalizations, diagnoses, medical procedures, external consultations, death causes, non-specific MS data including comorbidities, co-prescriptions, recourse to care.
RISM	Regional administrative data	Currently linkage to regional information of health administrative data (hospital discharges, prescription drugs, ticket exemptions, registration of patients, outpatient visits).
MSBase	Not specified	Not specified

The possibility to enrich the data collected directly at the MS registries via linkage is considered highly valuable. The quality and completeness of data obtained via linkage is less clear based on the submitted data and the consistency varies across the registries and the nature of the databases to be linked. Further development of linkage options is supported.

Feasibility study

Based on the recommendations of the initial QA in 2021, the Applicant conducted a feasibility study to demonstrate actual availability of key data elements in the registries (Annex 4). Due to time and financial constraints, the Applicant did not find it practical to perform a feasibility study for a *de novo* PASS but instead chose to demonstrate data availability based on ongoing PASS in which BMSD registries are involved: All BMSD registries but ReMuS are participating in the MANUSCRIPT study for ocrelizumab[7]; ReMuS provides data for an external cohort comparison study to support the ongoing OBS13434 study for alemtuzumab[8].

The feasibility study shows that relevant outcome data such as malignancies and serious infections are captured in the registries. Adverse event collection procedures in the BMSD registries are based on the neurologist asking whether the patient has experienced adverse events since the last visit. In DMSR and SMSR, this form of data collection was associated with a high degree of underreporting based on comparison of event rates with Danish and Swedish national databases via person-level linkage.

[6] https://www.ema.europa.eu/en/documents/report/report-multiple-sclerosis-registries_en.pdf
[7] Long-Term Surveillance of Ocrelizumab Treated Patients With Multiple Sclerosis (MANUSCRIPT Study) | HMA-EMA Catalogues of real-world data sources and studies
[8] A prospective, multicenter, observational, post-authorization safety study (PASS) to evaluate the long term safety profile of LEMTRADA® (alemtuzumab) treatment in patients with relapsing forms of multiple sclerosis (RMS) (GZ402673-OBS13434) | HMA-EMA Catalogues of real-world data sources and studies

Therefore, DMSR and SMSR will use linkage for the ascertainment of outcome data. This is supported and will enhance completeness of outcome data with regards to event rates. However, it may come at the cost of some clinical details (e.g. seriousness, clinical course, outcome), which can be important for regulatory decision-making.

Comparison of malignancy and infection rates from the Swedish and Danish national databases with those from the other registries in the BMSD showed that the underreporting issue seems to be less pronounced for registries that do not have access to national healthcare databases. Overall, rates are comparable, but a moderate level of heterogeneity between BMSD registries should be expected, depending on the outcome of interest.

The availability of other key data elements such as potential confounders necessary to produce valid comparative analyses between exposure groups, or other data facilitating further characterization of SAEs (e.g. event severity and risk factors) was not investigated in the feasibility assessment but supporting proof-of-concept is provided from other ongoing PASS.

Supporting proof-of-concept evidence from ongoing PASS

There are a number of ongoing and finished PASS in which registries part of the BMSD network are utilised as data sources (

Table **4**). While not part of this application, these results from interim and final analyses are considered as important proof-of-concept evidence regarding the availability of data elements. This is especially relevant with regards to data elements which have not been assessed in the feasibility study.

Table 4: Finalised or ongoing PASS utilising BMSD registries providing supportive proof-of-concept evidence regarding availability of data elements

Study name	RWD catalogue reference	BMSD Registries	DMT of interest	Type of results (currently)	Type of objective	Regulatory impact
MANUSCRIPT	[9]	OFSEP, DMSR, SMSR, RISM, MSBase	Ocrelizumab	Interim	Inferential	N/A
CLARION	[10]	MSBase, SMSR, DMSR, RISM	Cladribine	Interim	Inferential	N/A
TOP	[11]	OFSEP, DMSR, SMSR, RISM, MSBase	Natalizumab	Final	Descriptive	Update of SmPC section 4.8 and 5.1
EUPAS45445	[12]	ReMuS	Natalizumab	Final	Descriptive	Fulfillment of RMP requirement
Lemtrada mortality PASS	[13]	DMSR, SMSR, REMUS	Alemtuzumab	Final	Inferential/descriptive	Fulfillment of obligation

[9] Long-Term Surveillance of Ocrelizumab Treated Patients With Multiple Sclerosis (MANUSCRIPT Study) | HMA-EMA Catalogues of real-world data sources and studies
[10] Long term, prospective, observational cohort study evaluating the safety profile in patients with highly active relapsing multiple sclerosis (RMS) newly started on oral cladribine – CLARION | HMA-EMA Catalogues of real-world data sources and studies
[11] TOP: Tysabri® Observational Program | HMA-EMA Catalogues of real-world data sources and studies
[12] Long-term surveillance of patients with multiple sclerosis to report progressive multifocal leukoencephalopathy and other serious opportunistic infections among patients treated with natalizumab | HMA-EMA Catalogues of real-world data sources and studies
[13] A non-interventional post-authorisation safety study to investigate the risk of mortality in multiple sclerosis patients treated with alemtuzumab (LEMTRADA®) relative to comparable multiple sclerosis patients using other disease modifying therapies: a cohort study | HMA-EMA Catalogues of real-world data sources and studies

Lemtrada DUS PASS	[14]	REMUS	Alemtuzumab	Final	Descriptive (effectiveness of RMM)	Fulfillment of obligation

In the final report of the Lemtrada mortality PASS, propensity score (PS) modelling was applied to create balance between treatment groups on core confounding variables. There were strong differences on baseline variables between the Lemtrada exposed cohort and the comparator drug-exposed cohort and confounding by indication was a major challenge in this study. Nevertheless, the results of this study demonstrate that core variables important for confounder control methodologies can be obtained in the participating registries (DMSR, SMSR and ReMuS). A number of variables could have been useful to include in the PS models such as smoking, adiposity, JCV status, and socio-economic status, but were omitted due to high rates of missingness or insufficient validity. Moreover, additional clinical variables including results of MRI scans (lesion type and number, speed of progression, etc.) would have been valuable to inform about the level of disease severity, but they could not be included as confounders due to high levels of missingness across the data sources, which was an important source of unmeasured confounding. Comparative analyses in this study turned out non-feasible, but this was not due to missingness of variables, but primarily due to the very limited number of observed outcomes in the Lemtrada group and consequentially violations of modelling assumptions.

Based on the latest interim report from the MANUSCRIPT PASS, key covariates such as age, sex, calendar year at index, disease duration prior to treatment initiation, pre-baseline relapse activity, prior drug exposure, and level of disability score (EDSS) were adequately captured across registries. However, additional covariates such as comorbidities, BMI, familiar or genetic risk of malignancies, and concomitant medication use were largely not available.

Overall, ongoing and finalised PAS studies support the Applicant's conclusions on the feasibility study with regards to the collection of SAE data. In addition, some of the studies also provide important proof-of-concept evidence with regards to the possibility of collecting data elements needed for confounding control methodologies. However, the completeness of confounders is variable and additional non-core variables such as e.g. smoking are often not available. The Applicant confirmed that there are challenges with regards to confounding control but also highlighted future improvements such as linkage efforts gradually being implemented as well as the adaptability of the registries to collect additional elements if needed.

Pregnancy data

Pregnancy data elements can be collected by all BMSD registries, but the completeness is not validated. The DMSR and SMSR can get complete data by linkage. OFSEP has a sister pregnancy registry to which it can be linked. ReMuS has recently started collecting pregnancy data. MSBase collects data at a moderate level and RISM at a lower level.

There is currently no proof-of-concept study to assess the level of completeness of data elements important for a pregnancy PASS. Without linkage to e.g. birth registries, the data collected only at the MS registry may not be sufficient adequately to assess pregnancy outcomes of interest. As such, it can be concluded that the BMSD network can be a valuable data source for a pregnancy study, but not all of the individual registries can currently be considered fit-for-use in this context. Therefore, a feasibility assessment would be needed to determine which of the BMSD registries are most suitable to study pregnancy outcomes.

[14] A non-interventional post-authorisation safety study to investigate drug utilisation and safety monitoring patterns for Lemtrada (alemtuzumab) | HMA-EMA Catalogues of real-world data sources and studies

Risk characterisation and evaluation of effectiveness of RMM

In the context of a descriptive study, not only incidence rates of SAEs can be of interest, but also descriptive analyses on event severity, latency, clinical course, treatment of the event, and risk factors may be required. The availability of data elements to inform such aspects may be variable across BMSD registries and if collection of this information is a primary study aim, feasibility assessments need to inform specific data availability in the individual registries.

Moreover, PASS with an evaluation of effectiveness of risk minimization measures (RMM) scope are sometimes required. In addition to drug utilization, such studies typically address questions relevant to understand whether specific clinical measures are adhered to in clinical practice such as e.g. liver function monitoring prior to and during treatment, contraindications, pregnancy testing or immunizations. The Lemtrada DUS and safety study (abstract of final results available in the EMA RWD catalogue[15]) might be considered as a proof-of-concept regarding the conduct of evaluation of effectiveness of RMM PASS at least for the ReMuS registry. In this study, medical data related to contraindications and monitoring tests were manually extracted from patients' medical charts. However, this type of project-driven data collection does not seem readily available across the BMSD network.

The Applicant confirmed that all registries collect data on JC-virus antibody status which could be used to assess compliance with this specific contraindication. However, the availability of data to assess adherence to risk minimisation measures more broadly is context dependent. As an example, the Applicant discussed that data on liver function monitoring is not broadly available, but data collection could be implemented if needed for a specific study. As with JC-virus antibody status, if liver function testing would become a core data element, implementation across the BMSD is trusted to be possible.

Overall discussion on availability of data elements

The BMSD network demonstrates a high completeness of core variables crucial for the conduct of PASS, and actual availability of SAE data is demonstrated, which was a key outstanding issue in the initial QA. In addition, there is adequate demonstration of data availability of non-core variables important for confounding control methodologies. The availability of data elements to address other potential research questions relevant for PASS, such as those related to pregnancy outcomes, descriptive risk characterisation purposes, or evaluation of effectiveness of RMM is variable and context dependent across the individual registries. This is acceptable given that a feasibility assessment will be needed prior to the conduct of any PASS to determine fitness-for-use of the individual registries for a specific research question. Moreover, these limitations are not fixed considering ongoing developments of the BMSD registries with regards to linkage to external sources as well as the demonstrated adaptability of the registries to collect additional elements if needed.

Common Data Model

A common data model (CDM) is developed for the harmonisation of MS patient data from various registries to be analysed in a federated way based on aggregated data or based on pooled individual data depending on the complexity in safety data. The CDM is based on a common data dictionary, scripts for conversion of data into the CDM format and scripts for validation with the aim of reducing systemic and random errors (see Annex 3).

The Applicant informs that the granularity of source data, i.e. the precision of data, is kept during translation to the CDM format (Annex 5). Furthermore, risks in relation to transformation are mitigated

[15] Epidemiology Report Body

by the a) CDM script - which is documented and version-controlled, b) retrospective validation against published results, and c) a complete audit trail of each CDM transformation.

The CDM improves interoperability and consistency of analyses but does not, in itself, eliminate underlying heterogeneity between registries. It is not expected that the CDM will eventually expand to harmonise all datasets into a single data acquisition model and transformation of previously collected data to harmonise data.

Data dictionary

A data dictionary has been agreed upon for the core variables with definition and descriptions. This will increase the interoperability between data sources.

Translation script

The translation script translates each registry's specific data format into the CDM data format and produces a quality report on each transformed data set which can identify data quality problems in the original registry data as well as certify that the transformation has been performed correctly. This approach ensures that key performance indicators such as consistency, completeness, and accuracy are measured in a harmonised approach.

Validation script

The CDM validation script aims to assess and report on the data density and completeness of each translated data set. It generates a detailed report on data accuracy and consistency, covering range checks, patient clinical and demographic structure, cross-variable consistency, and average gap between consecutive visits.

Combining data across registries

For combining the data of the individual registries into a common analysis, the CDM facilitates meta-analysis with aggregated data or federated data analysis. For meta-analyses, aggregated results from the individual registries are shared with the coordinator responsible for the respective PASS and then combined centrally. In the federated approach, one universal script of CDM data format is disseminated across the contributing data sources generating individual data results which are then shared with the BMSD.

While not yet tested in any PASS, the Applicant confirmed that the federated analysis approach has been successfully applied in an effectiveness study. With regards to meta-analyses, these have been applied in finalised and ongoing PASS. For interim results of the ongoing MANUSCRIPT PASS[16], meta-analysis was performed but the results are advised to be interpreted with caution due to considerable heterogeneity across the participating registries.[17] However, a CDM is currently not used in MANUSCRIPT and the Applicant considers that a CDM could have overcome heterogeneity issues.

While there is also the possibility of pooling of individual-level data, the Applicant discussed that sharing of data has become increasingly difficult due to national data protection legislations. Therefore, the BMSD favours an approach where datasets can be established, managed and analysed locally for the results to then be shared within a coordinating center managing the common project.

Related to the issue of sharing individual-level data, it was also a matter of discussion with the Applicant to which extent case-level narratives could exceptionally be shared to assess rare serious adverse events. It was clarified that in addition to the above-mentioned data protection constraints in

[16] Long-Term Surveillance of Ocrelizumab Treated Patients With Multiple Sclerosis (MANUSCRIPT Study) | HMA-EMA Catalogues of real-world data sources and studies

[17] MANUSCRIPT: long-term surveillance of ocrelizumab-treated patients with multiple sclerosis interim comparative safety analysis - ECTRIMS-2025-poster-butzkueven-manuscript-long-term-surveillance.pdf

some countries, the collection of open text is usually avoided across BMSD registries. It is agreed that this type of data collection falls under the respective national spontaneous reporting requirements and is out of scope for the sought CoU of the BMSD.

Overall, and in addition to the quality management systems for the individual registries, the CDM constitutes a corner stone for the data quality of the end results in relation to data cleaning, completeness, comparability and interoperability of data, as well as consistency in data analysis across registries. The CDM is being further explored and developed, which is appreciated.

Life-cycle management, including inclusion of other registries

For the life-cycle management of the BMSD network, the Applicant proposed to publish annual PASS reports in which the continued performance of the registry in the context of PASS is assessed. These will contain the following elements (see Annex 6):

1. Key statistics per BMSD registry: Based on a prespecified table stratified by registry, these numbers will illustrate the level of reporting activity on a yearly basis, and with the possibility to compare between registries as well as over time.

2. PASS eligible population metrics: To focus on those patients most likely to contribute to PASS, a prespecified table is to be filled (data stratified by registry) for patients on DMTs with a last visit in the past three years with the aim to inform about key data quality elements (e.g. representativeness, completeness, consistency and accuracy).

3. Verification of processes of collection of key data elements: The Applicant states that it is not an option to compare PASS AE report rates annually due to variation in which PASS will be ongoing at each timepoint and inclusion of data sources. Instead, the Applicant proposes a questionnaire with 6 questions on changes in the registry-specific data collection processes for AEs. This could be agreed with the addition of emphasis on the provision of updated documentation (changes in routines for ensuring data integrity at collection, new SOPs for data handling, new capacities to identify critical data via linkages with external data sources such as health records or public health databases). For comparison of PASS-specific results, the Applicant should consider publishing, on a 5-year basis, the "golden standard" incidence rates based on national registry data in relation to AEs/SAEs, comorbid conditions, other medications, risk mitigation variables, and pregnancy information.

4. Common data model update management: The CDM will undergo further development which is acknowledged. The Applicant informs that the intention is to make the CDM repository publicly available under an open-source license. As transparency is key, and if, for some reasons the intention is not met, relevant information for the development of the CDM should nevertheless be made publicly available and updated annually. The overall strategy for updating the CDM is agreed, including PASS-specific extensions.

5. New registry requirements to join the BMSD consortium: The Applicant lists three requirements to be fulfilled to join the BMSD network. However, the Applicant also states that the EMA is to decide whether registries fulfilling these requirements can be included in the present QO. The principal requirements are as follows:

a. Adoption of BMSD CDM including adequate transformation log results

b. Documentation of similar data quality characteristics of a PASS eligible population cohort as established BMSD registries

c. Documentation of similar AE reporting as established BMSD registries

It is agreed that these three elements are essential for new registries to be included. A description of the data collection process and provision of additional background information – in line with the Briefing document and documentation of data elements – for a new database should also be made available upon request. If similar performance levels can be demonstrated for new registries (and presented online similar to the annual reports or indeed included in these) as for the six current registries included, no new formal QO should be sought. The Applicant is encouraged to notify EMA about the addition of a new registry and to update the entry of the network in the HMA-EMA Catalogue of RWD sources. However, in case it is not obvious that requirements based on data for existing registries are met, the applicant is expected proactively to submit the relevant documentation to EMA for review. This documentation should not only rely on publicly available information but should include all the necessary details (public and not public) to assess whether the requirements are met and to take a decision on whether a new formal QO is needed.

6. Publication of the Annual BMSD PASS report: The Applicant will publish annual reports for the life cycle management as stated above which is agreed and considered essential for transparency. Currently, publication of this report on the BMSD webpage and the HMA-EMA Catalogues of real-world data sources and studies is found sufficient[18]. It is also agreed that changes could be needed to future scripts for generating the annual BMSD PASS report. In such a situation and upon request, old scripts and results generated on these old scripts should be made available for direct annually comparisons. Moreover, the applicant is requested to include in the annual report:

- a list of all studies including the link to their dedicated webpage on the HMA-EMA catalogue that have been performed during the period covered by the report, and
- a list of all the data sources with which a linkage has been established together with the study name and HMA-EMA catalogue link where the protocols are uploaded. This list should preferably also contain potential new variables in data sources linked.

Overall, the quality assurance of the LCM of registries and registry data is the responsibility of the BMSD network, also for the purpose of supporting sustainability. Therefore, BMSD should proactively contact EMA when they notice a risk of decline in the quality of the data / availability of variables compared to the metrics of previous years, together with proposed actions on how to mitigate the risks. Alignment with the RWD Chapter of the EMA Data Quality Framework[19] as appropriate is recommended. Currently, it is assumed that the applicant has procedures in place to ensure data quality but a detailed mitigation plan on how deficiencies in data quality or performance of the registry, which may occur after joining, is not part of the application. Therefore, the applicant is expected to elaborate via the BMSD webpage on potential actions they will take (including communication with EMA) in the event of important deviations to the expected quality metrics are found. Provided adherence to these elements by the applicant, regular re-assessments of annual reports or other LCM related data by the EMA are not considered warranted. Furthermore, the BMSD Core PASS protocol is expected to be kept up to date with state-of-the-art methodology and to reflect relevant research questions regarding DMT safety.

Overall conclusion

The six registries included in the BMSD network collect rich clinical information relevant for the conduct of PASS for DMT products. A major strength of the BMSD is its multi-country setting covering a large number of MS patients on active DMTs. For the context of PASS requested in the EU risk management plan (RMP), the possibility to include a broad study population from multiple European countries is an

[18] Guideline on registry-based studies
[19] https://www.ema.europa.eu/en/documents/other/data-quality-framework-eu-medicines-regulation-application-real-world-data_en.pdf

important advantage. Each registry has a relatively high national coverage, which supports the generalisability of findings from the BMSD to a European target population. Moreover, large sample sizes enable the study of rare adverse events. Similar data collection processes, alignment between individual registries for some aspects of data management, and implementation of a common data model (CDM) support registry interoperability crucial in multi-country studies based on large datasets. Furthermore, the individual registries have previously shown the ability to adjust the data inclusion in a coherent fashion (e.g. for COVID-19), and this indicates that future needs of amendments are also feasible to be included.

The BMSD network demonstrates a high completeness of core variables crucial for the conduct of PASS, and actual availability of SAE data has been demonstrated, which was a key outstanding issue in the initial QA. In addition, there is adequate demonstration of data availability of non-core variables important for confounding control methodologies. The availability of data elements to address other potential research questions relevant for PASS, such as those related to pregnancy outcomes, descriptive risk characterisation purposes, or evaluation of effectiveness of RMM is variable and context dependent across the individual registries. This is acceptable given that a feasibility assessment will be needed prior to the conduct of any PASS to determine fitness-for-use of the individual registries for a specific research question, based on the principles laid out in the ICH M14 guideline and the EMA Reflection paper on use of RWD in non-interventional studies to generate RWE for regulatory purposes.[20,21]. Moreover, these limitations are not fixed considering ongoing developments of the BMSD registries with regards to linkage to external sources as well as further development of the CDM and the demonstrated adaptability of the registries to collect additional elements if needed. The BMSD also committed to a life cycle management plan. Overall, the BMSD network as well as the individual registries can be qualified within the specified context of use.

[20] ICH_M14_Step4_Final_Guideline_2025_0905.pdf
[21] https://www.ema.europa.eu/en/documents/other/reflection-paper-use-real-world-data-non-interventional-studies-generate-real-world-evidence-regulatory-purposes_en.pdf

Annexes to be published:

1. Final Qualification briefing book for BMSD
2. Core Protocol for PASS
3. Common Data Model (updated)
4. Feasibility study (FS)
5. Written responses to Lists of Issues
6. Proposed Life Cycle Management plan for the Big MS Data Network to sustain an EMA Qualification Opinion in the context of PASS