BIG MS

The big Multiple Sclerosis data network

Proposed Life Cycle Management plan for the Big MS Data Network to sustain an EMA Qualification Opinion in the context of PASS

Introduction:

Pending that the Big MS Data Network (BMSD) receives a qualification opinion (QO) for performing PASS, there will be a process ensuring that the collection of data maintains high quality. Here, we propose the principles of such a life cycle management (LCM).

The BMSD will **annually publish a PASS report** assessing the continued performance of the respective registry in the context of PASS. This report will have five parts.

First, we assess some key **overall statistics** for each registry to illustrate a continued high level of reporting activity (see Table 1).

Second, we assess **key data quality elements** for such patients in each registry that could be eligible to contribute to a PASS, i.e. a **"PASS eligible population"**, mainly prospectively but also retrospectively using data from recent years, given the specifics of a PASS (see Table 2).

The data for Tables 1 and 2 will be derived from an annual data export from each BMSD registry which is then translated into the **BMSD common data model (CDM)** after which the same script is applied to each registry's data to populate the tables.

The third item concerns the collection **data on adverse events and key confounding factors.** As shown in the Feasibility study document of the BMSD QO dossier, the reporting of adverse events within recent PASS reports from BMSD registries has been found to be comparable to the "gold standard" of events identified from linkage to the national patient registries in Denmark and Sweden, whereas adverse event capture in other settings is less complete. Since not all BMSD registries contribute to any one PASS, and since all PASS projects have a defined end date, it is not an option to compare PASS AE report rates annually. Instead, we propose to identify changes in data collection procedures at an annual basis by a short questionnaire. We propose to assess similar changes in processes also for the collection of other key elements needed to characterize adverse event patterns.

Fourth, as there will be further development of the CDM, any these modifications will be reported in the annual report.

Fifth, BMSD would like to outline, at a principal level, what would be required for a new registry to join BMSD PASS projects. Whether registries fulfilling these criteria will be included in a maintained QO will evidently be a decision by the EMA.

Last, the specific details of the annual BMSD PASS report, such as the exact variables chosen for Tables 1 and 2 may be subject to revision over time, as the definition of the PASS eligible population. In addition, details of the scripts used will be subject to change, e.g. when new DMTs are introduced.

1. **Key statistics per BMSD registry**

   The purpose is to assess whether the overall registry reporting is maintained over time e.g. reflected in a continued or improved high coverage for the national registries (not relevant for MSBase).

   Table 1. Key statistics per BMSD registry

Variable	DMSR	MSBase	OFSEP	ReMuS	RISM	SMSR
Data extraction date						
Total number of patients						
females						
males						
Number of new patients						
females						
males						
Number of patients on DMT						
females						
males						
National coverage		not relevant				
Number of visits in past year						
Number of EDSSs in past year						

2. **PASS eligible population metrics**

   As the BMSD registries have a long history, and as data collection has gradually improved in numbers and quality, an assessment of the full registry gives a less

relevant reflection of the current performance. Therefore, and as applied in the BMSD QO dossier, we propose instead to assess data quality for patients in principle eligible to contribute to a PASS, i.e. patients on DMTs with a last visit in the past three years.

Table 2. Characteristics and data availability of patients potentially eligible for PASS

Patients on DMTs with a last visit in the past 3 years						
	ReMuS	**DMSR**	**OFSEP**	**RISM**	**SMSR**	**MSBase**
Data extraction date						
Representativeness:						
Number of patients						
Mean age (SD) at data extraction date						
% women						
Median EDSS [IQR]						
Mean EDSS (SD)						
Mean age (SD) at MS diagnosis						
Mean age (SD)at MS onset						
Relapse past year						
Relapse past 2 years						
Completeness:						
Unknown sex						
Unknown age						
Missing diagnosis date						
Missing onset date						
Missing MS disease course						
Ever recorded relapse						
Consistency:						
Visits 2 years back						
MRI past two years prior to extraction date						
Accuracy:						
Discrepant onset year						

Discrepant diagnosis year						

3. **<u>Verification of processes of collection of key data elements</u>**

We propose a brief questionnaire where each BMSD registry reports on changes affecting the process of data collection for important variables. This could include improved routines for ensuring data integrity at collection, new SOPs for data handling or new capacities to identify critical data via linkages with reliable external data sources such as health records or public health data bases. The questionnaire is proposed to include the following items:

<u>Has there been a change in the collection of data items for the following data items:</u>

a. Collection of Adverse events/Serious adverse events?
   - ☐ Yes
   - ☐ No
   - ☐ If yes, please explain

b. Collection of comorbid conditions
   - ☐ Yes
   - ☐ No
   - ☐ If yes, please explain

c. Collection of other medication
   - ☐ Yes
   - ☐ No
   - ☐ If yes, please explain

d. Collection of risk mitigation variables (e.g. laboratory data)
   - ☐ Yes
   - ☐ No
   - ☐ If yes, please explain

e. Pregnancy information
   - ☐ Yes
   - ☐ No
   - ☐ If yes, please explain

4. **<u>Common Data Model Update Management</u>**

The BMSD Common Data Model (CDM) is maintained as an open-source, version-

controlled codebase (currently v0.12) operated by the CDM development team at ReMuS Endowment Fund. The repository contains R scripts for data transformation, error log and validation log generation, and centre benchmarking, together with supporting reference files (data dictionary, treatment mapping, ZIP codes). The BMSD network intends to make the repository publicly available under an open-source license; the specific licensing terms are under discussion within the BMSD Steering Committee.

The CDM is structured as a **core BMSD CDM** covering domains common to all registries and PASS (demographics, disease history, relapses, treatments, comorbidities, EDSS, MRI, CSF, diagnostic results, pregnancy, laboratory data), with the possibility to develop **PASS-specific extensions** for individual studies requiring additional variables (e.g., biomarkers, patient-reported outcomes). Extensions do not alter the core structure and may be incorporated into the core CDM where broader utility is demonstrated.

Updates may be triggered by new PASS requirements, evolution of registry data structures (e.g. introduction of new DMTs), updates to external terminologies (e.g., ICD-10–MedDRA mapping from WHO/MSSO, ATC codes), onboarding of new registries, or findings from the error/validation log feedback loop. Changes are categorised as minor, moderate, or major; moderate and major changes require BMSD Steering Committee approval. Each new version is tested before release, tagged with a version number and changelog, and adopted by all registries within an agreed timeframe. The CDM is reviewed at least annually by the BMSD Data Managers Subcommittee. External terminology resources subject to third-party licensing (such as the MedDRA dictionary) are not bundled in the repository; each registry obtains these independently through its own subscription.

A detailed description of the CDM update management process is available as a separate document from the BMSD network.

5. New registry requirements to join BMSD PASS consortium

As BMSD aspires to set standards for real world data research we also have the ambition to invite new MS registries to join the network over time. In addition, new registries are required to be able to join BMSD projects and need therefore to adopt the BMSD CDM and be able to transform their own data in a successful way. Then a script

will assess the data quality of patients eligible for PASS as outlined in Table 2. Last, new registries will also have to show a capability of collecting adverse events at an adequate level.

Thus, the principal entry requirements can be summarized as:

a. Adoption of BMSD CDM including adequate transformation log results
b. Show similar data quality characteristics of a PASS eligible population cohort as established BMSD registries
c. Show similar AE reporting as established BMSD registries

6. Publication of the Annual BMSD PASS report

This document, central to LCM of the BMSD PASS QO, will be published annually in relevant places, i.e. on the BMSD webpage (bigmsdata.org), in the HMA-EMA Catalogues of real-world data sources and studies (https://catalogues.ema.europa.eu/) etc.