8th progress report – December 2023

Big MS Data Network (BMSD)

The coordination of the Big MS Data Network is currently receiving financial support for 1-5 years from several pharmaceutical companies. These include Biogen, BMS, Merck, Novartis, and Roche.

This is the **8th progress report**, covering the period until December 2023.

The BMSD network has been able to maintain coordination, active collaborations, an EMA qualification opinion application and further efforts to develop and ensure the progression of the BMSD network. Lately, one of the main aims has been focused on development of principles and accompanying documents to describe how the BMSD network can influence the performance of safety studies using MS registry data.

BMSD coordinating centre

The BMSD network has been coordinated from Karolinska Institutet since 2019. It was always the intention that the coordination was going to rotate and the time has come to select another BMSD partner for this task. The decision has been made that the Italian MS registry with Maria Trojano and FISM with Mario Battaglia will be the next BMSD coordinating centre from 2025. During 2024 there will be parallel coordination from Italy and Sweden.

F2F meeting in Copenhagen

The BMSD network meeting in Copenhagen 10-12 May, 2023 was very productive.
On May 12, 2023, BMSD held its annual **BigMS PHARMA PASS Forum** IRL in Copenhagen, gathering representatives of pharma with ongoing or planned BMSD formatted PASS. The emphasis of this meeting was on the EMA QO application and pharma expectations of a core CDM and the design of future PASS.

F2F meeting in Bari

The 2nd BigMS Workshop - “Statistical methods to address specific RWE questions” - “Novel modelling approaches for RWD analysis” took place in Bari on 14-16 June, 2023. The meeting was very productive with talks and discussions on topics such as statistical approaches to the

study of treatment effects, machine-learning methods, Bayesian methods, comparative effectiveness and safety of DMTs' sequences in MS and safety analysis using RWD. The position of the conference participants on central aspects of MS epidemiology and pharmacoepidemiology in particular will be made in a joint position paper to be published and which at present exists as a manuscript.

F2F meeting Belfast 2024

The next **BigMS PHARMA PASS Forum** is planned for **17 May, 2024** in **Belfast.** There will be a separate invitation in the spring 2024.

EMA qualification opinion

BMSD has the ambition to play a role in developing the standards of PASS in the MS area and in order to be recognized by EMA, a qualification opinion would be important, both for BMSD as a network and for the individual participating registries and for pharma using registry data in PASSs.

A **BMSD PASS qualification opinion application was submitted to EMA** in 2021 and was shared with the BMSD sponsors. BMSD has subsequently been informed of the EMA decision to issue BMSD an EMA Qualification Advice and a letter of support. BMSD has been made aware of SAWP's considerations and concerns regarding the BMSD application and these will need to be addressed if BMSD would like to proceed with a QO application in the future.

Although EMA acknowledges that the use of MS registries participating in BMSD may have several advantages in terms of efficiency and consistency in the preparation and conduct of future MS PASS, there are two major aspects that, in the opinion of EMA, hamper qualification at this stage. The first one concerns perceived uncertainties regarding the extent to which the individual registries and the proposed generic protocol are able to capture the relevant safety endpoints required for successful conduct of a PASS. A feasibility study is recommended. The second concern is in regard to what EMA perceives as a lack of a concrete set of minimum quality requirements that apply equally to all participating registries. Harmonization of minimum quality requirements to improve quality assurance across the individual registries in a coordinated approach is needed. BMSD has received a **Letter of Support (LoS)** describing the methodology under evaluation which also has been published by EMA (January 2022).

There have been discussions between BMSD and some of the pharma as to how best to show fit-for purpose for the BMSD registries ability to capture SAEs. A **taskforce** has been formed to discuss this issue and all pharma currently supporting BMSD have been invited to participate in these discussions. The plan is to re-submit the QO application to EMA for BMSD PASS. The proposed feasibility study will be based on the Roche "MANUSCRIPT" PASS in which all BMSD registries participate (for ReMUS as a part of MSBase). Thus, rates of SAEs may be compared. In addition and for Sweden, data can be compared between SAEs reported through SMSreg and

linked data from the national patient registry. Once such a comparison has been made the plan is to compare number of reported SAEs between the registries that participate in the MANUSCRIPT study and to show data from other studies for those registries that are not part of the Roche PASS.

In order to assist with the application process and to offer regulatory experience, OXON which is a CRO with EMA experience, was contracted by Biogen. OXON has supported BMSD by collecting and systemizing additional information as part of the request tool from all the registries for a renewed EMA application as well as making suggestions to the core protocol. BMSD is grateful for this support but will remain applicant of the EMA application once this is submitted and will be fully responsible for the content of the application.

We are currently working on the final modifications of the **request tool**. The plan is to share the request tool with pharma supporting BMSD as soon as possible during the spring of 2024. The updated **core protocol** will also be shared as soon as there is a final version.

Data management

Data management development within BMSD is ongoing. In the past, pooled data has been used for joint BMSD publications but this is getting increasingly difficult with the development of national legislations. For this reason, individual registries as well as the BMSD network has been looking into approaches of *federated analyses* including *federated learning* where data can be analyzed in an orchestrated way although not leaving the respective organization. The choice of approach will likely depend on the type of project to be performed as well as the extent to which data sharing is permitted by local restrictions. Different data management approaches will be combined and further developed by the data manager group.

The development of a core common data model (**CDM**) is ongoing. It is important to remember that a CDM will always need to be adjusted to individual projects but will still be very useful to describe general data management and can also be used to assess new registries interested in joining BMSD.

Jiri has been leading the work on the CDM and will soon submit a manuscript where the CDM is described.

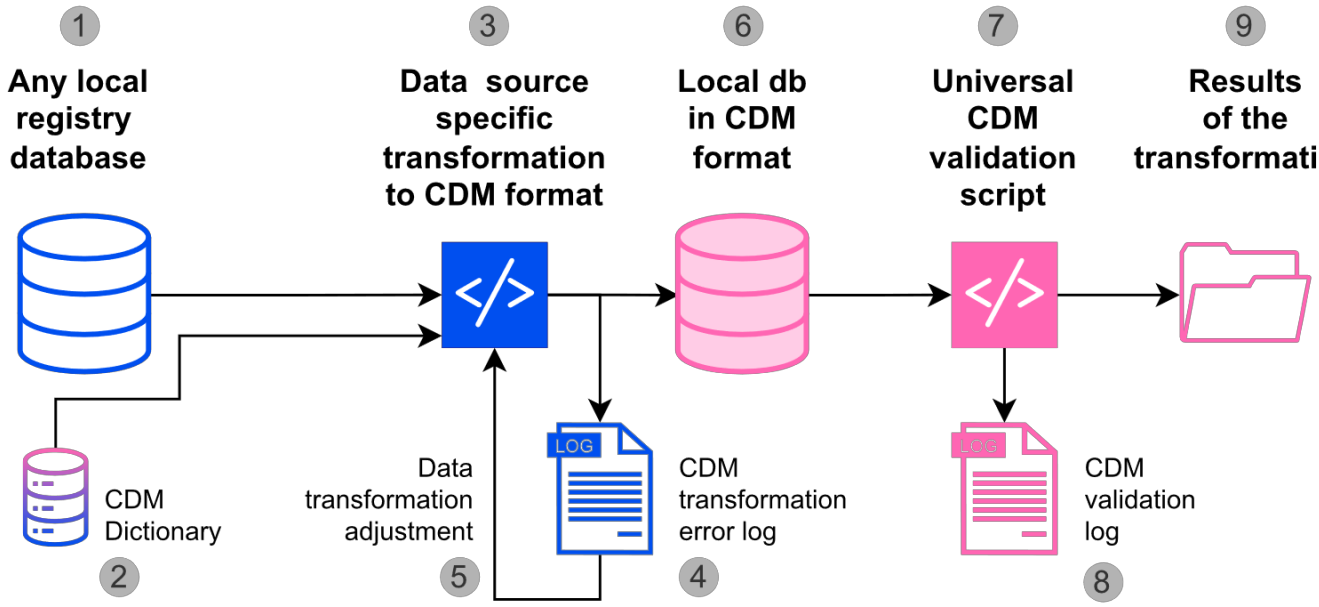

Figure 1 General Common Data Model concept

Jiri Drahota

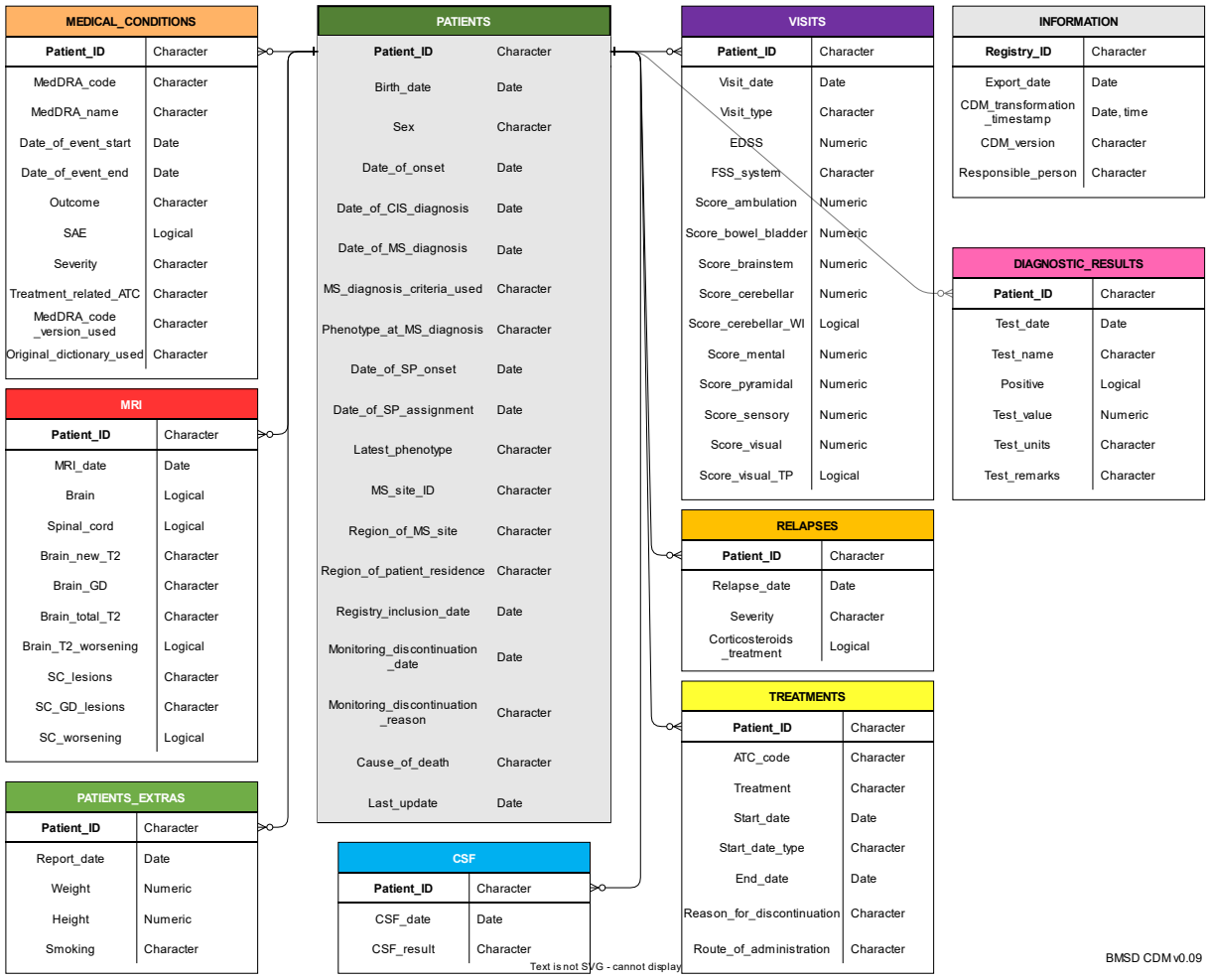

Figure 2 BMSD Common data model structure

Jiri Drahota

HORIZON-HLTH-2022_TOOL-02 call

BMSD, through KI, was invited to join an application for a HORIZON-HLTH-2022_TOOL-02 call which was successful and the project started in January 2023. The focus of the project, More EUROPA, is on how to use real world data from registries to enable regulatory decisions. The application covers several chronic diseases as well as other research areas and the MS part aims to compare the use of rituximab, which is commonly prescribed for MS in Sweden, with DMF and ocrelizumab in Sweden and other countries. Another major part of the study is how to analyze data in a federated manner where the different registries can perform analysis locally without sharing individual data. This part of the project will hopefully make valuable contributions to future projects involving MS registry data.

The MS registries in the Czech Republic, Denmark and Italy have joined the collaboration as sub-contractors. The process has recently been completed and the project is expected to be up and running early 2024.

Communications

The **BMSD homepage** https://bigmsdata.org/ is up and running. There is separate login information to access protocols and reports that can be shared with pharma. A sponsors' page is also available.

A **review paper** on the BigMS Data effort has recently been submitted. Four **manuscripts** have so far been published for the Biogen sponsored demonstrator projects: "Early treatment delays long-term disability accrual in RRMS: Results from the BMSD network" Iaffaldano P et al, Mult Scler. 2021 Apr 26 and "Treatment Switching Discontinuation Over 20 Years in the Big Multiple Sclerosis Data Network". Hillert J et al, Front Neurol 2021 Mar 17 and "Heterogeneity on long-term disability trajectories in patients with secondary progressive MS: a latent class analysis from Big MS Data network" Signori A et al, J Neurol Neurosurg Psychiatry 2022 Sep 28 and "Predictors of treatment switching in the Big Multiple Sclerosis Data Network." Spelman T et al. Front Neurol. 2023 Dec.

We conclude that the year 2023, like previous years, has been productive for the BigMS Data network and we thank all the sponsors for their support.

February, 2024

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