The big Multiple Sclerosis data network

6th progress report - December 2022

Big MS Data Network (BMSD)

The coordination of the Big MS Data Network has received financial support for 1-5 years from several pharmaceutical companies. These include Biogen, BMS, Merck, Novartis, Roche and Sanofi. BMSD is still in negotiations with Janssen.

This is the **6th progress report**, covering the period until December 2022.

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. Although the pandemic was challenging, we have managed to carry out TCs as well as one F2F meeting in 2022, which in a satisfactory way has kept the BMSD network as well as the pharma contacts active and productive.

F2F meetings in Prague

The BMSD network meeting in Prague on 9 June, 2022 was productive. The agenda covered ongoing and future studies, the EMA QO application and the possibilities of making BMSD into a legal organization, which is something that will be further explored in the next year.
On June 10, 2022, BMSD held its annual **BigMS PHARMA PASS Forum** IRL in Prague, gathering representatives of pharma with ongoing or planned BMSD formatted PASS. Common activities were discussed and the topics for the meeting included a pharma PASS update, as well as an update of the EMA qualification opinion application and next steps, BMSD current and future directions and some general discussions and conclusions from the meeting.

Seeking qualification opinion by EMA

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.

In January 2021 an application for a **BMSD PASS qualification opinion (QO) was submitted to EMA** and the EMA application was also shared with the BMSD sponsors. BMSD received a list of issues from EMA to consider prior to an EMA SAWP meeting with BMSD on 7 April, 2021 to discuss the application and the EMA comments. BMSD has subsequently been informed of the

EMA decision to issue BMSD an EMA Qualification Advice. 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.

There have been recent discussions between BMSD and some 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 submit the QO application to EMA for BMSD PASS as soon as possible but to ask for EMA pre-application advice for the feasibility study to be performed if encouraged by EMA. In order to help with the application process Biogen has contracted OXON which is a CRO with experience of EMA. OXON has supported BMSD by collecting additional information from all the registries for a renewed EMA application as well as making some suggestions to the core protocol and BMSD is of course very grateful for this effort. BMSD will be the only applicant of the EMA application once this is submitted and will be fully responsible for the content of the application.

There have been suggestions to also include a post authorization effectiveness study (PAES) in the EMA application as the previous version was focused on PASS and there seems to be a general interest from pharma to make a qualification application to EMA for PAES as well. BMSD has now decided to submit a separate PAES QO application once the PASS QO application has been completed in order to focus on one application at a time.

Data management

Data management development within BMSD is ongoing. The flowchart below describes the possibility of analyzing pooled individual data as well as a federated data approach. 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. In connection with one of the BMSD demonstrator projects, a script was developed as part of the checking and data merging. This will be combined with other data management approaches and further developed by the data manager group.

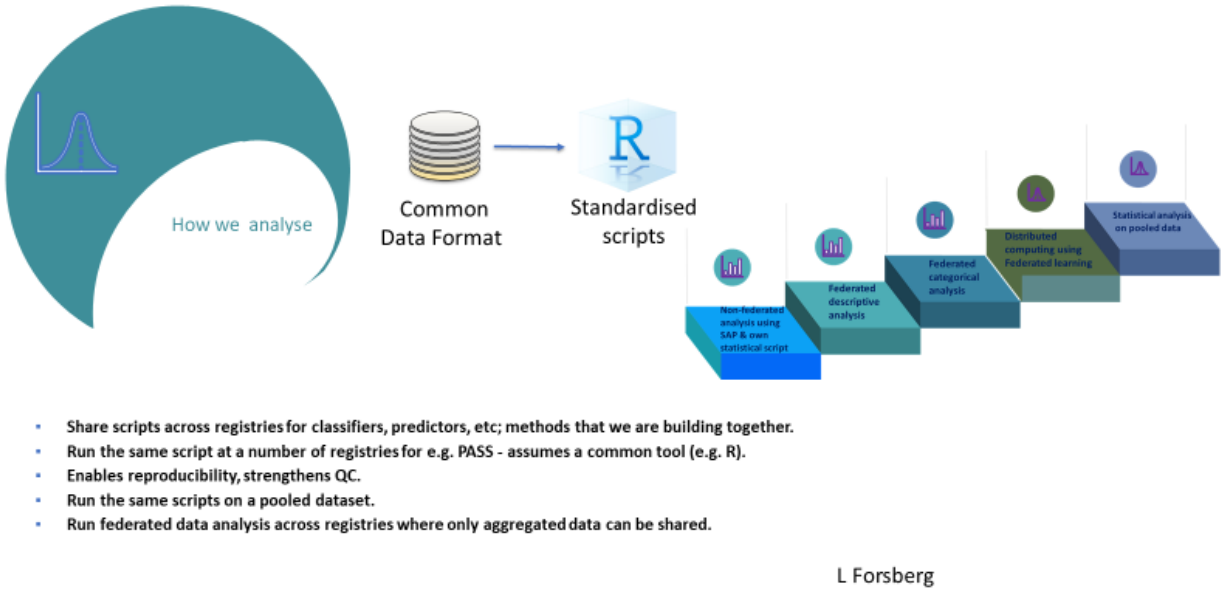

Figure 1. Different levels of data analysis depending on character of the study as well as registry conditions and local legislation.

There are currently ongoing plans to perform a safety study to describe how a CDM works within the BMSD. This would involve a further development on the models that have already been introduced as part of the demonstrator projects and would address both a CDM within BMSD and EMA's request for data management to be described in more detail within the network. Some issues to consider concern whether to include patient level data where data is analyzed centrally or to use more of a federated approach where data is analyzed locally.

MS-Covid19

As a consequence of the **SARS-CoV2 pandemic**, all BMSD registries have adapted their data collections to allow the gathering of information of MS patients with Covid-19. All registries have used their data for scientific analysis and reported results in different contexts. Based on this data, the Danish, Czech and Swedish registries as well as MSBase have contributed to the COVID-19 & MS global data-sharing initiative (GDSI). The French and Italian teams have been leaders in their national MS-Covid19 efforts. Altogether, the BMSD registries have been critical in capturing data allowing the identification of treatment related risks for severe Covid-19 infection.

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! The project will start in January 2023. The focus of the project, More

EUROPA, is on how to use RWD 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 in Sweden, with DMF and ocrelizumab in Sweden and other countries. The other BMSD registries will in early 2023 be invited to join as sub-contractors.

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. The sponsor page is also available.

A **review paper** on the BigMS Data effort has been delayed but will soon be circulated within the BMSD network. Three **manuscripts** have 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.

Upcoming meetings

BMSD Forum, May 2023 in Copenhagen

Conference on statistical analysis, summer 2023 in Bari

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

20 December, 2022

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