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Big Multiple Sclerosis Data project on Co-ordination of its establishment and further development, 2019-2024

Background:
Big Multiple Sclerosis Data, BMSD or "BigMS", is a network between five internationally leading multiple sclerosis (MS) registries and data bases: The OFSEP of France, the national MS registries of Italy, Denmark and Sweden and the international MS database MSBase, coordinated from Australia. The network was initiated in 2014 when the five registries in a year-long effort investigated the basis for a scientific collaboration focusing of joint analyses of pooled clinical materials to address scientific question each registry lacked statistical power to achieve on its own. The conclusion was that legal, governance and data format challenges could be readily overcome and three projects on pooled material are currently being performed, two of which have presented results at ECTRIMS2018 in Berlin (see reference list).

During 2017 and 2018, BMSD has participated in efforts to establish a platform for MS registry-based Post Authorization Safety Studies (PASS). In this work, representatives from six pharma within the MS field have contributed to the establishment of a Core Protocol for MS PASS projects: Biogen, Celgene, Merck, Novartis, Sanofi-Genzyme and Roche. In this process, the team has sought advice from EMA. Currently three such PASS projects are finalizing contracts with BMSD registries and three more are being planned.

BigMS from 2019 to 2024:
In a recent meeting in Stockholm on February 22, 2019, BMSD, the six pharma as well as a seventh pharma, MedDay, participated and reviewed the current situation. The five BMSD registries declared being committed to continue to develop BMSD and specifically to contribute to PASS project when possible.

This document is intended to outline how the BMSD registry chairs propose BMSD to be further developed in the coming years. This includes participation in the completion of the planned BMSD PASS projects but importantly also further development of BMSD itself.

Co-ordination of BMSD:
A development of BMSD to achieve its Aims and Missions require active co-ordination by a Coordination Center (CC). Karolinska Institutet, representing the Swedish MS Registry, has been selected to take on the co-ordination task of BMSD. This document is intended to describe the responsibilities of the CC and to list the tasks the CC is expected to perform. Accordingly, this will require manpower, and financial support will be sought from the

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BMSD supporting pharma. This issue was discussed in the February 22 meeting and BMSD informed that it would approach each pharma for support.

The co-ordination tasks have been identified in discussions within BMSD, with pharma and from the EMA Discussion paper currently being developed for possible publication. Many of these tasks are of general importance for BMSD whereas others are more specific to fulfill BMSD ambitions within the scope of PASS projects.

Project plan:

This project focuses on the establishment and development of the BMSD collaboration to reach an organization maturity to ensure sustainability for years to come, i.e. for the duration of the currently planned PASS projects for newly developed MS treatments. Its contents will therefore be the co-ordination tasks of the CC.

Aims of BMSD (provisional):

- To establish **BMSD** as a leading platform/organization/entity in MS (RWE) research
- **BMSD** will be Visible, Accessible, Expedient, Recognized, Involved/Engaged, Innovative

Missions (provisional):

- To propagate MS research
- To propagate development of MS care
- To benefit patient advocacy
- To promote new MS registries

General tasks of BMSD coordinating center, general:

Strategy

- Coordinate the further development of BMSD Aims and Missions
- Lead and coordinate the long-term strategic BMSD efforts with the aim of securing and developing a position of BMSD to fulfill BMSD Aims and Mission
- Lead and co-ordinate the development of BMSD into an organizational format which ensures fulfillment of BMSD Aims and Missions while being compatible with the governance structure of each of the participating registries.
- Lead the process to agreement on next steps in terms of scientific scope and defined scientific projects to be performed by BMSD including to seek financial support.

Central office tasks

- Point of contact for BMSD
- Home page, design and maintenance
- Organize and support meetings of the BMSD Steering committee, the Data Management Sub-committee and Statistical Analysis Committees, TCs, minutes, documentation
- Manage requests for collaboration, data access
- Support legal and contractual aspects including

Establish and develop BMSD structure and activities

- Harmonize definitions and data elements
- Map variables and terms between registries
- Map variables and terms to established classifications such as SNOMED
- Develop SOPs, manuals etc. defining format of BMSD activities
- Provide secure data hosting, eventually with login and remote access for analysis
- Provide procedures for data handling (in and out)
- Define criteria for registry partnership within BMSD, i.e. inclusion of new MS registries
- Establish linkage system (where feasible)
- Define and publish policy for collaboration with external stakeholder
- Support scientific aspects (data collection, protocols, templates for research contracts, etc.)
- Support ethical aspects

BMSD communication and promotion

- Promoting awareness of BMSD, its aims and activities to all stakeholders
- Positioning of BMSD externally including home page, position papers, other publications e.g. on registry characteristics
- Representing BMSD in relevant venues, conferences, workshops etc.

BMSD funding

- Lead BMSD coordinated efforts for funding from non-commercial and commercial entities
- Manage BMSD funds

Quality control activity

- QC of BMSD data contributors
- Benchmark between BMSD member registries
- Benchmark to external data sources
- Measure quality indicators periodically
- Facilitate potential audits

Promote the development of new and improved MS registries

- Support and advice to developing MS registries not yet having met criteria for entry into BMSD

Promote development of research methodology

- Organize workshops to propagate development of scientific methods in MS epidemiology
- Organize training sessions

Promote quality of care

- Represent BMSD in activities with health care authorities and patient advocacy groups

Coordination tasks specific to BMSD PASS

- Certification / Regulatory Qualification of BMSD registries with EMA for PASS projects
- Tracking progress of registries in adapting to requirements for PASS
- Quality control of registries, benchmarking of PASS relevant variables
- Co-ordination of patient level data merge and analysis
- Deal with questions from stakeholders such as EMA, pharma, EMSP etc
- Positioning of BMSD PASS efforts externally including home page, position papers, other publications
- Co-ordinate communication and publication of BMSD PASS efforts.

Achievements of BMSD and current activities:

Pilot BMSD projects

As summarized above, BMSD has already initiated three research projects on merged data sets as proof of principle, i.e. to demonstrate that merging of data is indeed possible, and that analyses can provide scientifically valid results. Two of the three have been presented at ECTRIMS2018 (Iaffaldano et al, 2018, Spelman el at, 2018). One project focuses on the long-term benefit of MS DMTs and utilizes over 15,000 MS patients followed up at least 10 years after initiation of first treatment. A second project focuses on discontinuation patterns of DMTs and is based on 269,822 treatment episodes in 110,326 patients. The third project will address the question of DMT effectiveness in progressive MS of which there are a few thousand patients. Manuscripts for these two studies are now under internal review and submission is expected later this year.

PASS projects

Two PASS projects are already initiated, one by Merck on oral cladribine and the other by Roche on ocrelizumab, both building on the principles of the BMSD Core Protocol. In the case of the Roche study, the BMSD Core protocol served as part of the documentation in their application to EMA. Our *modus operandi* is that the BMSD registries individually sign contracts for each pass, and a handful of such agreements have been signed and several are in the negotiation stage.

Propagation of methodologies in MS epidemiology

BMSD intends to support the development of improved methodologies in MS RWE research, in particular with regard to statistical methods. This will be done by arranging workshops and publishing position papers of "preferred methods". A first such workshop, of statistical methodologies, will take place in October in Bari, Italy, and will involve central statisticians and epidemiologist from the MS field but will also invite leading scientific researchers in the field of statistical epidemiology.

Future Big MS Data projects

As the central concept of BMSD is to jointly address issues in the MS field that a single registry would not be able to address for reasons of statistical power, the intention is to take on new projects with time, when funding permits. Thus, a new project may be proposed by researchers within BMSD but also by external researchers in academy or

pharma. We expect that the BMSD resources may be especially relevant in projects focusing on:

A) The course of MS:

- Heterogeneity of MS
- Progressive MS (PP and SP)
- Pediatric onset MS
- Late onset MS, including co-morbidities and DMTs
- Impact of comorbidities on disease course
- Studies of MS (natural) course and its evolution (trends) over time

B) Pharmacoepidemiology

- Comparative effectiveness and safety of DMTs and treatment strategies (e.g.escalation versus induction strategies) in MS and its subgroups
- Long term outcome as a function of timing and sequence of DMTs including first and second line treatments, as a basis for personalized medicine
- Integration of prognostic and predictive factors in the design and validation of tools for personalized medicine
- Evolution of natalizumab-associated PML incidence
- Safety during pregnancy
- Factors that determine or predict safety and tolerability (Comorbidities, Risk behaviours, co-medications, ethnicity)
- Access to DMTs in different countries and different health care systems

C) Validation of prognostic and predictive factors: Clinical, Imaging and Biomarkers

- Prognostic markers in subgroups of MS
- Predictive markers in patients on specific treatments
- Long term prognostic/predictive importance of MRI lesions
- Long term prognostic/predictive importance of MRI brain volumes
- Long term prognostic/predictive importance of body fluid biomarkers (e.g. sNf)

D) Validation of outcome measures

- Cognitive outcomes in MS
- Patient reported outcomes
- MRI outcomes
- Biomarkers outcomes
- Quality of life in MS outcomes
- Other outcomes reflecting motor or non-motor domains of MS consequences
- Socioeconomic outcomes in MS

Future outlooks of Big MS Data

BMSD does not intend to remain as a small group of select MS registries, but hopes to grow with time by including additional registries which reach sufficient maturity and quality. A measure of such a developmental stage is suggested to be when contribution to a BMSD PASS study is deemed feasible by aligning a minimal data set with the same definitions and syntax with reasonable data counts and completeness of data. There are several registries in Europe and elsewhere for which this is very doable within the coming few years.

BMSD will reassess its organizational principles over time and intends eventually to reach a formalized format, but with the overarching goal of reaching a sustainable collaborative model still respecting the governance principles of participating registries.

Budgetary considerations:

The coordination tasks of BMSD, including co-ordination of the BMSD PASS projects, is estimated to € 250,000 annually for the duration of five years. This will cover 0.75 FTE Project manager, 0.2 FTE Principal investigator, and 0.5 FTE Data manager plus costs for travels and facilities. The Karolinska group is currently organizing facilities for secure data storage for the centralized data management which will be covered. In addition, BMSD will organize annual workshops to promote the development of MS epidemiology, in particular focusing on biostatistical methods, by inviting MS key epidemiologists as well as international external experts and pharma representatives

BMSD is seeking support from pharma for these costs and ask for an evenly large contribution from supporting pharma. As we hypothesize that there will be 5 sponsors, we will ask each pharma for a support of € 50,000+overheads per year.

We are seeking support for an initial period of five years.

For a pharma performing a PASS project based on the BMSD Core PASS Protocol, this budget will thus cover costs for co-ordination of the joint patient level data analysis, including data management up to the creation of a joint data file for analysis, but not the project-specific analysis itself, which will reside with the research group/registry organization group selected for this task.

A more detailed budget will be developed.
Milestones and deliverables will be developed.

Final words:

We believe that a collaboration between five of the world's leading clinical MS registries is timely and will prove to be very useful in filling central knowledge gaps in the MS field of benefit for patients, pharma, society and researchers.

With hope of support for BMSD and its co-ordination!

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References:

Iaffaldano P, Lucisano, G.; Butzkueven, H.; et al. The optimal time to start treatment in relapsing remitting multiple sclerosis patients: results from the Big Multiple Sclerosis Data Network. MULTIPLE SCLEROSIS JOURNAL Volume: 24 Supplement: 2 Pages: 71-72, OCT 2018

Spelman, T.; Magyari, M.; Sorensen, P. Soelberg; et al. Treatment discontinuation in the Big Multiple Sclerosis Data Network: a descriptive analysis. MULTIPLE SCLEROSIS JOURNAL . Volume: 24, Supplement: 2, Pages: 674-675, OCT 2018