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Initial Qualification Procedure - List of Issues

Big MS Data Network (BMSD) and incorporated multiple sclerosis (MS)

Summary

This is a qualification procedure for the Big MS Data Network (BMSD) and six participating multiple sclerosis (MS) registries in the context of use (CoU) of post authorisation safety studies (PASS).

The BMSD Network, coordinated by the applicant, Karolinska Institutet, consist 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 in the report)
- The International MSBase Registry (MSBase)

The clinical data systematically collected in these registries could be a valuable source of safety data regarding the use of disease-modifying treatments (DMTs) for MS. At this point, an estimated 360,000 patients are included in the BMSD; almost 168,000 MS patients on active DMTs.

This procedure evaluates a qualification of the BMSD network and its individual registries for the context of use of performing post-authorisation safety studies (PASS).

The EMA issued an initial Qualification Advice (QA) for performing PASS in the BMSD network in 2021 (EMA/SA/0000050512). Two main issues that hampered qualification 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 they are fit for purpose, and to introduce a harmonised approach to quality assurance.

The BMSD network requests a qualification opinion (QO) from EMA to conduct both short-term and long-term PASS. The QO should be applicable both to PASS making use of data from all member registries of BMSD as well as PASS relying on only one or more of the registries.

The applicant submitted a briefing book containing general information of the BMSD network in support of qualification for the CoU of PASS. In addition, a feasibility assessment was provided to demonstrate collection of adverse events of special interest. The applicant updated the core protocol for PASS reflecting general principles of how to perform a PASS involving the BMSD registries. Moreover, a so-called Request tool with details for each of the registries regarding data availability, and a high-level description of the common data model (CDM) were provided.

Scientific discussion

As reflected in the initial QA, the proposal for qualification of the BMSD and its individual registries for PASS is overall supported. The registries 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. All registries state to comply with the General Data Protection Regulation (GDPR).

Since the initial QA, several improvements in terms of data quality processes, general description of the BMSD, and actual availability of key elements have been made. The coordinators consider a qualification of the BMSD a possibility at this stage, but discussion and/or clarification of a number of issues by the applicant is required. This would also enhance transparency and allow for a well-informed decision.

Fitness-for-use

The applicant provided a feasibility assessment (FA) to demonstrate actual availability of key data elements in the registries. Based on the FA, relevant safety outcome data such as malignancies and serious infections are adequately captured in the registries, and this is appreciated. 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. 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 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 data elements requested in the initial QA such as relevant confounding and effect-modifying variables, global characterisation of MS patients, information on treatment as well as quality and completeness of these was not part of the scope of the FA. The applicant submitted a so-called Request tool in form of an excel sheet providing details for each of the registries regarding data availability. Overall, this supports fitness-for-use of the BMSD for PASS. The registries state to have high completeness of key data elements such as demographics, MS diagnosis, disease, DMT treatments, and adverse events of special interest. As an example, some of the core variables for patients seen and treated during 2022-2024 in each of the six registries were reported. For each registry, more than 99% of the patients had a documented age and sex, and an MS onset date was registered for 98% or more of the patients. Documented diagnosis date ranged between 77.0% and 99.2%. Documented MS course was higher than 95% for all of the registries. From the Request tool, the start and stop dates of DMTs are registered for more than 90% of the patients in each register.

However, completeness of past or concomitant medical conditions is rather low for those registries without linkage. In addition, completeness counts regarding other elements such as e.g. concomitant medications are not provided. Specifically, for RISM and MSBase, it is noted that these two registries collect data overall, but also for selected groups of MS patients on a project-basis for specific PASS. Data completeness consequently seems to some degree to depend on agreements made for each PASS to be conducted using RISM and MSBase. This complicates an overall fitness-for-use assessment for these two registries.

BMSD registries are already actively utilised in ongoing EMA-requested PASS. At this point, interim/final results from five such PASS demonstrate at least in part that collection of other important data elements is possible. These results, although not included in the applicant's submission, provide supporting proof-of-concept evidence for the feasibility of PASS conducted using the BMSD registries. Importantly, some of these results are already informing regulatory decision-making.

At the same time, the results showcase some of the limitations of the BMSD. Further clarification is needed to understand fully the impact of these for the fitness-for-use of the BMSD. One specific example is the MANUSCRIPT PASS for Ocrelizumab in which all BMSD registries except ReMuS (CZ) are participating. Based on the latest interim report, 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. This limited the methods to create balance between exposure groups and the interpretability of measures of association.

There is also uncertainty regarding the availability of other data elements required for research questions not considered in the core protocol for PASS but which are likely to be of interest from a regulatory perspective. This includes data for descriptive risk characterisation purposes (e.g. event severity and clinical course), evaluation of effectiveness of risk minimisation measures (e.g. compliance to a contraindication), as well as uncertainty around the availability and precision of specific dates essential for survival analysis (e.g. date of death or loss to follow-up). Pregnancy outcomes are captured in SMSR and DMSR via linkage, but availability in the other registries is unclear and there is no ongoing study as proof-of-concept.

The registries are found to cover most of DMT treated MS patients, as special centers are needed for DMT. Patients with a very mild disease and patients who already have an important level of disability

are probably under-represented in some of the registries. All registries include untreated patients with some variability (between 3.2% to approximately 25% untreated patients in the registries). Consequently, the coverage of DMT treated MS patients in the registries are found to be sufficient.

Based on the provided documentation of the BMSD and interim/final results of ongoing PASS, the fitness-for-use of the BMSD network for PASS might be considered overall established, pending further clarification by the applicant on some aspects. However, it is also evident that not all individual registries might be fit to answer all research questions relevant in a PASS for DMTs (e.g. exposure during pregnancy studies). For a potential qualification of the BMSD and each individual registry for the context of use of conducting PASS, it needs to be considered that the BMSD registries complement each other and feasibility assessments need to be performed for each specific PASS to determine which of the individual BMSD registries are fit to answer the particular research question of interest, potentially in combination with other non-BMSD data sources.

Despite supranational guidelines and recommendations, the choice of the disease modifying agent varies within member-states and even regionally due to reimbursement factors and local experience. Even the sequence of treatments, namely upgrading MeDMTs to HeDMTs or reducing from HeDMTs to MeDMTs is dependent upon the readiness of use of the individual agents. Therefore, the pattern of use of individual countries (and registries) may modulate the occurrence and frequency of ADRs. Seldom used agents also decrease the chance of identifying AEs or classifying it as an ADR due to the lower experience of the clinician with the product. It is thus important to know to what extend individual registries are representative of the overall EU prescription patterns in terms of the presently used DMTs and - within reasonable limits - the sequence of use of DMTs.

Governance and response to external requests may vary significantly within registries from 4 months response (ReMuS, SMSreg), to slower >8-10 months (OFSEP). It is known that PASS studies deal with large time-windows. This may nevertheless be a bottleneck given the possibility to implement protocol amendments and the need to merge data from various registries. This should be further addressed.

Data quality

Data quality is affected at both the individual MS center, the individual MS register in charge of national data managing, and the BMSD which overall facilitates data analysis.

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 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. This initiative is welcomed.

The applicant states that the CDM, in association with a federated analysis procedure as well as the BMSD Core PASS protocol will constitute the basis for a standardized methodology. These aspects are agreed to be minimum quality requirements. However, the description of the CDM is rather high-level. The recommendation from the previous QA to establish a coordinated approach for the individual registries in relation to rules for data storage, quality-control procedures, and internal audits has not been explicitly commented on by the applicant. It is noted that some of the aspects are handled similarly between registries, and that all individual registries state to be GDPR compliant, which is expected also to cover data storage. Given the heterogeneity between the registries, individual measures might be sufficient, however more information is needed for transparency. Furthermore, it is unclear whether all individual registries as well as the BMSD support/allow external monitoring besides national competent authorities (NCAs) and allow other EU regulatory authorities inspection overall and in relation to specific PASS.

Some key performance indicators such as data consistency, completeness, and accuracy can be measured in a harmonised approach by the CDM. Based on the CDM validation script applied to the translated data sets, a detailed report in relation to data accuracy and completeness has been completed according to the applicant. However, this specific report has not been presented with the application, even though it might be valuable for the interpretation of the data quality. Furthermore, the potential impact of the CDM methodology on reliability (e.g. transformation can increase risk of error, lower level of precision for individual datasets, and negatively influence timeliness) has not been addressed.

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 are translated into MedDRA based on the Observational Health Data Sciences and Informatics (OHDSI) methodology. The quality of this translation has not been further specified.

In terms of combining data from the individual registries, the applicant states that both federated analyses run locally without sharing of patient-level data and pooling of individual data would be possible. However, it seems that a federated approach is preferred, but as such the sharing of person-level data might not be feasible for all registries due to GDPR restraints. Further, while this approach is acknowledged, the impact of data aggregation on the granularity of data should be discussed. Specifically, the applicant should clarify if important clinical circumstances relating to SAEs can be maintained for descriptive analyses. Moreover, both in the ongoing MANUSCRIPT study and in the finalised Lemtrada mortality PASS, meta-analyses could not be performed due to heterogeneity. The applicant should clarify if such issues would be solved with implementation of the CDM in future PASS.

Scope of the qualification

The applicant seeks qualification of the overarching BMSD network, as well as qualification of each of the six individual registries that are currently part of the BMSD for the context of use of conducting PASS. Moreover, the applicant presented a strategy regarding potential addition of new registries to the BMSD network.

Provided submission of satisfactory responses to the LoI, qualification of the overarching BMSD network is considered a possibility at this stage, in view of an overall acceptable level of fitness-for-use and data quality requirements.

A qualification of each of the six individual registries that are currently part of the BMSD is complicated by the fact that not all registries seem to demonstrate fitness-for-use for all research questions relevant for potential PASS (e.g. pregnancy outcomes). Clarification regarding availability of certain data elements in the individual registries will further inform these uncertainties. Acknowledging that a robust overall relevance and reliability of each registry is demonstrated and that improvements are ongoing (e.g. greater level of linkage), qualification of each individual registry might be supported. However, the qualification would not alleviate the requirement to conduct a feasibility assessment prior to the conduct of any future PASS to confirm fitness-for-use of the registries for a given research question, and potentially to identify those BMSD registries which are best suited for the particular research question. The applicant is asked to discuss an appropriate framing of the CoU.

Regarding the addition of new registries to the BMSD network, the applicant proposed that candidate registries are required to be capable of converting data into the CDM format and show a validation report at the same level as the existing BMSD registries. For fitness-for-use, SAE incidences would need to be demonstrated. While these principles are supported, it should be emphasized that the

SAWP does not consider that a potential qualification of the current BMSD network would automatically apply to new registries joining the BMSD network in the future.

Other aspects

A potential qualification of the BMSD and the associated registries is without prejudice to the potential commitments of monitoring and reporting of adverse events that already pertain to the data collection.

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 completeness of data in the individual registries.

For adaptability of the registries to cater for e.g., new safety concerns it is noted that timeliness/ governance is heterogenous between registries. The successful inclusion of such new variables in the CDM remains to be shown.

List of issues to be addressed in writing and/or during the discussion meeting

Based on the coordinators' reports, the Scientific Advice Working Party (SAWP) determined that the Applicant should discuss the following points, before advice can be provided:

BMSD responses have been added in red

Issues to be addressed only in writing by 2 March 2026

1. For survival analyses used in e.g. comparative studies of adverse reactions it is essential to be precise regarding the estimation of each individual's time contributed to each cohort. Consequently, status of and dates of potential death, loss to follow-up, change in treatment etc. are essential to capture with precision. However, from the briefing book, it is not entirely clear how this information is captured and which level of quality the information collected will have. For transparency, the applicant is asked to provide further details.

BMSD response: We fully agree that the time of patients´contributions on cohorts is an essential element of data quality relevant for PASS as correct times of exposure and follow-up are key. In general, these MS registries were indeed initiated to evaluate treatments, although primarily more for effectiveness than for safety. Therefore, this has been a major focus the data collection and efforts have consistently been made to ensure accurate documentation of time events. Table 1 below summarizes the BMSD registries' approach in this regard.

For death and loss of follow-up, documentation is always recorded by the clinician, but additional data is obtained by linkage in some cases, either on a regular basis or as an activity within a given project, such as a PASS. If should be noted that according to statistical analysis plans of a PASS, patients are typically censored at the time of the last documented contact.

For all BMSD registries, change of treatment is central to registration and in addition, the reason for discontinuation is mandatory. We have two joint publications focusing on discontinuation of DMT to which all BMSD registries contributed, where the reasons and predictors were analysed for 270,000 treatment episodes in 110,000 patients, based on a data export from 2018, indicating the extent of this information (Spelman, 2021, Front Neurol, 2021 Mar 17:12:647811. Spelman 2023 Front Neurol, 2023 Dec 22:14:1274194).

	REMuS	DMSR	OFSEP	RISM	SMSR	MSBase
Date of death	Date of death is recorded in ReMuS when reported by the treating neurologist. In addition, ReMuS has established a data linkage agreement with the Czech Institute of Health Information and Statistics (ÚZIS) enabling cross-validation with national mortality data. This linkage provides an independent source for verification and ascertainment of death dates. To date, 88% of patients have consented to this linkage.	Available from individual-level linkage to administrative registries, on a project base Also available as variable collected within the DMSR (i.e. registered by the clinician), when variable Termination Date is not missing and termination reason == “Death”. Please see Loss to follow up reasons below.	Opportunistic collection of this data in OFSEP database (=collected if known by neurologist but no specific research of death). Fortunately, for a given project, it is from now on possible to link OFSEP to the national SNDS platform assuring correct information on vital status.	The date and cause of death are available in RISM. They are collected from the attending physician and/or the patient's family members annually.	The SMSreg is linked twice annually to the population registry from Statistics Sweden to provide vital status of patients. Date of death is thus obtained.	Data captured by MSBase investigators in specific outcome field.

Loss to follow up* reasons such as migration, no more visits	Loss to follow-up is determined based on the date of the patient's last recorded visit or an actual loss-to-follow-up record with its date. If no such record exists and no visit has been recorded for more than 36 months prior to data extraction, the patient is considered lost to follow-up from the last available dated record. Reasons for loss to follow-up include: transfer to another MS centre patient decision to discontinue follow-up or informed consent withdrawal; death other/unknown.	Termination Date and Reason for termination available in the DMSR. Reasons include: - Death (registered by the clinician) - Emigration (registered by the clinician. - The information can also be obtained via individual-level linkage to national administrative registries, on a project base - Patient choice (the patient waives continued care/follow up) - Other (recorded by the clinician. It can include moved to another centre)	Data are censored to the last date of clinical visit so no lost to follow up, no reason collected.	Subjects with no recorded visits for at least two consecutive years are considered lost to follow-up. The date of the last visit is considered the termination date	Termination date and termination reason available in the SMSR. Reasons include: - Death (see above) - Migration (registered by the doctor, information also available by linkage to the population registry but not on a regular basis), - The patient waives continued care/follow-up - Other (recorded by doctor)	The only reason for lost to follow-up recorded in MSBase is Death. Records are marked and are considered inactive if no data recorded for 24 months.
Change of treatment	All DMT treatment episodes are recorded in ReMuS with start and stop dates, including the reason for treatment	Available from DMSR and considered a mandatory data element.	Collected in OFSEP database: DMT stop date with reason for stopping, start date.	Information about change of treatment (treatment end date, reasons for treatment discontinuation, start	Available from SMSR as reported by treating neurologists and a compulsory variable. In a validation study	Available in MSBase and considered a key information

	discontinuation or switch. DMT treatment start dates are obligatory; stop dates and switch reasons are also systematically recorded.			date of the new treatment and treatment follow-up) is available in RISM	(Alping P et al. Epidemiology. 2019;30:230–233. PMID: 30721167) on 6,049 therapy events, 91 % were found to be fully correct. For infusions, the rate was 97 %. We believe the data would be better today.	

Table 1. Individual time contributed to cohort

2. Based on the CDM's validation script applied to the translated data, a detailed report in relation to data accuracy and completeness is stated by the applicant to have been completed, however has not been presented. Such a report is of value for the interpretation of the data quality and depending on the content it might contribute to the verification of the validity of the data cleaning, extraction and transformation processes performed. Furthermore, the applicant informs that a 100% success rate is found for translation from the local registry data formats into the CDM, however this has not been documented, and the applicant is asked to present such documentation. Furthermore, the CDM's potential impact on reliability (e.g., transformation can increase risk of error, lower level of precision for individual datasets, and negatively influence timeliness) is valuable for transparency and the applicant is asked to elaborate.

BMSD response: The CDM validation script has been completed by all six BMSD registries. The results of a validation based on an entire registry with a long history will be clearly less generally useful and poorly reflect data availability and quality for specific studies on current treatment. For this reason examples of error and validity log documents have been enclosed presenting simulated data in order to provide an understanding of the format without specific registry information (CDM_error_log and CDM_validation_log)**.**

Translation completeness:

The high success rate refers to the technical success of the Extract-Transform-Load (ETL) process — all records from source registries were successfully parsed and mapped to the CDM schema. This does not imply 100% data completeness — fields that are empty in the source registry remain empty in the CDM. **Across all six BMSD registries, the first CDM transformation covered 348,371 patients (CZE 23,401; DNK 19,097; FRA 77,463; ITA 92,851; SWE 23,832; MSB 111,727) with an information retention rate of 98–100%** (Drahota et al., ECTRIMS 2025, Poster P075; Multiple Sclerosis Journal 2025; 31: (3S) 136–762). Documentation of the transformation process, including mapping rules and any exceptions, is provided (Common Data Model (CDM)_update). CDM transformation success rates by variable group have been presented here (Table 2).

Variable Group	CZE	DNK	FRA	ITA	SWE	MSBase
Patients	100.0%	100.0%	100.0%	100.0%	100.0%	100.0%
Patients Extras	98.7%	N/A	100.0%	51.6%	100.0%	97.0%
Visits	100.0%	100.0%	100.0%	100.0%	100.0%	99.7%
Relapses	100.0%	100.0%	100.0%	100.0%	100.0%	96.8%
Medical Conditions	100.0%	100.0%	100.0%	100.0%	100.0%	100.0%

Variable Group	CZE	DNK	FRA	ITA	SWE	MSBase
CSF	99.9%	99.9%	99.9%	100.0%	100.0%	93.8%
Treatments	100.0%	100.0%	100.0%	100.0%	100.0%	100.0%
MRI	99.5%	100.0%	100.0%	100.0%	100.0%	71.2%
Diagnostic Results	99.8%	N/A	N/A	100.0%	100.0%	98.7%
Pregnancy	100.0%	N/A	N/A	100.0%	100.0%	100.0%

Table 2. CDM transformation success rate

Validation report:

The CDM validation script generates a detailed report on data accuracy and consistency, covering range checks (e.g., discrepant MS onset dates, overlapping treatment dates, discontinuation of a treatment before its initiation); patient clinical and demographic structure (e.g., age, sex, disease duration, geographical region distribution, MS phenotype distribution, DMT history and DMT group structure); cross-variable consistency (e.g., patient records after date of death, age at MS onset/diagnosis distributions); and average gap between consecutive visits (overall visit record density). This report is available for each registry and is demonstrated as simulated data (not reflecting real data) in the accompanying document (CDM_validation_log).

Impact on reliability:

Transformation risks are mitigated by:

- (i) the CDM script being **documented and version-controlled**
- (ii) retrospective validation against published results
- (iii) the federated approach where original data remains at the source registry and CDM conversion is performed locally, reducing transfer-related errors
- (iv) a complete audit trail of each CDM transformation run, documenting the script version, input data timestamp, transformation parameters, and any exceptions or warnings generated

Precision: the CDM preserves the granularity of the source data — no rounding, aggregation, or loss of temporal resolution occurs during transformation.

Timeliness: initial development of a CDM transformation script typically requires 1–4 weeks depending on the source database complexity. Once established, the script requires only minor adjustments when raw database content changes (i.e. when new treatments are to be mapped), CDM updates are implemented, or project-specific requirements arise, adding approximately 1–2 days to the data preparation timeline. A key advantage of CDM adoption is script reusability — since CDM-based scripts are interchangeable across data sources, they need to be developed only once, yielding significant time savings for subsequent projects.

3. Regarding analysis of aggregated vs. individual data, the impact on granularity of data should be discussed. The ability to conduct federated analyses is welcomed, but the applicant should clarify if important clinical circumstances for SAE can be maintained for descriptive analyses based on the

federated approach. It should be elaborated if pooling of individual-level data via meta-analysis is feasible for the entire BMSD network, or if this – due to GDPR restraints – would only be an option for specific PASS using a subset of the BMSD registries as data sources. Moreover, both in the ongoing MANUSCRIPT study and in the finalised Lemtrada mortality PASS, meta-analyses could not be performed due to heterogeneity between registries. The applicant should clarify if such issues are expected to be mitigated with implementation of the CDM in future PASS.

BMSD response: Meta-analysis has been done for some ongoing PASS. Although pooling of data has been possible in the past, reflected in joint BMSD publications, it has become increasingly difficult due to national legislations, and we have recently sometimes had to do without it.

We have not yet tested federated learning in the context of PASS but we have successfully applied the method in the context of an effectiveness study. The way that we perform federated learning the results will be mathematically equivalent to using pooled data so we do not anticipate that federated analysis will pose limitations regarding data. However, it is possible that some methods will be more difficult to carry out within a federated setting. So far, we have applied logistic regression as part of federated learning but we have not yet tested log binomial or (Cox) regression. We do not expect problems using these methods but believe that the challenges will be more pronounced in the context of e.g. random effect and mixed effect models.

It is our understanding that the difficulties in performing meta-analysis in the Lemtrada mortality study were related to differences in treatment strategies in the different countries which is of course a problem not to do with the registries per se but rather a consequence of real-world data reality. Meta-analysis was for these reasons not possible for the Lemtrada study. For the MANUSCRIPT study, meta-analysis was attempted but the results are advised to be interpreted with caution because of inconsistent data qualities across the participating registries (Butzkueven et al, ECTRIMS 2025, Poster P295; Multiple Sclerosis Journal 2025; 31: (3S) 136–762). A CDM is currently not used in MANUSCRIPT and it is our opinion that a CDM would be helpful in this study.

4. For SAE coding, four registries use MedDRA coding, and SMSR as well as DMSR use ICD-10 which are translated into MedDRA based on the OHDSI methodology. For transparency, the quality of this translation should be further discussed in relation to data quality.

BMSD response: We believe this is a somewhat less important aspect as expected. First, in ongoing major MS PASS, there is no translation, ICD-10 and MedDRA-coded events are listed separately. Second, we understand that the ICD-10 to MedDRA list is updated and will be even more complete with time. Third, the PASS we are involved in usually present a specific list for selected adverse events, usually a list of infections plus cancers, so a complete list of translation is not necessarily required. Fourth, we have made an exercise showing that even though translation is not always possible, for the adverse events relevant for a PASS, translation is unproblematic in the vast majority of cases.

Transformation Result	Count of ICD-10 Records	%
Equivalent	3,985	96.40%
Loss of Information	131	3.17%
Unmapped	18	0.44%

Total	4,134	100.00%

Table 3: Real-world validation in ReMuS: In a sample of approximately 1,000 ReMuS patients with 10,720 ICD-10 records, 4,134 records (38.6%) fell within the PASS-relevant code set

5. As stated in the previous QA in relation to data quality, a coordinated approach for the individual registries in relation to rules for data storage, quality-control procedures, and internal audits has not been explicitly stated in the present briefing book. It is acknowledged that some of the aspects are handled similarly between registries, and that all individual registries state to be GDPR compliant, which is expected also to cover data storage. Given the heterogeneity between the registries, individual measures might be sufficient, however more information is needed in relation to the feasibility of a more uniform approach to a minimum data quality standard. In addition, in relation to timeliness it is noted that governance of data requests differs between registries. The applicant is asked to clarify, for transparency, whether it is feasible to have a more uniform approach with shorter timelines.

BMSD response:

Data quality: It is correct that the BMSD registries each are subject to their own governance tradition, technical details and constraints and national legislations. Therefore, it has been a challenge to impose changes to harmonize practices. Instead, we have concentrated to assess the end result, i.e. the coverage, completeness, comparability and interoperability of data, and key to this is obviously the common data model and the validation report.

However, there are principal similarities in how the BMSD registries approach data quality assurance even if the details differ. This includes principles for a) safe data storage with back-ups, traceability of logins and entry of data, b) measures to minimize of errors at data entry with logical checks, drop-down menus and avoidance of open text fields, c) practices for data verification, d) measures to decrease missingness and e) auditing practices. Details for the respective registries are described in the Request Tool Addendum under 2. Methods.

Processes and timelines of data export: To respond to this question, we have forwarded the EMA question on whether timeliness could be improved and received the following responses. Our conclusion is that even though legal constraints and governance structures put limits to the expedience, efforts are being made to optimize the situation. The ability to contribute to the ongoing PASS is also evidence of the feasibility of the registries' practices.

Please find below the individual responses from the BMSD registries:

ReMuS

ReMuS has a governance timeline of from 6 to 12 weeks for the full process, where the difference depends on the study specifics. Project approval and governance processes are fully electronic and use the internally developed system "Argos" utilizing multi-factor authentication (MFA) access.

ReMuS Scientific Board: evaluates the scientific merit and feasibility of each data request. The Board convenes as needed and can provide approval within 1-2 weeks for straightforward or pre-agreed requests.

ReMuS Endowment Fund Managing Board: authorizes the contractual and financial aspects of data access agreements, including Data Transfer Agreements (DTAs) within 1-2 weeks. This step runs in parallel with the scientific review where possible.

Data extraction and delivery: 2-8 weeks, depending on complexity of data set.

Possibilities for shortening processing time:
Pre-approved PASS protocols: For PASS conducted under the BMSD framework with pre-agreed protocols, ReMuS can expedite governance by pre-authorizing data access for the defined scope.

CDM-based federated analysis: When analysis scripts are run locally on CDM-transformed data, no patient-level data transfer is required, eliminating the need for lengthy DTA negotiations.

Standing agreements: ReMuS is developing standing data access agreements with recurring PASS sponsors to minimize re-negotiation for protocol amendments.

DMSR
The expected time for governance of data request is 3-6 months from Steering Committee Approval (plus 8 weeks if data is to be transferred outside of EU). The steps are as follows:

1.The DMSR steering committee meets every 3 months. The applicant should contact the DMSR in advance for guidance on completing the data application and get next meeting date.
2. If the project is approved by the steering committee the aim, documentation, and data request are subject for legal scrutiny before data transfer can be granted.
3. If data is to be transferred outside of EU an approval from The Danish Data Protection Agency – which adds another 8 weeks to the time of governance.

The time is shorter if the application is well prepared and meets the requirements for aim, understanding of the data, sufficient documentation for needed data etc.

OFSEP
6 to 9 months from the first contact until the first report availability.
The delay has been shortened for EMA/FDA/ANSM validated protocols (scientific board information instead of full evaluation, steering committee's validation only required).
Contracting for projects is facilitated and therefore accelerated by the establishment of prior partnerships.
Communication with pharmas organized to encourage them to consult us as soon as the protocol is drafted.

RISM
Data requested for research projects must follow the following procedure: submission of the project to the Management Committee (Prof. Maria Trojano and Prof. Mario Battaglia), then to the Scientific Committee of the Italian MS Registry for approval; feasibility analysis, data extraction. The estimated time for this process is approximately 3 months. However, requests from institutions or Regulatory Agencies may be handled promptly (less than 1 month).

SMSreg
Applications for data extraction for research projects are submitted to the Swedish Neuroregistry and the forwarded to the research committee provided an ethical permit is in place (an ethics review procedure itself takes approximately one month from submission to approval). Final approval is granted by the register holder before data is released. In recent years, the research committee, which assembles digitally when required, takes around one month on average to reach a decision. A final approval is then made by the registry chairman. All-in-all, time from application to data export will be approximately two months.

However, changes are being imposed on all Swedish quality registries regarding their governance, giving hospital bodies a more important role and decisions transferred from registry chairmen and research committees to hospital officials in order to make the administration of different registries more similar. Whether this will mean a briefer or longer turn-around time for the SMSreg is uncertain.

MSBase
MSBase data access approvals are completed, on average, in 6 weeks. Rapid approvals can be done by request and with approval of the Scientific Leadership Group.

6. Please discuss whether all individual registries as well as the BMSD network support/allow external monitoring besides NCAs and allow other EU regulatory authorities inspection overall and in relation to specific PASS. National monitoring?

BMSD response: The auditing practice and audit trail have been described for the BMSD registries as part of the REQueST tool (tabs "2. Methods" and "7. Additional elements"). At the national level monitoring can vary within the network but all the BMSD registries have auditing procedures in place and some are also in the process of further development. These auditing procedures include mainly IT / software solutions but there can also be some semi- manual audits performed. Audits can be performed on a regular routine basis or in connection with potential specific issues or projects.

Below is a brief description of of the audit procedures of the BMSD registries:

ReMuS: Auditing procedures includes quality audits in place such as iMed software. There is also an IT audit in place, which is focused on general IT and data security. All the MS centres are also monitored on semi-annual and yearly basis. All research contracts between the ReMuS Endowment Fund and MAHs or study sponsors for PASS conducted using ReMuS data include a binding provision requiring ReMuS to allow regulatory inspection of the registry-based study. This clause is consistent with the EMA requirement that research contracts shall include a requirement to allow a possible regulatory inspection.

DMSR: Auditing procedures include the Regional Clinical Quality Databases performing audits to parts of the DMSR at some years intervals. In addition, the registry itself conducts frequent ad hoc quality checks. The current audit capacity is limited by comparing monthly full data extracts to each other and performing internal checks on core variables. Ad hoc audits are performed in connection to specific projects (several times a year).

OFSEP: Auditing procedures include on-site audits for all centers, required for participation in the OFSEP registry. The audits are not conducted specifically for safety studies or a project, but rather at the behest of OFSEP coordination team if certain conditions apply. With respect to the software, there is no audit trail, just a date of modification and name of the person who performed the change in the file. This makes comparisons between different time points possible. Furthermore, it is possible to perform, if necessary, a local verification from the source paper medical file. In the future, the next EDMUS software version (called "Plateform") is slated to have an audit trail for each data field.

RISM: Auditing procedures include periodical contact of the different sites with ad hoc reports of specific queries. The current audit capacity is limited by comparing six-month performances on data quality indicators. The data entry system runs a site-visible audit file which is uploaded to a central server. A SOP to define the audit procedures is being developed.

SMSR: Auditing procedures include the Karolinska Hospital and the Karolinska Institutet. The hospital can audit registry activities including data storage and handling of the data until it is formally exported.

The Karolinska Institute itself can be audited by the MPA as well as by the National Board of Health and Welfare.

MSBase: Auditing procedures include an external IT company performing annual, full security reviews on all MSBase systems. Auditing of the completeness of the minimum dataset is suggested to all member sites but not enforced or audited. The missing data elements to achieve complete minimum dataset records is always available to investigators. For the safety studies, site payment/reimbursement for administrative costs is linked to data completeness. In MSBase, the current audit capacity is limited to comparing monthly full data extracts to each other. However, in 2021 MSBase launched an audit trail in it is data entry system that can be accessed at the centre level. Commercial partners can audit relevant MSBase data onsite. Regarding a data integrity audit at the site level, this is possible but needs to be performed at each site as MSBase only stores de-identified data.

As regards PASS and external partners all participants will have to agree to the conditions specified in the study agreements. Conditions for audits are thus contractually specified.

7. Given the regional variability of readily available agents (in relation to experience of use and reimbursement), and that this may modulate the representativeness of the findings from individual registries for particular research questions (e.g. drug utilization, other descriptive risk characterization issues, and identification of ADRs), the network is invited to discuss which measures are in place to deal with variability of use. Specifically, the applicant is asked to elaborate on the representativeness of each individual registry with regards to the overall EU prescription patterns in terms of the presently used DMTs and - within reasonable limits - the sequence of use of DMTs.

BMSD response: Representativeness is indeed a critical quality aspect of real-world data. In the setting of PASS, however, where most typically the safety of a newly approved DMT is compared to one or a group of already approved DMTs, the critical condition for a national registry to contribute to a study is that the DMTs in focus are indeed used, i.e. approved and reimbursed in the respective country. This is not always the case for MS DMTs, for instance in an ongoing PASS on Vumerity (diroximel fumarate, Biogen) only France, Denmark and Sweden could participate due to this DMT not being in use in Italy or Czechia.

As noted in the List-of Issues document, the five European national MS registries within Europe have a high or very high population coverage, making them obviously representative of the respective population. In a pan-European perspective, BMSD mainly represents countries with a high degree of DMT use for MS making them somewhat less representative for countries in eastern Europe or in the Balkans. MSBase, which is center-based, may partly compensate for this.

Table 4 below shows the distribution of DMTs in the five national BMSD registries according to the last recorded information for each patient compared with what has been reported for Europe by the WHO, in general high income countries and globally, as reported by the World Atlas of MS, published in 2020 by the International MS Federation. Although there is some variation in prescription patterns, the patterns align rather well, except for Sweden (see next paragraph).

% of people treated with each DMT	Czechia	Denmark	France	Italy	Sweden	High income countries*	WHO region European*	Global results*
	Feb-26	Feb-26	Dec-25	Jan-26	Jan-26	Of people with MS on DMT, proportion on each DMT		
Alemtuzumab	1%	<1%	0%	1%	<1%	1%	2%	1%
Cladribine (oral)	9%	5%	1%	5%	3%	3%	3%	2%
Dimethyl fumarate	6%	13%	7%	14%	6%	21%	21%	19%
Diroximel fumarate	not used	1%	1%	not used	<1%	0%	0%	0%
Fingolimod	7%	7%	8%	7%	4%	12%	12%	13%
Glatiramer acetate	9%	2%	7%	8%	1-2%	12%	11%	10%
Interferon-beta 1a	9%	3%	10%	12%	1-2%	9%	10%	11%
Interferon-beta 1b	1%	<1%	4%	3%	<1%	6%	6%	6%
Natalizumab	7%	11%	8%	9%	9%	8%	8%	7%
Ocrelizumab	18%	19%	14%	13%	<1%	9%	10%	8%
Ofatumumab	11%	15%	5%	5%	1-2%	0%	0%	0%
Peginterferon-beta 1a	3%	<1%	1%	2%	<1%	3%	3%	3%
Ponesimod	5%	not used	1%	1%	<1%	0%	0%	0%
Rituximab	1%	7%	5%	1%	63%	2%	3%	5%
Siponimod	3%	<1%	0%	2%	<1%	1%	1%	1%
Teriflunomide	8%	12%	9%	9%	2%	10%	9%	10%
Ublituximab	Not used	2.7%	Not used	Not used	Not used			
Ozanimod	4%	Not used	Not used	Not used	Not used	*From Atlas of MS, 3rd Edition, IMSF, 2020		

Table 4. Treatment patterns in the national BMSD registries

The oddity of the Swedish DMT prescription pattern where rituximab, although formally off-label, dominates to the extent that other DMTs may be used only in special situations. This was highlighted by the Lemtrada mortality PASS (referred to in the List-of Issues document) where in the end patient groups were found to be so different in characteristics, that they could not be meaningfully combined. We believe, therefore that any given PASS would anyhow need to be adapted to the study specifics based on the availability of patients. We also believe that the issue of representativeness is foremost important in studies of natural course rather than PASS or PAES.

The question of sequencing of treatments is clearly relevant and a topic of much debate in the MS community, where the practice to initiate treatment with a moderately efficacious DMT and change to a highly efficacious DMT only in case of breakthrough disease. Here, the BMSD registries, representing countries of different practices, have been able to shed light on the importance of early use of highly efficacious DMT through the differences between the registries rather than through similarities through two important publications (Spelman T, et al. Treatment Escalation vs Immediate Initiation of Highly Effective Treatment for Patients With Relapsing-Remitting Multiple Sclerosis Data From 2 Different National Strategies. JAMA NEUROLOGY 2021 78;10 1197-1204; Hrnciarova T, et al. Does initial high efficacy therapy in multiple sclerosis surpass escalation treatment strategy? A comparison of patients with relapsing-remitting multiple sclerosis in the Czech and Swedish national multiple sclerosis registries. Multiple sclerosis and related disorders 2023 76; 104803-).

Issues to be addressed both in writing and during the discussion meeting with a Powerpoint presentation due by 5 March.

8. Fitness-for-use of the BMSD has been largely demonstrated. However, some aspects regarding the availability of data element remains unclear. In ongoing causal PASS, covariates such as comorbidities, BMI, familiar or genetic risk of malignancies, and concomitant medication use were largely not available in the registries where linkage is not yet established, thereby limiting confounding control methodologies. There is also uncertainty regarding the availability of other data elements required for research questions not considered in the core protocol for PASS, but

which are likely to be of interest from a regulatory perspective. This includes data for descriptive risk characterisation purposes (e.g. event severity and clinical course) and evaluation of effectiveness of risk minimisation measures (e.g. compliance to a contraindication). Pregnancy outcomes are captured in SMSR and DMSR via linkage, but availability in the other registries is unclear and there is no ongoing study as proof-of-concept. The applicant is asked to clarify these aspects, discuss the impact on overall fitness-for-use and how these limitations could be further minimised in the future.

BMSD response: It is obviously a challenge to use registry data to assess adverse events with regard to severity and confounding factors as is possible in a formal phase IV study. In fact, ordinary pharmacovigilance reporting of AEs also struggles with confounders, and the severity assessment is probably less precise compared what can be obtained in a clinical setting. So, we admit that this is weak spot for registry-based PASS. However, we already have some experience from ongoing PASS to refer to.

With regard to severity assessment of adverse events, data are indeed collected, and there is a methodology to assign severity from linked data. It is described in the Feasibility Study report on page 21 how this is done for the SMSR. For instance all malignancies are by definition severe. A similar approach has been applied in the ongoing MANUSCRIPT PASS. For linked data from DMSR, all AEs derive from hospitalizations and are therefore considered as severe. OFSEP has a severity rating for AEs. The Italian and Czech registries as well as MSBase collect only AEs considered severe or of special interest.

Regarding confounders there is indeed a limitation as described above, and for instance concomitant medications are collected for MSBase but at an unknown rate. However, there is indeed some information available to analyse contraindication, e.g. JC-virus antibody titer index which is collected by all registries for patients where treatment with natalizumab is considered or ongoing.

MS course (RRMS, PPMS, SPMS) is indeed collected mandatorily by all registries.

Pregnancy data are indeed collected by all BMSD registries although the completeness is not validated (described in the request tool). Thus, 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 collect data at a moderate level and RISM at a lower level. Pregnancy variables are indeed part of the CDM. Thus, it is possible to collect pregnancy data for BMSD however with variable coverage. Accordingly, there are ample opportunities but lacking track record.

Future: As has been shown in the case of the Covid-19 pandemic and the mandatory questions regarding malignancies, non-melanoma skin cancer and treatment-related infections included for PASS, new variables of great importance can indeed be included when motivated. We foresee that linkage to external data bases will gradually be made possible outside of the Nordics, where efforts are being made in France, Czechia and Italy.

Here is more information from the BMSD registries, collected to respond to this issue:

ReMuS

Since 2024**,** recording of comorbidities has been substantially improved and standardised to MedDRA nomenclature**.** ReMuS has established a data linkage agreement with ÚZIS, which maintains comprehensive national administrative healthcare data including ICD-10 coded diagnoses from all healthcare encounters. For specific PASS protocols requiring detailed comorbidity information, enhanced prospective data collection can be implemented at participating MS centres.

Concomitant (non-MS) medication is not systematically captured in ReMuS. However, MS-specific treatments (DMTs, corticosteroids, symptomatic MS treatments) are comprehensively recorded. For non-MS concomitant medication, the ÚZIS linkage will provide access to national pharmacy dispensation data, enabling reconstruction of the patient's full medication history. The National Register of Reimbursed Health Services (NRHZS) maintained by ÚZIS contains records covering all reimbursed healthcare services and pharmaceuticals for all patients within the Czech Republic healthcare system.

ReMuS systematically captures pregnancy-related data. A published registry-based analysis demonstrated the breadth of available data: 1,533 pregnancies were analysed from the period 2013 to 2019, evaluating the impact of pregnancy, delivery, and miscarriage/abortion on MS disease course in Czech women with MS (Hradilek, P., Meluzinova, E., Zapletalova, O., Hanulikova, P., Horakova, D., Woznicova, I., Pavliska, L., Stetkarova, I., Valis, M., Stourac, P., Adamkova, J., Ampapa, R., Vachova, M., & Mares, J. (2022).

The CDM transformation achieves 100% success rate for the Pregnancy variable group in all registries where pregnancy data are collected. While ReMuS does not have linkage to national birth registries at present (unlike SMSR and DMSR), the direct clinical capture of pregnancy events combined with the benchmarking-driven quality assurance programme ensures that pregnancy data in ReMuS are fit for purpose for PASS requiring DMT safety evaluation during pregnancy.

DMSR

The DMSR does not collect information about neither concomitant medical conditions nor concomitant medications. This information is however available through patient-level linkage to national administrative databases on a project-base.

OFSEP

Concomitant medical condition and concomitant medication not available in OFSEP database. OFSEP data linked to the SYSTÈME NATIONAL DES DONNÉES DE SANTÉ (SNDS) database can be used to include concomitant conditions and medications collection in specific studies.

RISM

In RISM, comorbidities are recorded in a dedicated section using ICD-9 codes. The estimated level of completeness reported in the Request tool (approximately 10-25%) refers to the overall data collected throughout the registry in over 180 MS centres since 2000. In patient subgroups such as patients treated with DMDs or patients with first access to centres after 2014, the percentage reaches more than 50%. With regard to concomitant medications, data completeness is similar to that of concomitant medical conditions.

SMSreg

Information on concomitant medical conditions and concomitant medications is not systematically collected within the registry. Such information can be obtained through patient-level linkage to national health registers on a project-specific basis, co-morbidities from the National Patient registry and Cancer registry and medications from the national prescription data base, which handles all prescribed drugs and soon will be expanded to also include infusion medications given by health care units.

MSBase

MSBase allows for full documentation of medical conditions using the Medical Dictionary for Regulatory Activities (MedDRA). However, this is not part of the minimum dataset, and data completion is 50-

74% as stated. In the safety cohort study nested in MSBase, which involves 41 centres and prospective safety monitoring of around 28000 patients, significant medical conditions are well documented. Overall, Cardiovascular risk factors are the most common medical conditions recorded. Concomitant Medications are poorly documented in MSBase. The MSBase allows for documentation of symptomatic treatments for MS and can record other medications, but these fields are not mandatory and not used often.

9. For RISM and MSBase, it is noted that these two registries collect data overall, but also for selected groups of MS patients on a project-basis for specific PASS. Data completeness consequently seems to some degree to depend on agreements made for each PASS to be conducted using RISM and MSBase If possible, for specific PASS, the applicant should present percentages of missing information on essential variables based on the RISM/MSBase to clarify further whether the completeness information in the Request tool applies both to the overall registry or also to specific PASS. Please also discuss the feasibility of using RISM/MSBase in relation to retrospective data, or whether the RISM/MSBase mainly provide sufficient data based on specific protocols for prospective data collection.

   RISM / MSBase responses:

   RISM: The collection of adverse events in RISM is not limited to the context of specific PASS studies, but it is an integral component of the routine general clinical data collection framework. Adverse events are coded using MedDRA terminology (version 24.0), ensuring standardized and harmonized reporting across centres. LLT is mandatory.
   With regard to the statement in the Request tool that less than 10% of adverse events are collected, this figure refers to the overall percentage of adverse events collected throughout the registry in over 180 MS centres since 2000. Importantly, in recent years targeted training activities have been implemented for all RISM-App data users to improve the characterization and consistency of adverse event reporting across the registry, with the objective of enhancing overall data quality and completeness. Therefore, in patient subgroups such as patients treated with DMDs or patients with first access to centres after 2014, the percentage reaches more than 50%. Moreover, the level of data capture within dedicated PASS settings, where adverse event reporting is typically more systematic and comprehensive, is much higher (80-90%). Therefore, RISM is able to collect adverse event data and can support retrospective PASS analyses, acknowledging the usual limitations inherent to real-world observational data.

   MSBase: MSBase is conducting a large prospective safety study at 41 centres, involving more than 28000 patients. In this study, investigators report both the incidence of new significant and serious adverse events at least annually and also document their absence. For example, Investigators are questioned: did the patient have a cancer/skin cancer/ herpes zoster/serious infection /other serious/significant event since the last visit? Each of these 5 questions is answered with yes/no, and responses are recorded at each clinic visit. We use this dataset to participate in various PASS projects (currently three). These data are around 90% complete and comprehensive. Outside the safety study, safety data completion varies widely by centre, ranging from 25% to 95%.

10. At this point, not all individual BMSD registries demonstrate fitness-for-use for all relevant research questions for PASS (e.g. pregnancy outcomes, evaluation of effectiveness of risk minimization measures, though pending responses to this list of issues). However, the network as a whole might be fit-for-use for most conceivable research questions, considering that those BMSD registries

most suitable for a specific PASS (and a specific research question) would be identified via feasibility assessment as part of study planning - i.e., a pregnancy PASS would be conducted only using those registries from the BMSD network which adequately cover relevant pregnancy data elements (e.g. DMSR & SMSR at present). The CoU for each single registry on the other hand may need to be refined based on fitness-for-use for relevant research questions. The Applicant is asked to discuss how the CoU for the individual registries could be phrased/refined to reflect which kinds of PASS/research questions can be addressed in each of the registries and which (currently) cannot while acknowledging that the registries are still evolving. The applicant is invited to comment and amend the following potential CoU wording:

BMSD response: We recognize that study specific details will in many cases determine if a certain BMSD registry can or cannot participate in a given PASS. As an example, in the Vumerity PASS, as mentioned above, only DMSR, SMSR and OFSEP participate given that Vumerity is not used in many countries. In addition, in a recent drug utilization study, with safety aims, on Lemtrada, the SMSR could not contribute due to requirement of extensive laboratory data, and linkage to lab data is not yet in place in Sweden (although efforts are ongoing), whereas DMSR and ReMuS could join. A third example is a recent comparative study between the intravenous and subcutaneous administrations of Tysabri which was performed only in the SMSR due to availability of dosing information only there. In contrast, all BMSD registries contribute to the MANUSCRIPT PASS except for ReMuS, which no doubt would have joined if the study had been initiated somewhat later. We foresee such study specific challenges to be common in future studies too resulting in variable numbers of BMSD taking part in each study.

Accordingly, we agree with the following statement that a BMSD-based PASS can be:

A) Conducted using on data from the BMSD network applying the common data model. Selection of BMSD registries (all or a sub-set) as data sources for a PASS will be based on a study-specific feasibility assessment, or

B) Conducted using data from a single BMSD registry only (DMSR, SMSR, ReMuS, RISM, MSBase, or OFSEP). A study-specific feasibility assessment would confirm the suitability of a given registry for the PASS.