BMSD Feasibility Study

This document aims to describe how adverse events (AEs) are captured across the individual BMSD registries and to assess the comparability of the reported serious AE (SAE) incidence rates (IR) between them. In the absence of absolute reference values for SAE rates, we utilize the possibility to link registry data to national healthcare databases, available in Sweden and Denmark, to capture reported events of malignancies and serious infections and apply those as a measure of comparison. The national healthcare databases in both countries include data from the cancer registry which contains verified primary tumours, data from hospitalizations and data from outpatient specialist care. For this purpose, we make use of data used in an ongoing post-authorization safety study (PASS) - the MANUSCRIPT study by Roche (protocol number BA39730) – and data used in the External Cohort Comparison Study (ECCS) to support OBS13434 feasibility study by Sanofi.

Material

MANUSCRIPT study by Roche

The MANUSCRIPT study is a multi-source, multi-country, non-interventional, longitudinal cohort study based on secondary use of data. The research question is to assess and characterize the long-term safety profile of ocrelizumab in the real-world setting. This study was initiated in 2019

Participating registries: MSBase registry (study period: January 2018 – November 2023), French MS registry (OFSEP) (study period: January 2018 – June 2023), Danish MS registry (DMSR) (study period: January 2018 – May 2023), Swedish MS registry (SMSR) (study period January 2018 – July 2023) and Italian MS registry (RISM) (study period: January 2018 – November 2024). The data used in the analysis here were part of the 2nd interim report (for MSBase, France, Denmark, and Sweden) or part of the 12th semi-annual report (for Italy) of the MANUSCRIPT.

Population: Relapsing MS (RMS) patients over the age of 18 years from the comparator cohort were included in this analysis. These were newly treated patients with any disease modifying treatment (DMT) starting after the date of Ocrelizumab approval within each country. The DMTs included in the comparator cohort were Interferons, Glatiramer acetate, Natalizumab, Fingolimod, Teriflunomide, Alemtuzumab, Dimethyl fumarate, Cladribine and Mitoxantrone.

Outcomes: The outcomes of interest for this study were malignancies, overall and by subtype, and serious infections, overall and by subtype. All outcomes were defined as the first new event during the exposure period based on extensive lists of Medical Dictionary for Regulatory Activities (MedDRA) codes and lists of codes from the 10th revision of the International Classification of Diseases (ICD-10).

Exposure period: Two different follow-up period models were considered depending on the outcome of interest. For malignancy outcomes an ever-exposed follow-up model was applied where the follow-up started on the day of DMT initiation and ended on the date of the adverse event, date of death/loss to follow-up, last date of data availability in the registry or study end, whichever occurred first. For the serious infection outcomes, a time-on-drug follow-up model was adopted where the follow-up period started on the day of DMT initiation and ended at the earliest of the end date of the risk window after the treatment stop, the date of the adverse event, date of death/loss to follow-up, last date of data availability in the registry or study end.

External Cohort Comparison Study (ECCS) to support OBS13434 feasibility study by Sanofi

This study aimed to evaluate the feasibility of employing an external cohort design focusing on the incidence rates of adverse events of special interest (AESI) in multiple sclerosis by efficiently leveraging the then ongoing investigations from the Alemtuzumab Mortality Post Authorization Safety Study (PASS, EUPAS42543). This study was performed during 2024.

Participating registries: Danish MS registry (DMSR) (study period: September 2013 – November 2022), Swedish MS registry (SMSR) (study period: September 2013 – December 2021) and Czech MS registry (REMUS) (study period: January 2015 – October 2022).

Population: Eligible patients were patients with MS over the age of 18 years who initiated high efficacy DMTs (Alemtuzumab, Rituximab, Ocrelizumab, Cladribine, Fingolimod, Mitoxantrone, Natalizumab, Ofatumumab, Ponesimod, Ozanimod and Siponimod) after the date of alemtuzumab's approval within each country.

Outcomes: The outcomes of interest for this study were serious infections overall including opportunistic infections and malignancies overall excluding non-melanoma skin cancer where the incident cases were defined as the first occurrence of an adverse event identified based on extensive ICD-10 code lists.

Exposure period: For each patient the start of the follow-up period corresponds to the first day of the DMT initiation and the end of the follow-up period was defined as the first occurrence of an adverse event, the date of death, emigration, last update of vital status, lost to follow-up or end of study whichever occurs first.

Methods

The BMSD feasibility study is made up of three sections listed below:

1. **Adverse event collection routines.**
   In the first part of this study, each participating registry provides a comprehensive description of the procedures in place for adverse event collection. This includes the expectations placed on the neurologists, the workflow and routines followed, and the key variables and data fields used in the respective data collection platforms. Visual summaries or performance indicators are presented whenever available, to illustrate the effectiveness of these systems in practice. This detailed overview is intended to give a broader understanding of how the AE collection systems function across countries/registries and highlight potential sources of variation in AE reporting.
2. **Comparison between MS registry collected adverse events and events captured in public healthcare databases.**
   For the Swedish and Danish MS registries that have the possibility to link their patient data to national healthcare databases containing all possible diagnoses, a direct comparison of SAE IRs calculated separately from the two sources (MS registry and national database) is performed using data from the ongoing PASS, MANUSCRIPT. The outcomes of interest are malignancies overall and by sub-type and serious infections overall and by sub-type. Crude incidence rates for all outcomes are calculated as number of incident cases per 100 person-years as described in the study's statistical analysis plan (SAP). The comparison of the crude IRs within each country is done by means of rate ratio as: crude IR based on national healthcare data / crude IR based on MS registry data and presented with 95% confidence interval (CI). The national healthcare databases include data on specialist care, hospitalizations and morphologically determined

cancers in both countries and are considered good comparators for this purpose as they have high, nation-wide coverage and are not disease specific, so are therefore considered unbiased.

3. **Comparisons between BMSD registries.**
   National healthcare databases are not readily available for linkage in the rest of the BMSD countries and therefore a direct comparison of the MS registry-based IRs to the national healthcare-based IRs, as for Sweden and Denmark above, is not possible. For this reason, we implement an indirect comparison using the Swedish national healthcare data-based IRs as reference. We use the data from the MANUSCRIPT PASS study, as before, and from the ECCS feasibility study. Crude incidence rates are calculated for malignancies and serious infections as number of cases per 100 person-years as per the studies' respective SAP. To account for differences in age and sex distribution among the BMSD populations standardized incidence rates (SIRs) are calculated by direct standardization method using the combined population as reference. The comparison between the BMSD registries and the Swedish national healthcare databases is done by means of rate ratio as: BMSD SIR/Sweden SIR and presented with 95% CI.

Results

1. Adverse event collection routines

Czech Republic (REMUS)

Adverse event collection is an integral part of the monitoring process in REMUS. Neurologists are required to ask patients about potential AEs at every visit, and to record them systematically. The data entry process follows a structured workflow in the registry recording system, iMed, which is designed to ensure standardized reporting.

An overview of the process:

- **Patient Reporting:** Neurologists ask patients about any potential AEs since the last visit. Serious or important events (with regards to presence of MS) are required to be reported. Also, absence of such event is required to be positively confirmed in 5 security questions at every visit. This is a mandatory step in the patient's visit documentation.
- **Data Entry:** The patient's response is recorded directly in the hospital information system and simultaneously *(or subsequently - depending on local setting of the MS centre processes)* also in the registry recording system (iMed), where a structured form is used (Figure CZE1 and CZE2).
- **Classification & Coding:** AEs are categorized using MedDRA (currently version 27.0). MedDRA coding is mandatory for all the newly entered events from June 2023 with free-text entry available for additional details. Retrospective records on AEs were captured by predefined lists and can be converted to their MedDRA equivalent event, if needed, based on the clinical documentation or local investigation.
- **Verification & Submission:** The iMed system does not allow entering any non-MedDRA records *(since June 2023).* Data on AEs are an integral part of the registry exports from local MS sites to the registry repository (performed regularly every 6-months or as needed). Once the data is in the repository, multiple checks are being run such as completeness of the security questions, missingness of an AE record if the response to any safety question is positive, benchmarking of incidence rates across MS sites to detect any eventual systematic error.
- Pharmacovigilance (PV) reporting is solely the responsibility of the medical personnel directly to the regulatory bodies or MAHs as required by the PV rules. The iMed system is however

notifying the user about this obligation anytime when entering AE relevant for the need of PV reporting.

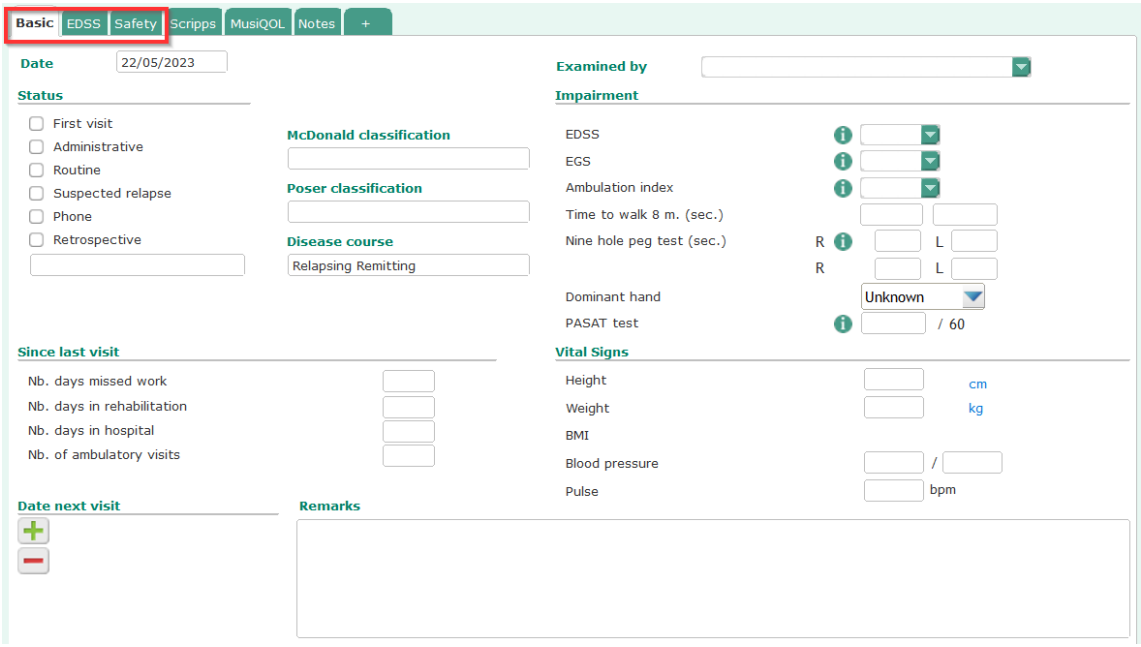

Figure CZE1. iMed data entry module dedicated to patient visit recording.

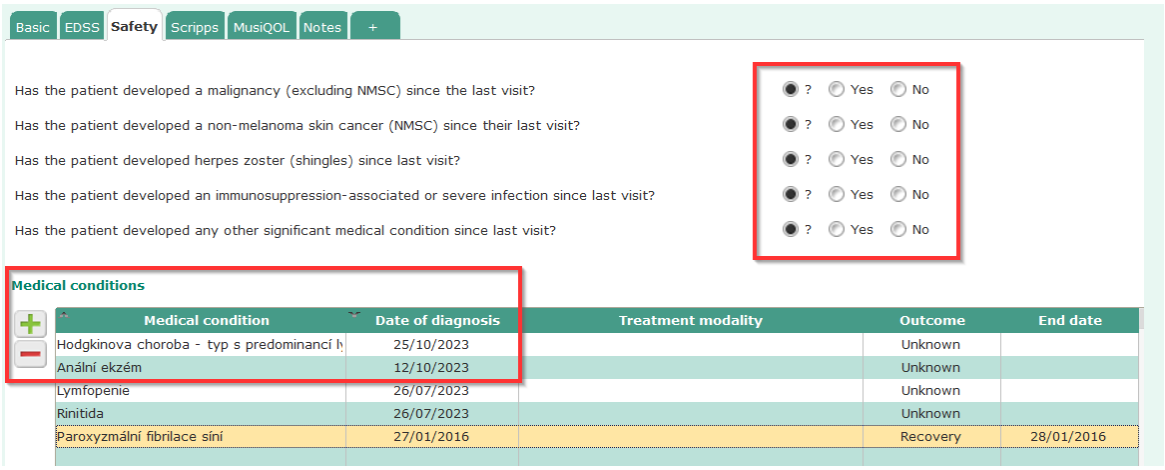

Figure CZE2. iMed data entry module for reporting safety events with the 5 security questions.

As the systematic routine reporting of AEs is still quite recent, no measurements/indicators of global registry incidence rates are yet available. However, preliminary figures from the latest analyzed data show that the general response rate to the 5 security questions is over 98 %.

Denmark (The Danish Multiple Sclerosis Registry - DMSR)

Data on the occurrence of adverse events are collected during the patient's visit to a neurologist at each MS centre in Denmark. The neurologists are required to ask the patient regarding adverse experiences since the last visit and record it. The COMPOS platform that the Danish MS registry (DMSR) is using provides an easy way to register all relevant information and in the *Besøg* (*Visit*) module (Figure DEN1) there are several mandatory fields that need to be filled in during a visit including the question "*Har der været bivirkninger siden sidste besøg?*" (*Have there been adverse*

events since last visit?). The neurologist selects an option *Ja/Nej* (*Yes/No*) from a drop-down menu. However, although the fields are mandatory to fill in, they are not transferred to DMSR but serve as a reminder for the neurologist and a quality control for the DMSR.

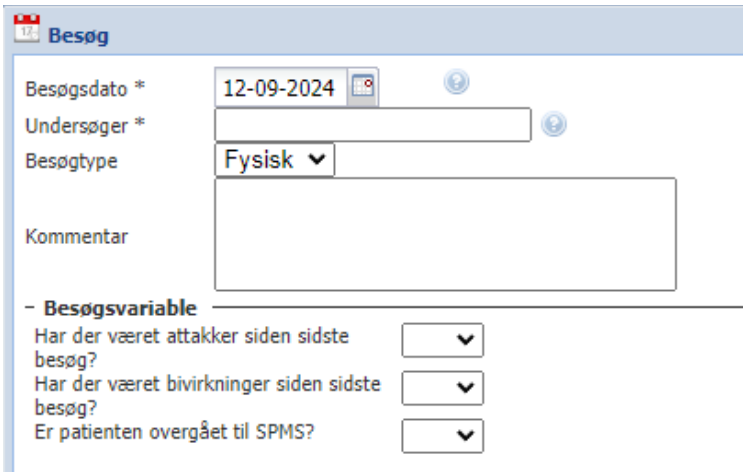

Figure DEN1. Screenshot of the Visit (Besøg) module in the DMSR COMPOS system.

In case there has been an adverse event (answer “Ja” to this field), when the *Besøg* module is saved the Adverse Event module opens and the neurologist can enter the AE details (this can also be done later).

To complete an AE report, information about the date of the event, the treatment suspected, and the action taken regarding the treatment are required. The platform automatically lists all ongoing treatments at the time of the event and the neurologist can select the suspected treatment from the available list or register a new drug at a later step. The options available for the action taken field in the drop-down menu are: *unchanged, lowered dosage, increased dosage, temporarily stopped, permanently stopped, unknown, and Irrelevant* (Figure DEN2).

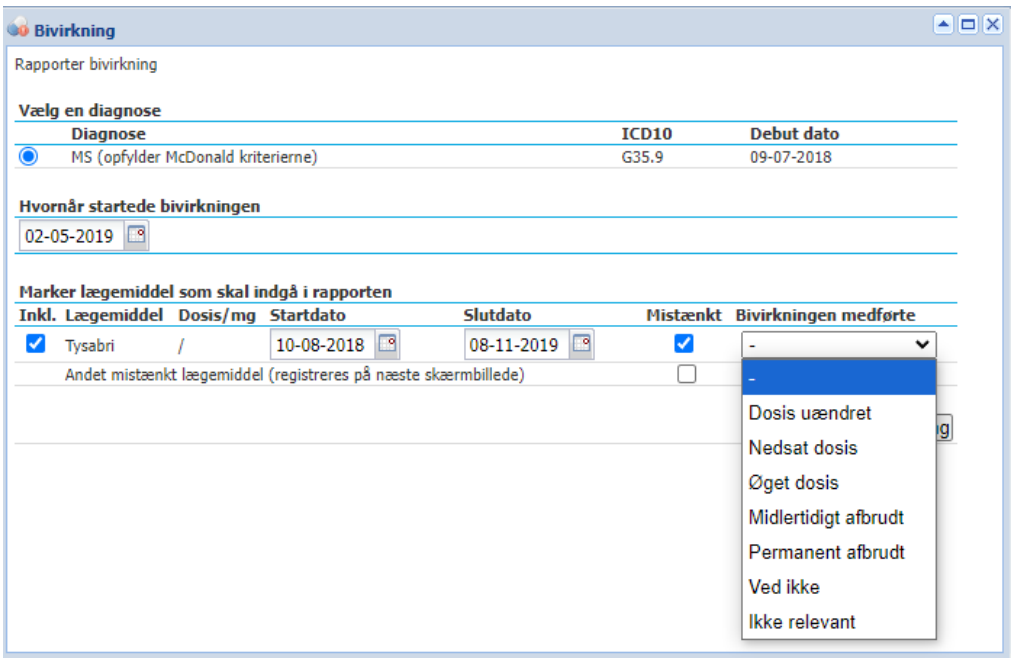

Figure DEN2. Screenshot of the DMSR Adverse Event (Bivirkning) module

Next, detailed information about the event is required such as the diagnosis (*Bivirkningens diagnose)* and ICD-10 code of the adverse event, as well as the level of seriousness of the event (*serious or*

mild/moderate). If the AE is serious the seriousness criteria (*the patient has died, life-threatening, need for extended care, disability, resulted in birth defect, other serious adverse event*) need to be filled in along with what the course entailed (*life-threating condition, prolonged care/hospitalization, death, disability or significant functional impairment, none of the above*) all with options in drop-down menus (Figure DEN3). If the AE is *Mild/Moderate* only the information on what the course entailed is available.

The AE diagnosis can be selected from a drop-down menu which includes around 90 items, and the corresponding ICD-10 code is added automatically. The diagnosis can also be selected from the ICD-10 code drop-down menu in which case the corresponding text will be added automatically. If the diagnosis is not among the pre-defined, 'Other' can be selected and the ICD-10 needs to be added manually. The drop-down list can be expanded with new diagnosis if needed.

Figure DEN3. Screenshot of the DMSR Adverse Event (*Bivirkning*) module cont.

Once all the necessary information is recorded in the system, the report is saved.

The fields regarding adverse event reporting at each visit were introduced in 2018 for the "*Har der været bivirkninger siden sidste besøg?*" (*Have there been adverse event since last visit?*). As mentioned above, this field is not transferred to the DMSR. While the DMSR do not register the number of annotations, the number of visits has increased throughout the years (Figure DEN4).

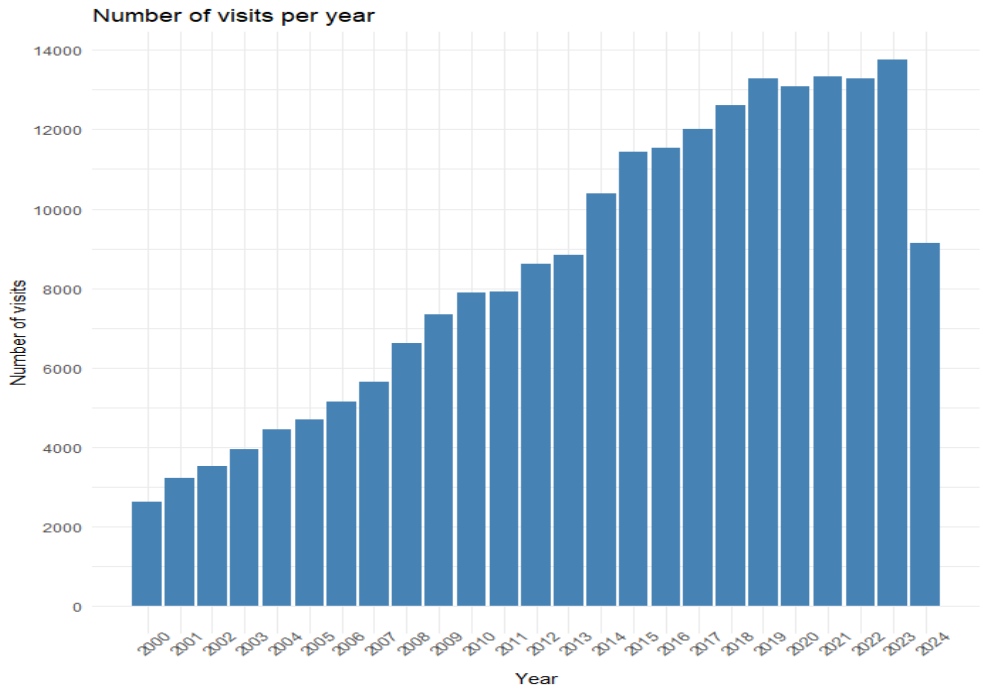

Figure DEN4. Number of visits per calendar year recorded in the DMSR between 2000 and 2024.

France (OFSEP)

Data on the occurrence of adverse events are collected during the patient's visit to a neurologist participating to OFSEP (France). The neurologists are required to ask the patient regarding serious adverse experiences (SAE) since the last visit and record it. Moreover, most treating neurologist receive letters from other physicians or results of laboratories if an important health problem is detected in their patients, which increases the completeness, and the robustness of the data collected. The minimal dataset form (https://www.ofsep.org/fr/FicheMinimaleOFSEP) has a dedicated question related to SAE (Figure FRA1) which in association to the SAE form (https://www.ofsep.org/fr/FicheMinimaleOFSEP_EIG) proposed to neurologist, is an easy way to collect all relevant information. The collection of SAEs is mandatory whatever the treatment of the patient and even if he is untreated and it is specified that the collection include non-melanoma skin cancers.

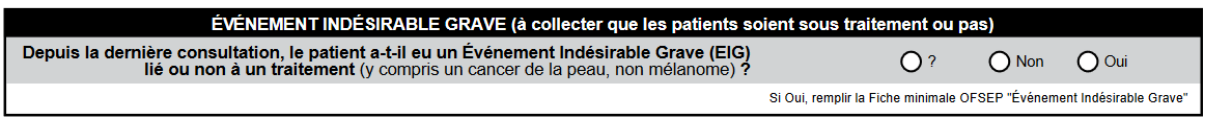

Figure FRA1. Question in the minimal dataset form regarding serious adverse experiences.

Data collection in EDMUS software

Specific rules for data collection in the EDMUS software are available (https://www.ofsep.org/fr/Guide_Utilisation_Saisie_FicheOFSEP). If no SAE occurred, by consign all "intercurrent diseases" needs to be assigned to "No" (Figure FRA2a/FRA2b).

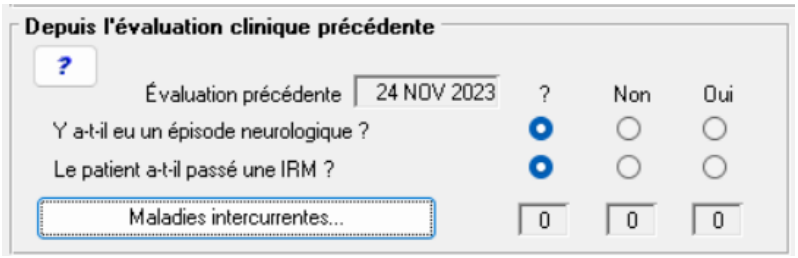

Figure FRA2a. Questions on intercurrent diseases in the EDMUS software

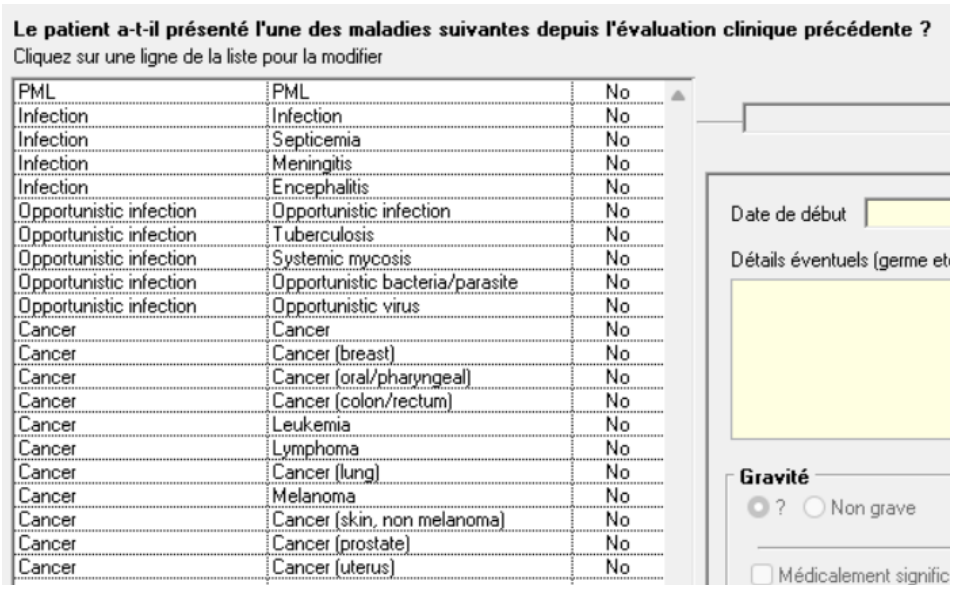

Figure FRA2b. Questions on intercurrent diseases in the EDMUS software

If a SAE is reported, it is collected in EDMUS (Figure FRA3) in an AE report form: information about the date of the event and the manifestation (as a pre-coded terms + verbatims) of the AE are required. The seriousness of the event (*non-serious/serious*) and the seriousness criteria (*medically significant, hospitalization, congenital anomaly, persistent or significant disability, life-threatening, death)* are mandatory by consign. The other fields (treatment suspected, evolution…) are not mandatory so they are poorly collected.

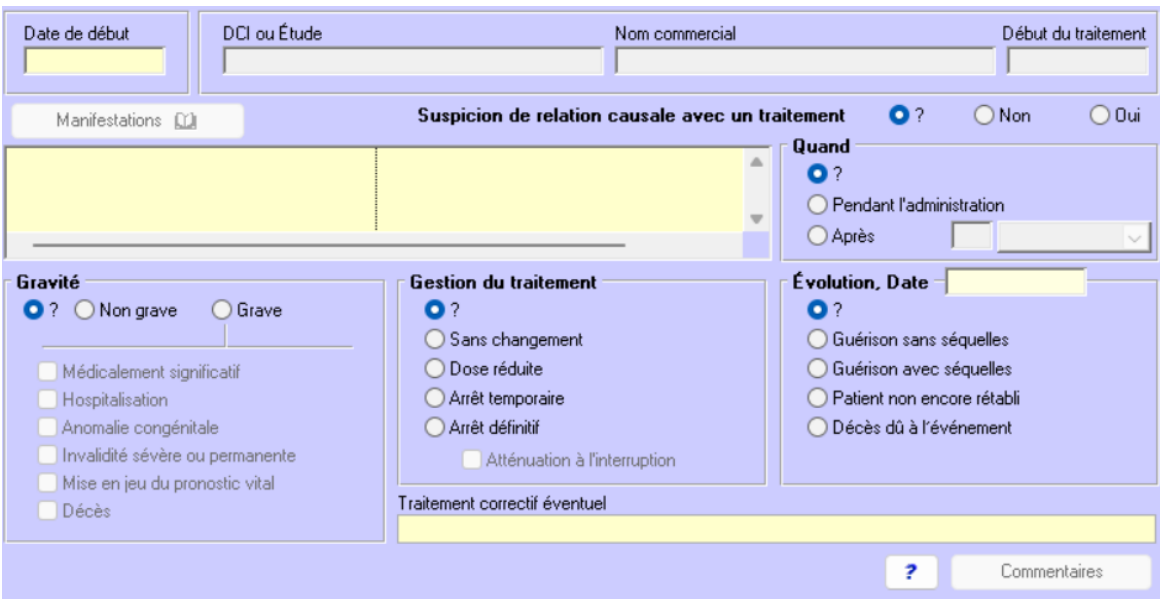

Figure FRA3. EDMUS AE report form

Twice a year the data are centralized, and the SAE are MedDRA coded by a specifically trained Certified Research Administrator (CRA). If necessary, queries are sent to centres to collect more details, revaluate seriousness, etc. Currently, except in case of awaiting information from centres, all SAE since 2017 and all cancers whenever occurred are coded (about 32 000 events in June 2024) before the implementation for analysis of the half-yearly database.

Given the strategic importance of the quality of serious adverse events collection and to assess the robustness of central MedDRA coding, the coding activity was monitored in 2022 by VIGIPHARM, a health vigilance company providing services. The results showed a good overall quality of coding and allowed OFSEP to improve its methods by identifying confounding factors and writing down specific OFSEP 'MedDRA Term Selection: Points to Consider' (PTC), built on MedDRA PTC and adapted to OFSEP activities. Moreover, it outlined the limits of our choice of a single term coding and led us to add the possibility of coding a secondary term in the EDMUS Platform (cf. infra).

The item related to SAE exists in the minimal dataset since 2016 and SAE data collection is mandatory since 01/01/2017. Nowadays the completeness of these variables is very high and has been high for all years since their introduction as seen in Figure FRA4: since 2017 the information related to presence/absence of SAE is missing for only 1% to 5% of visits by year.

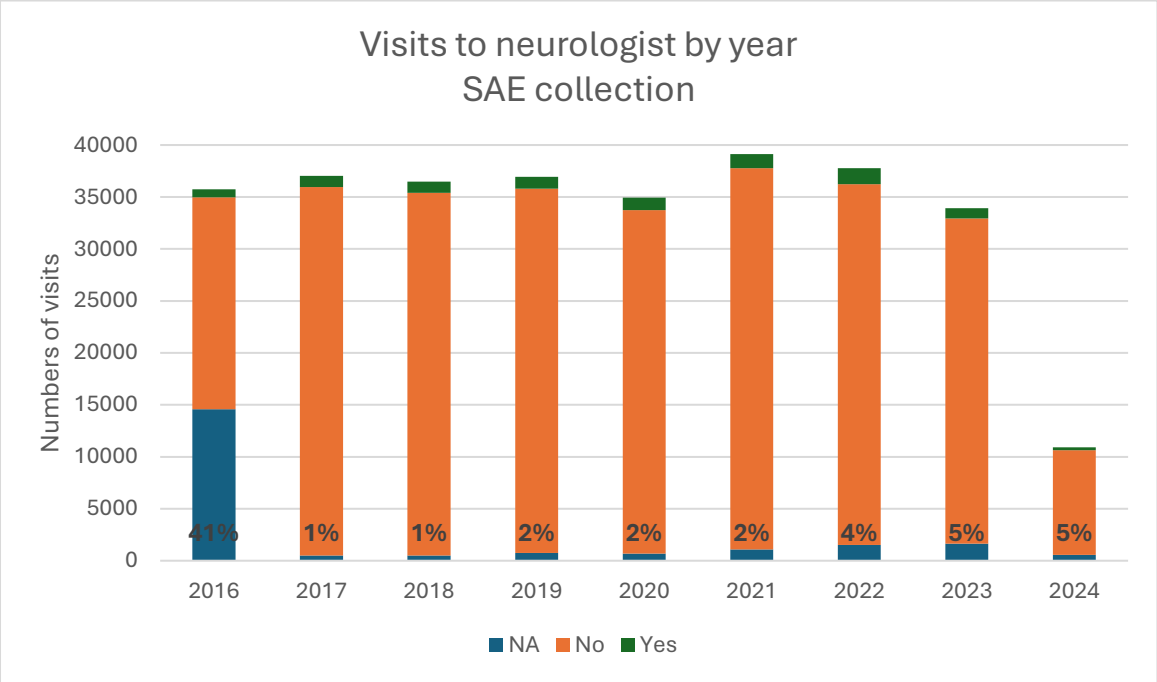

Figure FRA4. Numbers of visits to a neurologist per year between 2016 and 2024 (incomplete year, until June). The first visit of a patient is not considered because the question related to SAE is not applicable. Blue = visits with no reporting (NA) on the question "Since the last visit has a serious adverse event occurred?" Orange = visits with reporting "no SAE". Green = visits with reporting a SAE.

Data collection in the new EDMUS Platform

In the new EDMUS Platform system, data collection will be improved with a dedicated item related to NSAE and SAE in the clinical assessment interface (Figure FRA5) and an integrated MedDRA coding system in case of the declaration of an AE (Figure FRA6a/FRA6b). It allows in particular to code, if necessary, an event with two MedDRA codes.

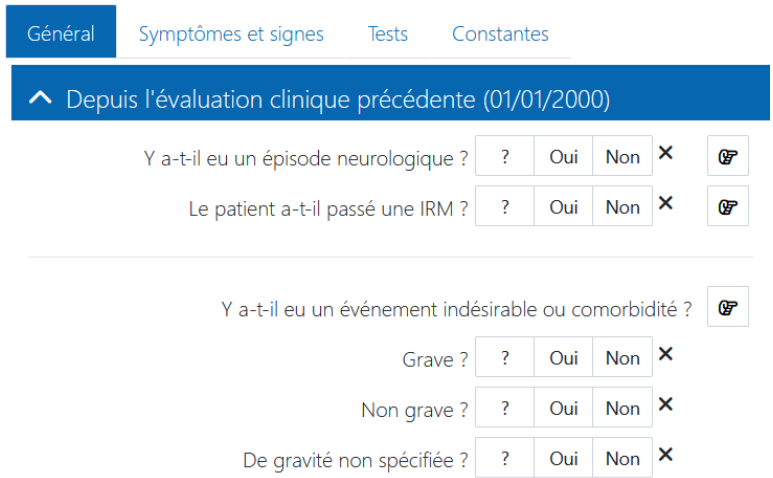

Figure FRA5. New EDMUS interface for clinical assessment

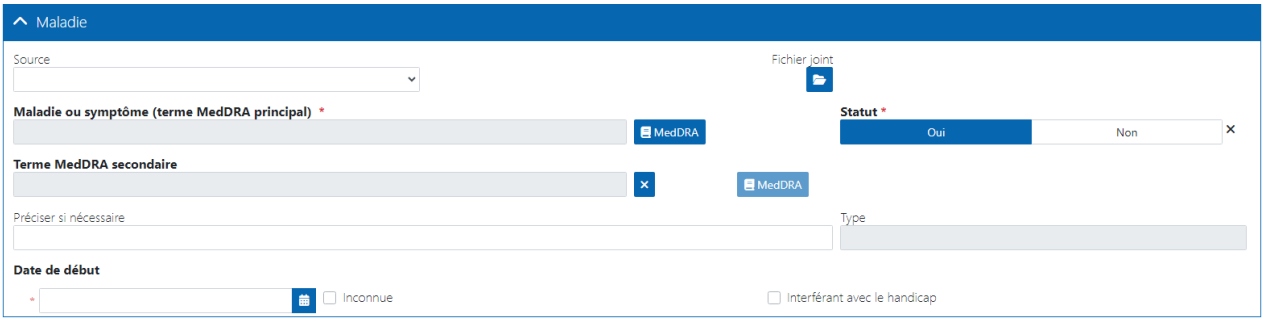

Figure FRA6a. New EDMUS interface for SAE recording

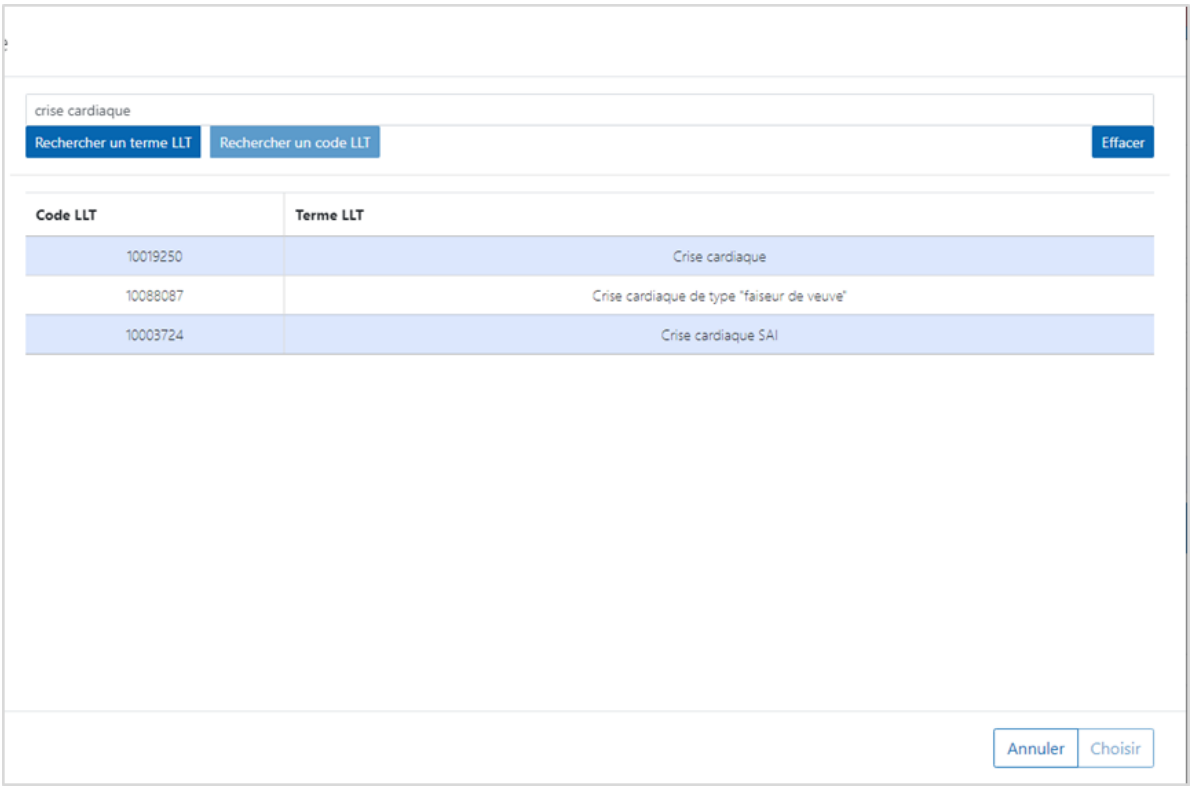

Figure FRA6b. New EDMUS interface for SAE recording

The Italian Multiple Sclerosis and Related Disorders Register (RISM)

General data collection report

Data are collected through a web-based system – called the RISM-App - developed ad hoc for RISM, and available at https://registroitalianosm.it/index.php?page=areariservata. Each centre can enter the data after identification through a personalized password (direct login at https://registroitalianosm.it/index.php?page=areariservata). Any physician or health care professional working at the centres may, in agreement with the principal investigator (PI), request access credentials that are unique and non-transferable. In the "Italian Multiple Sclerosis and Related Disorders Register", each patient has a unique valid code identifier, obtained through the patient-encrypted fiscal code, and each patient is assigned to a unique centre. The RISM-App respects the standards required by the European Union General Data Protection Regulation (GDPR) 2016/679 and each centre can enter data through a secure personalized profile. To boost the quality of data collection and data entry in RISM, a network of research assistants (RAs) has been trained and allocated to one or more centres.

SAEs reporting system in RISM-App

Data about the occurrence of adverse events can be collected using the appropriate section on the RISM-App "Eventi clinici", whose variables are reported below (Table ITA1). In the RISM, adverse events are entered by research assistants, doctors and health personnel and are encoded through MedDRA database. The data entry system has been upgraded to collect SAEs, with the MedDRA safety coding system included in the web application starting from 2020. Currently, the version of the MedDRA used in the webapp is 24.0 (LLT is mandatory). Safety data before 2020 were collected in RISM through free text.

Variable name	Variable description	Datatype	Format	Values	Comment
paziente_id	Patient ID	numeric			
evento_dt	date of the event	date	dd/mm/yyyy		
SOC	SOC (MedDRA)	multiple-choice variable from MedDRA code			
HLGT	HLGT (MedDRA)	multiple-choice variable from MedDRA code			
HLT	HLT (MedDRA)	multiple-choice variable from MedDRA code			
PT	PT (MedDRA)	multiple-choice variable			

		from MedDRA code			
LLT	LLT (MedDRA)	multiple-choice variable from MedDRA code			
gravità	severity	multiple-choice variable	multiple-choice variable	lieve/moderato/severo/rischio della vita	mild/moderate/severe/life-threatening
cond_med_grave	serious medical conditions	yes/no variable	yes/no variable	yes/no	
cond_med_grave_sp	if yes, specify…	multiple choice variable	multiple choice variable	causa del decesso/mette a rischio la vita/invalidità permanente e grave/necessita o prolunga degenza in ospedale/anomalia congenita o difetto di nascita/altra importante condizione medica	cause of death/life-threatening/severe permanent disability/need or prolongation of hospital stay/congenital abnormality or birth defect/other important medical condition
esito	outcome	multiple choice variable	multiple choice variable	sconosciuto/in corso/guarigione/decesso	unknown/in progress/healed/died
decesso_sm_nmo	death related to SM / NMOSD-MOGAD	yes/no variable	yes/no variable	yes/no	
esito_dt	outcome date	date	dd/mm/yyyy		
corr_trattamento	correlation with treatmet	multiple choice variable	multiple choice variable	no/si, improbabile/si, possibile/si, probabile/si, certo	Yes/no, improbable/si, possible/si, probable/si, certain
trattamento	if yes, specify treatment…	multiple choice variable			
decis_terap	therapeutic decision after the event	multiple choice variable	multiple choice variable	cambio trattamento/nessun farmaco specifico	change of treatment/no specific medication

Table ITA1. Variables, and specifications, included in the “Eventi clinici” section of the RISM-app.

In case of a SAE, a pop-up reminder for reporting SAEs to the competent authorities shall appear. In addition, there is a sub-section in the follow-up section (“Visite”) with some questions that must be filled

out at each visit about the occurrence of neoplasms or infections during the follow-up period (Table ITA2).

Variable name	Variable description	Datatype	Format	Values
neoplasia	The patient developed cancer (excluding NMSC) from the last visit	multiple-choice variable	multiple-choice variable	yes/no/not available
neoplasia_cutanea	The patient has developed a non-melanoma skin neoplasm (NMSC) since the last visit	multiple-choice variable	multiple-choice variable	yes/no/not available
herpes_zoster	The patient developed a reactivation of herpes zoster infection from the last visit	multiple-choice variable	multiple-choice variable	yes/no/not available
infezione_grave	The patient has developed a severe infection or immunosuppression associated with the last visit	multiple-choice variable	multiple-choice variable	yes/no/not available
altre_condizioni_patologiche	The patient has developed other pathological conditions of particular importance since the last visit	multiple-choice variable	multiple-choice variable	yes/no/not available
trattamento_corrente	Current treatment and treatment history (Yes/No DMT)	multiple-choice variable	multiple-choice variable	yes/no/not available

Table ITA2. Questions about the occurrence of neoplasms or infections during the follow-up period in the follow-up section ("Visite") of the RISM app.

Assessment of the severity of adverse events and the correlation with treatment is the sole responsibility of the doctor. Neurologists are directly involved in detecting, collecting and assessing SAEs, with research assistants supporting.

We consider the following definition. A SAE/SAR is any AE/AR, which also meets at least one of the following seriousness criteria:

- causes death.
- is dangerous for life.
- requires hospitalization or prolongation of an existing hospitalization.
- leads to persistent or significant disability/incapacity.
- results in congenital abnormality/birth defect.
- is considered medically important.

Patients are asked about infectious episodes, malignancies etc. during visits, but it is unlikely that a serious adverse event will not be reported to the doctor if it happened. However, it is necessary to stress that it is impossible to standardize the questions that the doctor asks the patient during the examination.

We point out that research assistants and clinicians in the registry centers have had specific training throughout 2023 about standardizing data entry and improving data quality, through training on the characteristics and history of PASS studies and on RISM-App updates. There are not patient-reported data in RISM.

In addition, for each drug a specific clinical risk management card (https://registroitalianosm.it/index.php?page=docprogetto) has been drawn up to guide the neurologist in the monitoring and management of drugs in daily clinical practice.

MSBase Neuro-Immunology Registry

Setting and Method of collection

The MSBase Safety collection for pharmacovigilance includes 41 centres who are following over 27,000 MS patients according to a mutually agreed protocol. The Investigators (PI) at participating centres submit coded clinical information using either a locally installed or a web-based software. The software products contain a system to identify consented patients. The software then creates a highly codified data extract from only the consented patients that can be sent securely to the MSBase web server. The patient data that is sent from the participating centres to MSBase comprises both the defined minimum dataset as well as other data, all relating to demographics, disease rating scales, diagnostic tests descriptors, treatment exposures, comorbid diseases, pregnancy outcomes and safety events. All safety events are described using the Medical Dictionary for Regulatory Activities (MedDRA) at the time of data entry by the physician. MedDRA versions are updated when available (appx annual). Principal Investigators (PIs) need to upload their complete codified dataset to MSBase servers at least 6-monthly.

Definition of AESI and SAE

The MSBase Safety collection for pharmacovigilance aims to assess and characterize the risk of serious and/or significant safety events in patients with MS by collecting serious adverse event (SAEs) and Adverse event of special interest (AESI) information. Please note that the aim is not to capture all adverse events, but only SAEs and AESI. SAEs are defined as any untoward medical occurrence that results in death, is life-threatening, requires or prolongs hospitalization, results in significant disability of incapacity, is a congenital anomaly or birth defect. AESI are adverse events of special interest. These are either pre-defined or are significant in the opinion of the investigator. SAE and AESI are recorded regardless of their likelihood of a causal relationship to treatment.

Details of data collection

The clinician needs to ask the patient about the occurrence of events at each clinical visit. The absence or occurrence of an SAE/AESI must be specified at least annually at the time of a visit, with either “yes/no” answers provided for 5 tabs (Figure MSB1)

Did the patient, since the last visit, experience a new onset of:

- Malignancy including Melanoma
- Non-melanoma skin cancer (AESI)
- Herpes zoster (shingles) (AESI)
- Severe or immunosuppression-associated Infection
- Other (AESI)

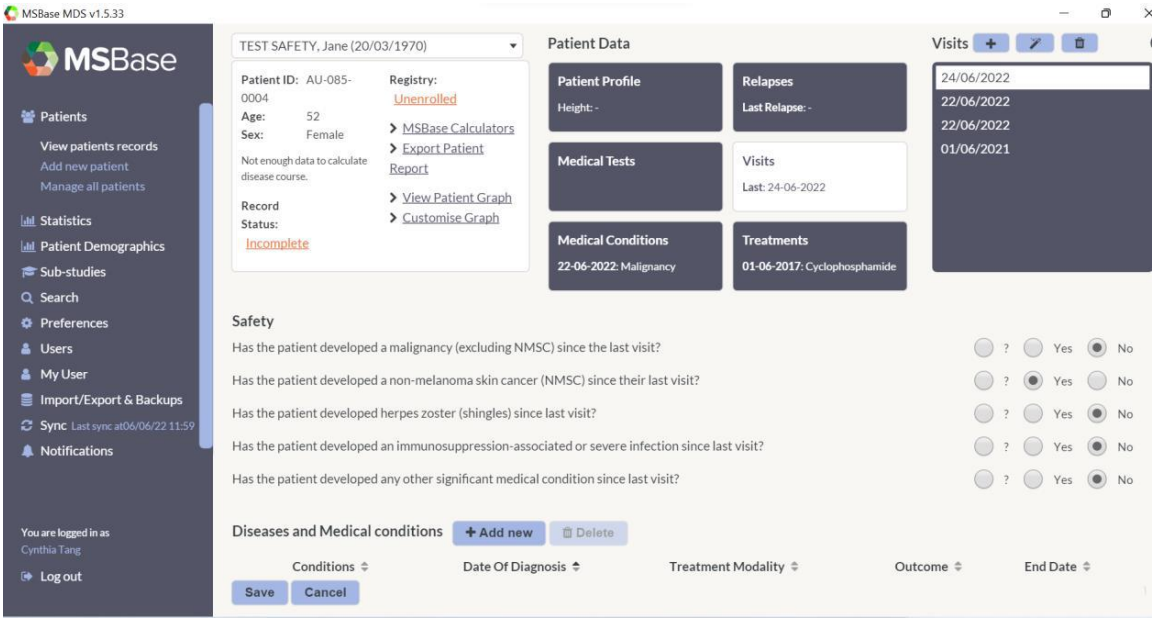

Figure MSB1: Safety tab in the VISIT section of MDS Data collection Software

Any identified event must have a date of onset and must be classified using MedDRA coding (Figure MSB2). Any identified event from the list of pre-defined AESI, must be reported even if they do not meet SAE definition (MSBase SAP excerpt)

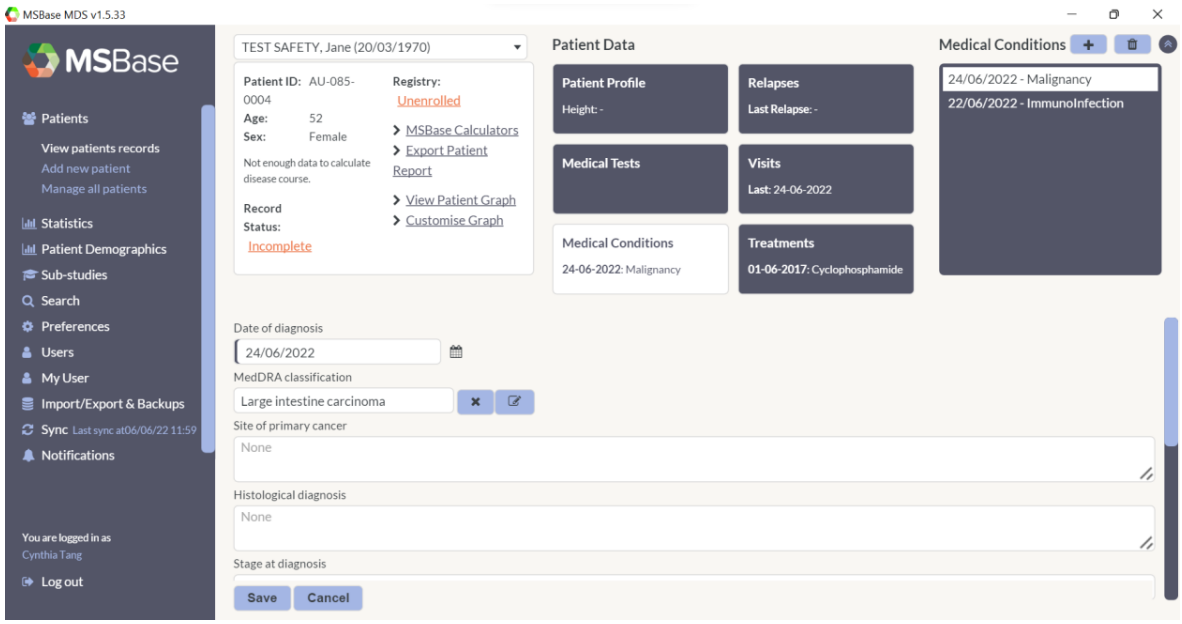

Figure MSB2: Minimum data is a date of onset and MedDRA description - cancer example

<u>AESI list</u>

- Significant new diagnoses (Myocardial Infarct, Coronary Ischemia, Stroke, Transient ischemic attack, Seizure, Epilepsy, Heart Failure, Deep Vein thrombosis, Pulmonary Embolus, Alzheimer's Disease, Dementia, Liver Failure, Renal Failure)
- Lower Respiratory tract infections (Pneumonia, Bronchopneumonia, Empyema)
- Significant and Immunosuppression-associated Infections (e.g. Hepatitis B reactivation, Tuberculosis, Tuberculosis reactivation, PML, Cryptococcal Disease, Cryptococcal Meningitis,

HSV encephalitis, Meningitis (any type), Septic Shock, Pyelonephritis, cryptosporidial diarrhoea, Measles, Tetanus, Pertussis, Scarlet Fever, Streptococcal sore throat, Sinusitis)
- Significant Mental Health Conditions (e.g. Depression, Psychosis, Anxiety, Suicide Attempt)
- Autoimmune Disease (e.g. Hypothyroidism, Hyperthyroidism, Rheumatoid Arthritis, Psoriasis)

Events that should not be reported

- Symptom descriptions including Pain Syndromes (Cough, Headache, vomiting, diarrhoea, lassitude, runny nose, sore throat, back pain, restless leg syndrome)
- Terms containing "Inflammation" (Skin inflammation, breast inflammation, middle ear inflammation)
- Common abnormal blood test results unless medically significant (hypercholesterolemia, hypertriglyceridemia, lymphopenia due to S1Ps, anaemia, vit D deficiency, iron deficiency)
- MS symptoms (optic neuritis, spasticity, urinary urgency, urinary hesitancy, MS relapse)
- Elective surgery (knee replacement, hysterectomy, hernia operation, vulva biopsy)
- Conditions that are almost always benign (uterine fibroid, benign prostatic hypertrophy, obesity, injection site reaction, skin rashes)
- Trauma and Assault (fracture, mandible fracture, head injury, car accident, concussion)
- Musculo-skeletal conditions (Osteoarthritis knee, Disc protrusion, lumbago)
- High level terms – *essentially uninterpretable* (bone and joint disease, skin condition, adverse event)
- Surgery if condition also named (e.g. do not report mastectomy as event if reporting Breast Cancer)

Data retention

The entire MSBase dataset is archived and saved in multiple secure locations on the 1st day of every month

Data change log

All data entry and all changes to data are recorded in a site log. For every new field or field change, the log records the identity of the recorder (per log-in), and the data and time of the new or changed field state.

The Swedish Multiple Sclerosis Registry (SMSR)

Data on the occurrence of adverse events are collected during the patient's visit to a neurologist at each MS centre in Sweden. The neurologists are required to ask the patient regarding adverse experiences since the last visit and record it. The COMPOS-DS platform that the Swedish MS registry is using provides an easy way to register all relevant information and in the *Kontakt* module (Figure SWE1) there are several mandatory fields that need to be filled in during a visit including the question "*Har du haft en möjlig medicinbiverkan sedan föregående vårdkontakt?*" (*Have you had a possible medication adverse event since previous care contact?*). The definition of this question includes all types of pharmacological treatments, including disease modifying treatments (DMTs) for MS as well as symptomatic treatments and treatments for other conditions other than MS. The neurologist chooses an option *Ja/Nej* (Yes/No) from a drop-down menu.

In case there is an adverse event reporting (answer "Ja" to this field), 4 new fields related to the type of the adverse event become available and are mandatory to be filled in as well. These new fields ask if the event reported is a malignancy (*Ja/Nej*), skin cancer other than melanoma (*Ja/Nej*), infection

related to the treatment (*Ja/Nej*), or other serious or unexpected adverse event (*Ja/Nej*). The definitions/instructions provided to help the categorization are:

- Malignancy: *applies to all malignancies/cancers, including malignant melanoma, regardless if you as a reporter consider that the connection with the treatment is likely.*
- Skin cancer other than melanoma: *Eg basalioma, basal cell carcinoma, squamous cell carcinoma*
- Infection related to the treatment: *The infection that you as the reporter perceive may be related to the pharmacological treatment received.*
- Other serious or unexpected adverse events: *Consider other adverse events that you as a healthcare provider must report.*

Once this information is filled in, the system shows a pop-up message asking if the neurologist would like to register the adverse event where the doctor has the option to continue with the AE reporting immediately or complete it later.

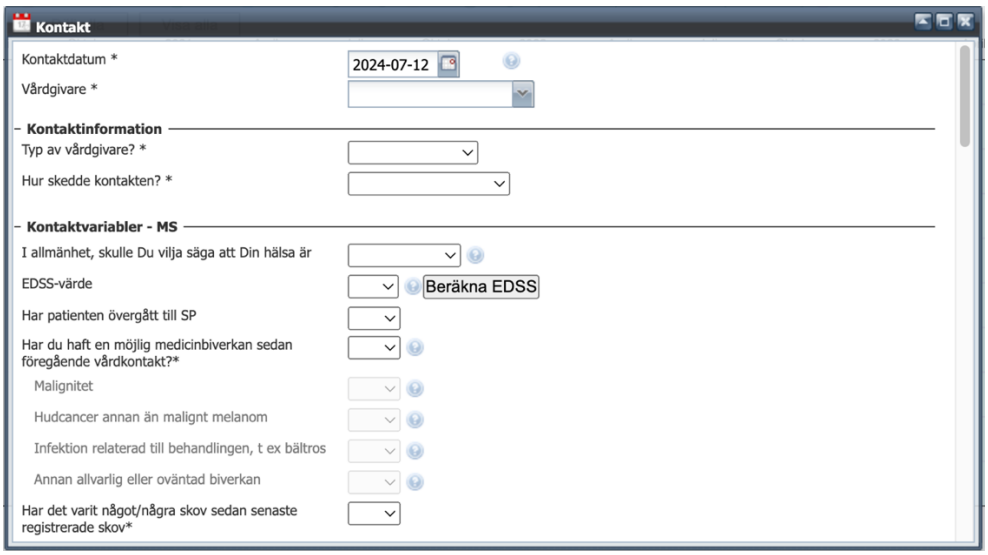

Figure SWE1. “Kontakt” (Contact) module in the COMPOS-DS platform

To complete an AE report, information about the date of the event, the treatment suspected, and the action taken regarding the treatment are required. The platform automatically lists all ongoing treatments at the time of the event and the reporting doctor can select the suspected treatment from the available list or register a new drug at a later step. The options available for the action taken field in the drop-down menu are *unchanged, lowered dosage, temporarily stopped, permanently stopped and unknown* (Figure SWE2).

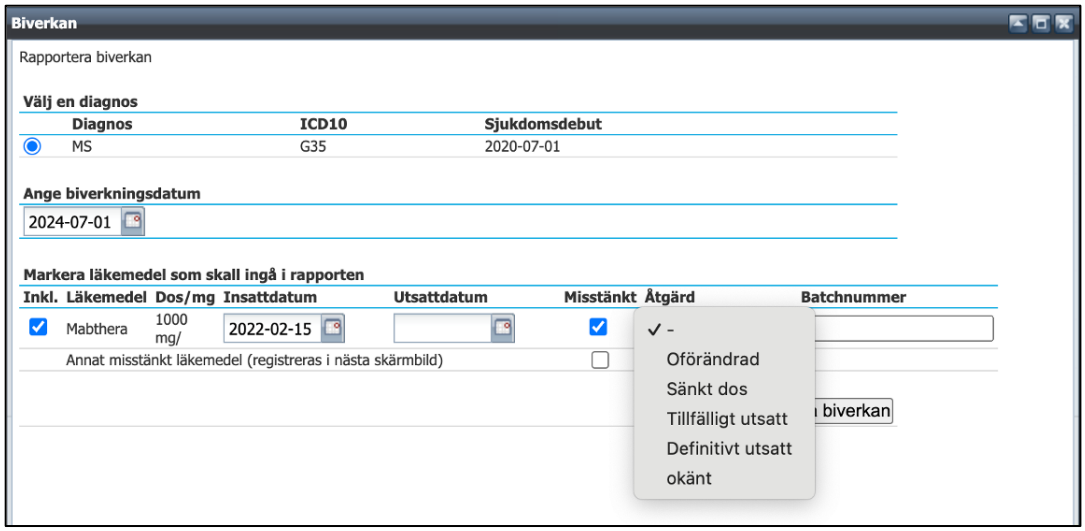

Figure SWE2. “Biverkan” (Adverse event) module in the COMPOS-DS platform

Next, detailed information about the event is required such as the level of seriousness of the event (*serious/not serious*), the seriousness criteria (*the patient has died, life-threatening, prolonged care/hospitalization, disability, resulted in birth defect, other serious adverse event, none of the above*) and the outcome of the case (*recovered, under recovery, not recovered, recovered but with, dead, unknown*) all with options in a drop-down menu (Figure SWE3). Finally, the reporting doctor gives the diagnosis and a detailed description of the event in free text (*Biverkningsdiagnoser* and *Händelsebeskrivning* fields) and selects the diagnosis from a drop-down menu of ICD-10 codes. The platform also allows for inclusion of attachments (e.g. Lab tests) relevant to the event recorded.

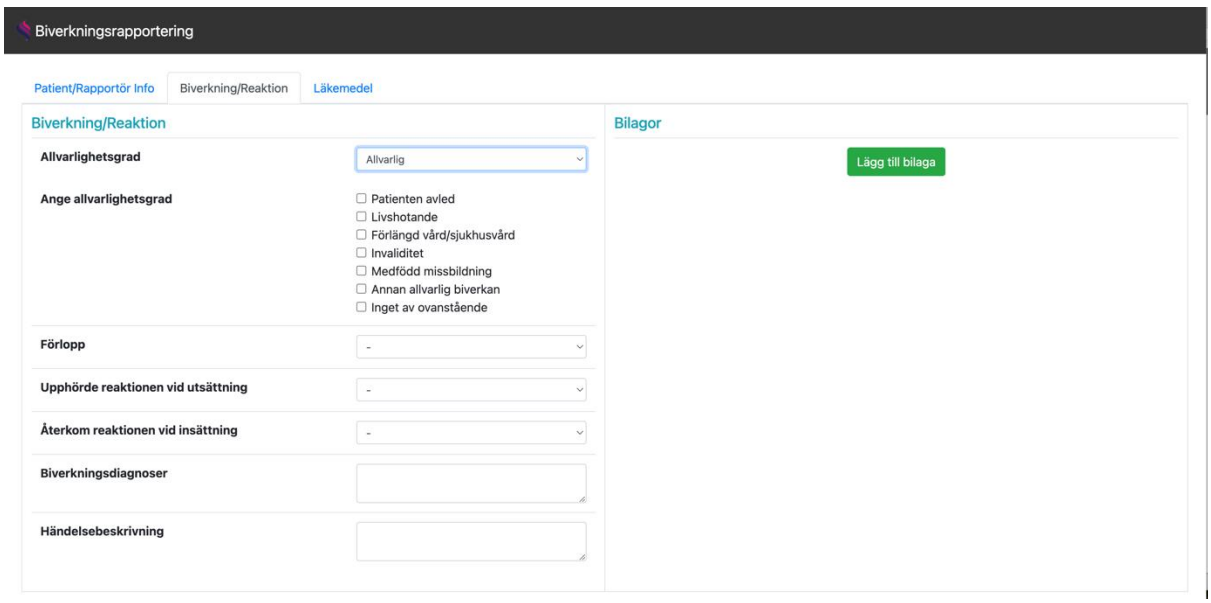

Figure SWE3. Adverse event report form in COMPOS-DS platform

Once all the necessary information is recorded in the system, the report is saved in the COMPOS data base and COMPOS opens the Swedish Medical Product Agency (MPA) pharmacovigilance (PV) e-form with critical information already filled-in, and the doctor is expected to complete the form and file the report. In this way, COMPOS facilitates the PV-reporting in Sweden.

The fields regarding adverse event reporting were introduced in 2010 and 2019 for the “*Har du haft en möjlig medicinbiverkan sedan föregaende vardkontakt?*” (*Have you had a possible medication adverse event since previous care contact?*) variable and the type of adverse event (*malignancy, skin*

cancer other than melanoma, infection related to the treatment, or other serious or unexpected adverse event) variables, respectively. Nowadays the completeness of these variables is very high and has been high for all years since their introduction as seen in Figure SWE4.

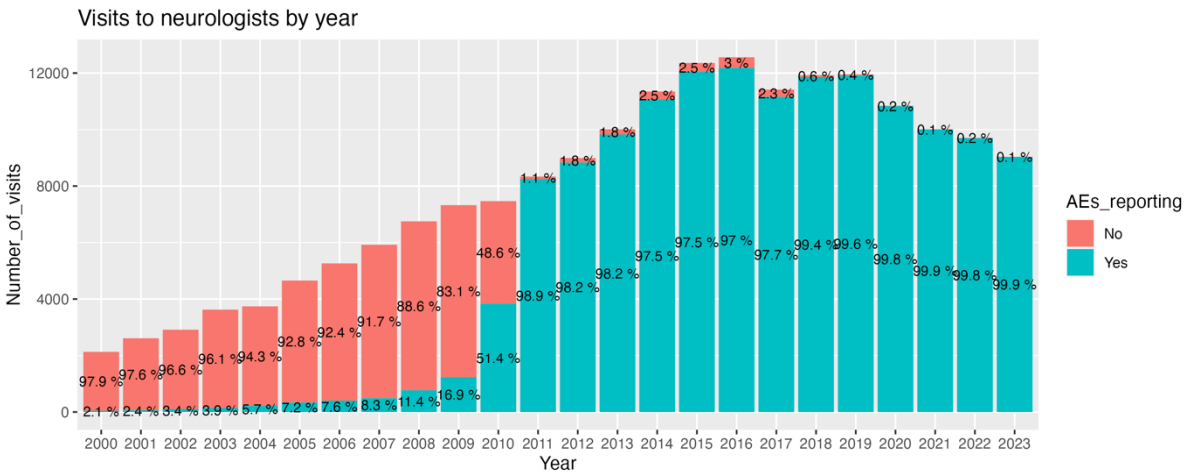

Figure SWE4. Number of visits to a neurologist per year between 2000 and 2023. Red = visits with no reporting (NA) on the "*Har du haft en möjlig medicinbiverkan sedan föregaende vardkontakt?*" (*Have you had a possible medication adverse event since previous care contact?*) field. Blue = visits with reporting (Ja/Nej) on the "*Har du haft en möjlig medicinbiverkan sedan föregaende vardkontakt?*" (*Have you had a possible medication adverse event since previous care contact?*) field. Numbers on each column and colour represent the % of visits per year with or without the AE reporting variable completed.

Similarly, Figure SWE5 shows that the variable regarding the type of reported event has also very high completeness since the year it was introduced (2019).

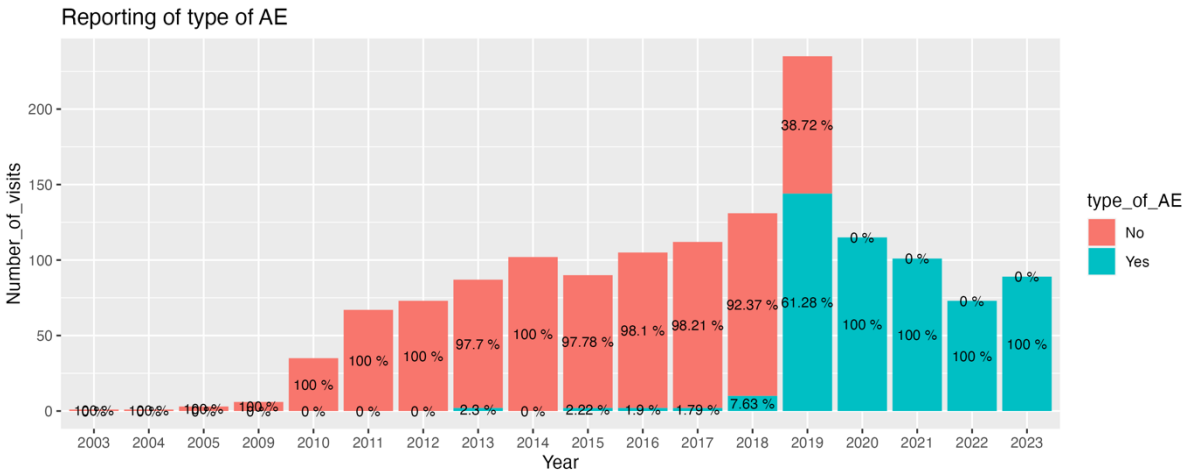

Figure SWE5. Number of visits to a neurologist with a reported adverse event per year between 2000 and 2023. Red = visits with complete information on the type of event. Green = visits with missing information on the type of event. Numbers on each column and colour represent the % of visits per year with or without the type of AE information completed.

Finally, other healthcare professionals engaged in the MS care of a patient can report an adverse event through the same platform. For example, during a patient's visit for an infusion of a DMT a nurse will be present and can report any adverse event observed during the infusion or mentioned by the patient.

2: Comparison between MS registry collected adverse events and events captured in public healthcare databases

The Swedish and Danish MS registries have the possibility to link their patient data to national healthcare databases that contain all possible diagnoses. To evaluate the level of SAE capture in these MS registries a direct comparison of SAE incidence rates calculated separately from the two sources (MS registry and national database) is performed using data from the ongoing PASS, MANUSCRIPT.

Sweden

The DMT comparator cohort in the MANUSCRIPT study contains 2,556 patients from the Swedish MS registry. The results showed that the IR of overall malignancy was substantially lower in the SMSR compared to the IRs calculated from the Swedish National Cancer Registry (SNCR) (Table 1). The IR was 0.03 per 100 person-years (95% CI 0.01 – 0.10) in the SMSR, compared to 0.33 per 100 person-years (95% CI 0.22 – 0.49) in the SNCR. This yielded an incidence rate ratio (IRR) of 12.46 (95% CI 2.95 – 52.61; p < 0.001), indicating a significant underreporting of malignancies in the SMSR.

When stratified by malignancy type, zero haematological malignancies were recorded in the SMSR, while three events were identified in the SNCR, with an incidence rate of 0.04 per 100 person-years (95% CI 0.01 – 0.12). Non-haematological malignancies mirrored the overall malignancy findings, showing the same rate ratio and statistical significance as above since this subtype consisted of the majority of the codes of malignancies overall.

Zero melanoma skin malignancies were reported in both sources of data. For non-melanoma skin cancer, the SMSR recorded one event compared to four in the SNCR. The IRs were 0.01 (95% CI 0 – 0.09) and 0.05 (95% CI 0.02 – 0.14) per 100 person-years, respectively but this difference was not statistically significant (IRR 4.00, 95% CI 0.45 – 35.83; p = 0.18).

Table 1. Crude incidence rates (IR) and incidence rate ratios (IRR) of malignancy overall and by sub-type calculated from data collected in the Swedish MS Registry (SMSR) and from the Swedish National Cancer Registry (SNCR).

Outcome		***SMSR (N=2556)***	***SNCR (N=2556)***	***IRR (95% CI) p-value***
Malignancy overall	N events	2	25	12.46 (2.95 – 52.61) p < 0.001
	Follow-up (person-years)	7655	7589	
	IR (95% CI)	0.03 (0.01 - 0.10)	0.33 (0.22 - 0.49)	
Haematological malignancy	N events	0	3	-
	Follow-up (person-years)	7659	7656	
	IR (95% CI)	0 (0 - 0.05)	0.04 (0.01 - 0.12)	
Non-haematological malignancy	N events	2	25	12.46 (2.95 – 52.61) p < 0.001
	Follow-up (person-years)	7655	7589	
	IR (95% CI)	0.03 (0.01 - 0.1)	0.33 (0.22 - 0.49)	
Melanoma skin malignancy	N events	0	0	-
	Follow-up	7659	7659	

	(person-years) IR (95% CI)	 0 (0 - 0.05)	 0 (0 - 0.05)	
Non-melanoma skin cancer	N events Follow-up (person-years) IR (95% CI)	1 7655 0.01 (0 - 0.09)	4 7647 0.05 (0.02 - 0.14)	4.00 (0.45 – 35.83) p = 0.18

SMSR = Swedish Multiple Sclerosis Register, SNCR = Swedish National Cancer Registry, CI = Confidence Interval, IR = Incidence Rate, IRR = Incidence Rate Ratio, IRR calculated as IR SNCP / IR SMSR

In a similar pattern as previously, the overall incidence rate of serious infections was substantially lower in the SMSR compared to the Swedish National Patient Registry (SNPR) (Table 2). Specifically, the incidence rate was 0.02 per 100 person-years (95% CI 0 – 0.13) in the SMSR, versus 3.46 per 100 person-years (95% CI 2.99 – 4.01) in the SNPR. This corresponds to an IRR of 190.78 (95% CI 26.73 – 1361.71; p < 0.001).

No events of potential opportunistic infections, herpetic infections, urinary tract infections, or respiratory tract infections (upper or lower) were recorded in the SMSR. In contrast, the SNPR captured several events in each of these categories, with IRs ranging from 0.05 (Potential opportunistic infections, 95% CI 0.02 – 0.17) to 0.96 (Lower respiratory tract infections (RTIs), 95% CI 0.73 – 1.26) per 100 person-years.

It should be noted that for the serious infections outcomes only events classified as serious by the reporter were considered and non-serious events were excluded. The events collected through the SMSR include information of seriousness but not the events collected through the SNPR. For that reason, proxies for seriousness were applied. These proxies were defined as: an infection diagnosis was considered serious if it was identified in the hospitalization records or from an emergency outpatient contact, if it appeared in the cause of death of a patient or if it was included in the EMA Important medical event list (https://www.ema.europa.eu/en/human-regulatory-overview/research-development/pharmacovigilance-research-development/eudravigilance/eudravigilance-system-overview#reference-sources-and-services-7044).

Table 2. Crude incidence rates (IR) and incidence rate ratios (IRR) of serious infections overall and by subtype calculated from data collected in the Swedish MS Registry (SMSR) and data from the Swedish National Patient Registry (SNPR).

Outcome		***SMSR (N=2556)***	***SNPR (N=2556)***	***IRR (95% CI) p-value***
Serious infections overall	N events Follow-up (person-years) Inc. rate (95% CI)	1 5506 0.02 (0 - 0.13)	180 5195 3.46 (2.99 - 4.01)	190.78 (26.73 – 1361.71) p < 0.001
Potential opportunistic infections	N events Follow-up (person-years) IR (95% CI)	0 5511 0 (0 - 0.07)	3 5505 0.05 (0.02 - 0.17)	-
Herpetic infections	N events Follow-up (person-years)	0 5511	13 5496	-

	IR (95% CI)	0 (0 - 0.07)	0.24 (0.14 - 0.41)	
Urinary tract infections	N events	0	25	-
	Follow-up (person-years)	5511	5461	
	IR (95% CI)	0 (0 - 0.07)	0.46 (0.31 - 0.68)	
Lower RTIs	N events	0	52	-
	Follow-up (person-years)	5511	5434	
	IR (95% CI)	0 (0 - 0.07)	0.96 (0.73 - 1.26)	
Upper RTIs	N events	0	40	-
	Follow-up (person-years)	5511	5446	
	IR (95% CI)	0 (0 – 0.07)	0.73 (0.54 – 1.00)	

SMSR = Swedish Multiple Sclerosis Register, SNPR = Swedish National Patient Registry, CI = Confidence Interval, RTIs = Respiratory tract infections, IR = Incidence Rate, IRR = Incidence Rate Ratio, IRR calculated as IR SNPR / IR SMSR

These results highlight a marked discrepancy in the capture of both malignancies and serious infections between the two data sources, suggesting underreporting in the SMSR relative to the more comprehensive national health database.

Denmark

*Due to data protection rules, Denmark does not report exact number of events if those are below 5. Therefore here, the incidence rates and rate ratios are calculated with the minimum number of cases that can be shown (5) and presented as less than (< for number of events and IRs) and more than (> for RR).

The Danish DMT comparator cohort of the MANUSCRIPT study included 5,190 individuals with MS. A substantial underreporting of malignancies was observed in the DMSR compared to the Danish national cancer registry (DNCR) (Table 3). Overall malignancy incidence was 0.05 per 100 person-years (95% CI 0.02 – 0.09) in the DMSR, versus 0.50 per 100 person-years (95% CI 0.40 – 0.62) in the DNCR, resulting in an IRR of 10.83 (95% CI 5.00 – 23.49; $p < 0.001$).

Haematological malignancies were rare in both data sources with < 5 cases and corresponding incidence rates less than 0.032 per 100 person-years. Non-haematological malignancy IRs, which mirrored the overall malignancy results, had an IRR of 10.83 (95% CI 5.00–23.49; $p < 0.001$), confirming significant underreporting in the DMSR.

Melanoma skin malignancy had IRs below 0.032 (from DMSR data) and of 0.06 (from DNCR data) per 100 person-years, with an IRR higher than 2.00 (95% CI 0.68 – 5.86; $p = 0.196$). Non-melanoma skin cancer showed the largest discrepancy: < 5 cases in the DMSR versus 31 in the DNCR, corresponding to an IRR of more than 6.22 (95% CI 2.42 – 16.00; $p < 0.001$).

Table 3. Crude incidence rates (IR) and incidence rate ratios (IRR) of malignancy overall and by subtype calculated from data collected in the Danish MS Registry (DMSR) and data from the Danish National Cancer Registry (DNCR).

Outcome	***DMSR (N=5190)***	***DNCR (N=5190)***	***IRR (95% CI)***

				p-value
Malignancy overall	N events	7	77	10.83 (5.00 – 23.49) p < 0.001
	Follow-up (person-years)	15596	15473	
	IR (95% CI)	0.05 (0.02 - 0.09)	0.50 (0.40 - 0.62)	
Haematological malignancy	N events	< 5	< 5	-
	Follow-up (person-years)	15610	15609	
	IR (95% CI)	< 0.032 (0.030 - 0.035)	< 0.032 (0.03 - 0.035)	
Non-haematological malignancy	N events	7	77	10.83 (5.00 – 23.49) p < 0.001
	Follow-up (person-years)	15596	15473	
	IR (95% CI)	0.05 (0.02 - 0.09)	0.50 (0.40 - 0.62)	
Melanoma skin malignancy	N events	< 5	10	> 2.00 (0.68 – 5.86) p = 0.196
	Follow-up (person-years)	15603	15593	
	IR (95% CI)	< 0.032 (0.030 - 0.035)	0.06 (0.04 - 0.12)	
Non-melanoma skin cancer	N events	< 5	31	> 6.22 (2.42 – 16.00) p < 0.001
	Follow-up (person-years)	15603	15545	
	IR (95% CI)	< 0.032 (0.030 - 0.035)	0.20 (0.14 - 0.28)	

DMSR = Danish Multiple Sclerosis Register, DNCR = Danish National Cancer Registry, CI = Confidence Interval, IR = Incidence Rate, IRR = Incidence Rate Ratio, IRR calculated as IR DNCR / IR DMSR

The incidence of serious infections was consistently higher in the Danish national patient registry (DNPR) across nearly all categories, highlighting significant underreporting in the disease-specific registry (Table 4). Overall serious infections were reported at an incidence rate of 1.64 per 100 person-years (95% CI 1.41 – 1.90) in the DMSR versus 3.68 per 100 person-years (95% CI 3.33 – 4.08) in the DNPR, yielding an IRR of 2.25 (95% CI 1.88 – 2.70; p < 0.001).

Potential opportunistic infections were substantially underreported in the DMSR (< 5 vs. 26 in DNPR), resulting in an IRR higher than 5.22 (95% CI 2.00 – 13.59; p < 0.001). Herpetic infections were not identified at all in the DMSR, while the DNPR recorded 6 events (IR: 0.06, 95% CI 0.03 – 0.13).

Urinary tract infections (UTIs) showed also a substantial discrepancy: 15 events in the DMSR vs. 105 in the DNPR, with respective IRs of 0.14 (95% CI 0.09 – 0.24) and 1.01 (95% CI 0.84 – 1.23) per 100 person-years. This corresponds to an IRR of 6.99 (95% CI 4.07 – 12.01; p < 0.001). Lower respiratory tract infections (RTIs) were also underreported in the DMSR (13 events vs. 44 in DNPR), with an IRR of 3.41 (95% CI 1.84 – 6.33; p < 0.001).

Upper RTIs were a notable exception: the DMSR recorded more cases (100 vs. 77). The incidence rate was slightly higher in the DMSR (0.95 (95% CI 0.78 – 1.16) vs. 0.74 (95% CI 0.59 – 0.93), per 100 person-years), though the difference was not statistically significant (IRR: 0.78; 95% CI 0.58 – 1.05; p = 0.10).

*Note: In the Danish data, seriousness of the event was not considered, as for the Swedish data, and all captured events were included in the analysis from both sources.

Table 4. Crude incidence rates (IR) and incidence rate ratios (IRR) of serious infections overall and by subtype calculated from data collected in the Danish MS Registry (DMSR) and data from the Danish National Patient Registry (DNPR).

Outcome		***DMSR (N=5190)***	***DNPR (N=5190)***	***IRR (95% CI) p-value***
Serious infections overall	N events	171	367	2.25 (1.88 – 2.70) p < 0.001
	Follow-up (person-years)	10454	9964	
	IR (95% CI)	1.64 (1.41 - 1.90)	3.68 (3.33 - 4.08)	
Potential opportunistic infections	N events	< 5	26	> 5.22 (2.00 – 13.59) p < 0.001
	Follow-up (person-years)	10511	10475	
	IR (95% CI)	< 0.05 (0.04 – 0.05)	0.25 (0.17 - 0.37)	
Herpetic infections	N events	0	6	-
	Follow-up (person-years)	10511	10501	
	IR (95% CI)	0 (0 - 0.04)	0.06 (0.03 - 0.13)	
Urinary tract infections	N events	15	105	6.99 (4.07 – 12.01) p < 0.001
	Follow-up (person-years)	10487	10367	
	IR (95% CI)	0.14 (0.09 - 0.24)	1.01 (0.84 – 1.23)	
Lower RTIs	N events	13	44	3.41 (1.84 – 6.33) p < 0.001
	Follow-up (person-years)	10507	10436	
	IR (95% CI)	0.12 (0.07 - 0.21)	0.42 (0.31 - 0.57)	
Upper RTIs	N events	100	77	0.78 (0.58 – 1.05) p = 0.10
	Follow-up (person-years)	10503	10377	
	IR (95% CI)	0.95 (0.78 – 1.16)	0.74 (0.59 – 0.93)	

DMSR = Danish Multiple Sclerosis Register, DNPR = Danish National Patient Registry, CI = Confidence Interval, RTIs = Respiratory tract infections, IR = Incidence Rate, IRR = Incidence Rate Ratio, IRR calculated as IR DNPR / IR DMSR

The results from Tables 1-2 (Sweden) and 3-4 (Denmark) compare the incidence rates of malignancies and serious infections based on reports collected in the respective MS registries and national healthcare databases for the DMT comparator cohort of the MANUSCRIPT study. As the results demonstrate, there is generally a higher rate of events reported from the national databases compared to the MS registries. For this reason, the Swedish and Danish registries have resolved to using linked data for PASS.

3: Comparisons between BMSD registries

Due to the lack of access to national healthcare databases for the rest of the BMSD registries (Czechia, Italy, France and MSBase), a direct comparison, as performed for Sweden and Denmark earlier, is not possible. An indirect comparison was performed where the IRs of malignancies and serious infections calculated from data collected in each MS registry were compared to IR calculated from the Swedish national healthcare databases. To account for differences in population structures (see Table 5 and 6) that may affect the IRs we standardized the IRs (SIRs) for age and sex by direct standardization method (see Methods section). The comparison of the SIRs was done by means of incidence rate ratio (IRR).

*To avoid confusion in this section, the BMSD registries are referred to as their country name (except MSBase). Where Denmark and Sweden are mentioned, the data used are from the respective national cancer and patient registries. For the other countries the data used are from the respective MS registries.

The number of patients included in this study varied from one country to another and ranged from 933 patients with MS in Czechia for the data used in the ECCS feasibility study to 20,364 patients in Italy for the data used in the MANUSCRIPT study. The mean age of the cohorts ranged between 41.6 (standard deviation (sd): 11.4) years in Denmark for the MANUSCRIPT study cohort to 38.3 (sd: 11.6) years in Italy for the same study. The proportion of females in each cohort also varied between the BMSD registries, from 68% in the Danish ECCS study cohort to 76.1 % in the French MANUSCRIPT study cohort (Table 5 and 6).

Table 5. Population size, age and sex distribution of the cohorts in this study from the data used in the MANUSCRIPT study.

	Denmark (N=5190)	***France (N=6658)***	***Italy (N=20364)***	***MSBase (N=4058)***	***Sweden (N=2556)***
Mean age (sd)	41.6 (11.4)	39.3 (11.1)	38.3 (11.6)	39.3 (12.0)	38.5 (11.1)
N° Females (%)	3706 (71.4%)	5065 (76.1%)	14097 (69.2%)	2992 (73.7%)	1804 (70.6%)

Table 6. Population size, age and sex distribution of the cohorts in this study from the data used in the ECCS feasibility study.

	Denmark (N=4630)	***Czechia (N=933)***	***Sweden (N=8606)***
Mean age (sd)	40.6 (10.6)	40.0 (9.8)	41.2 (11.6)
N° Females (%)	3148 (68.0%)	642 (68.8%)	5936 (69.0%)

A. Results from the analysis of the data used in the MANUSCRIPT study

Malignancies

Standardized incidence rates (SIRs) for malignancy overall ranged from 0.20 (Italy 95% CI 0.18 - 0.23) to 0.44 (Denmark 95% CI 0.40-0.48) per 100 person-years (Table 7). Denmark showed the highest malignancy burden (SIR: 0.44; 95% CI 0.40 – 0.48), significantly higher than Sweden (IRR: 1.31; 95% CI 1.14 – 1.49; $p < 0.001$) (Table 8) even though in both countries the source of the events was the national cancer registries. This difference could partially be explained by the different registration practices in the Swedish and Danish cancer registries such as the use of information from death certificates, the lack of which leads to a 4%-unit higher proportion of non-registered cases in Sweden than other Nordic countries (Pukkala et al 2018). Moreover, Ferlay et al (2018) showed that Denmark has higher age standardized rates (ASRs) for cancers overall compared to Sweden (489.9 (Den) vs 424.7 (Swe) cases per 100,000 for males and 432.9 vs 365.4 for females). Nonetheless, our estimates in this study are not too different compared to those reported in the Ferlay et al (2018)

study. France, with a SIR of 0.32 per 100 person-years (95% CI 0.29 – 0.35) and MSBase, with a SIR of 0.40 per 100 person-years (95% CI 0.36 – 0.44) had comparable rates to Sweden (IRRs of 0.94 (95% CI 0.81 – 1.08, p = 0.39) and 1.18 (95% CI 1.03 – 1.35, p = 0.02), respectively) indicating a similar level of event capture in their disease registries as in the Swedish cancer registry. These estimates were also close to the reported average EU-28 IR of 0.40 per 100 person-years by Ferlay et al (2018). Italy had a notable lower malignancy rate compared to Sweden (SIR 0.20, 95% CI 0.18 – 0.23) and IRR: 0.59; 95% CI 0.51 – 0.70, p < 0.001). D'Amico et al (2019) using the Integrated Cancer of Catania-Messina-Siracusae-Enna database reported malignancy rates in an Italian cohort of pwMS of 0.37 (95% CI 0.36 – 0.38), a value similar to the Swedish estimate in this study, indicating indirectly a possible underreporting in the RISM. We should note here though that RISM went through a change in AEs registration practices in 2020 where the free text format was replaced with MedDRA coding. The MANUSCRIPT study uses extensive MedDRA and ICD-10 code lists to identify relevant events and AEs reports in free text format are not compatible with these code lists. While RISM is actively working on updating the older reports into more usable MedDRA coded versions, the follow-up period from the study start (January 2018) until the change of recording practise (2020) in this study may be void of AEs just due to the format of the reports being in free text and not necessarily due to underreporting in the RISM.

Stratifying by malignancy type the results showed significantly lower rates for all registries compared to Sweden for haematological malignancies (from Italy with SIR of 0 per 100 person-years (95% CI 0 – 0.01, to Denmark and MSBase with SIRs of 0.02 (95% CI 0.01 – 0.03) per 100 person-years), especially Italy (IRR: 0.11 (95% CI 0.04 – 0.27)) and France (IRR: 0.14 (95% CI 0.06 – 0.32); p < 0.001). Denmark and MSBase also had significantly lower IRRs (0.41 (95% CI 0.24 – 0.70) and 0.47 (95% CI 0.28 – 0.78), respectively; p < 0.01). The results for the non-haematological malignancies followed generally those of the overall malignancies for all registries except for MSBase which showed the lowest rate (SIR: 0.06 per 100 person-years (95% CI 0.04 – 0.07)) and a notably low IRR of 0.17 (95% CI 0.13 – 0.22). Italy's rate was lower than Sweden's (SIR: 0.20 per 100 person-years (95% CI 0.17 – 0.22); IRR: 0.58 (95% CI 0.49 – 0.69); p < 0.001), while France was statistically comparable to the Sweden (IRR: 0.92 (95% CI 0.80 – 1.06); p = 0.26). An important clarification needed here is that Sweden and Denmark use the ICD-10 code lists to identify the relevant events while the rest of the registries use the MedDRA code lists. Differences in the way the codes are defined in each malignancy type can affect the interpretation of the results of the subtype analysis. An example of such difference is that in the ICD-10 code lists the 100% of the haematological codes are also included in the non-haematological type while in the MedDRA code lists the percentage of common codes between these subtypes is less than 1%.

Rates for melanoma skin malignancies ranged between 0.06 (95% CI 0.05 – 0.08) per 100 person-years in Denmark and 0.02 per 100 person-years (95% CI 0.02 – 0.04 in France and 95% CI 0.01 – 0.03 in MSBase), while there were 0 cases reported in Sweden. The results from all registries (with exception of Sweden) agree with the published age standardized rate in EU-28 of 0.02 per 100 person-years (Ferlay et al 2018). On the other hand, Denmark and MSBase showed significantly higher incidence rates for non-melanoma skin cancers (SIRs: 0.17 (95% CI 0.15 – 0.20) and 0.16 (95% CI 0.14 – 0.19) per 100 person-years), with IRRs of 2.94 (95% CI 2.24 – 3.89) and 2.76 (95% CI 2.09 – 3.64), respectively (both p < 0.001). France had a IRR of 0.94 (95% CI 0.67 – 1.32) (p = 0.73), while Italy again had a notably lower rate ratio (IRR: 0.39; 95% CI: 0.25 – 0.61; p < 0.001).

Table 7. Crude incidence rates (IR) and standardised incidence rates (SIR) for sex and age distributions per 100 person-years of malignancy overall and by subgroup for all registries.

Outcome		***Denmark****	***France***	***Italy***	***MSBase***	***Sweden****
Malignancy overall	N events	77	45	133	42	25
	Follow-up (person-years)	15472	13902	67913	10212	7587

	IR (95% CI)	0.50 (0.40 - 0.62)	0.32 (0.24 - 0.43)	0.20 (0.17 - 0.23)	0.41 (0.30 - 0.56)	0.33 (0.22 - 0.49)
	SIR (95% CI)	**0.44** (0.40 - 0.48)	**0.32** (0.29 - 0.35)	**0.20** (0.18 - 0.23)	**0.4** (0.36 - 0.44)	**0.34** (0.31 - 0.37)
Haematological malignancy	N events	< 5	1	3	2	3
	Follow-up (person-years)	15609	13954	67913	10274	7654
	IR (95% CI)	< 0.032 (0.03 – 0.035)	0.01 (0 - 0.05)	0 (0 - 0.01)	0.02 (0 - 0.08)	0.04 (0.01 - 0.12)
	SIR (95% CI)	0.02 (0.01 - 0.03)	0.01 (0 - 0.01)	0 (0 - 0.01)	0.02 (0.01 - 0.03)	0.04 (0.03 - 0.05)
Non-haematological malignancy	N events	77	44	130	6	25
	Follow-up (person-years)	15472	13903	67913	10267	7587
	IR (95% CI)	0.50 (0.40 - 0.62)	0.32 (0.24 - 0.43)	0.19 (0.16 - 0.23)	0.06 (0.03 - 0.13)	0.33 (0.22 - 0.49)
	SIR (95% CI)	0.44 (0.40 - 0.48)	0.31 (0.28 - 0.34)	0.20 (0.17 - 0.22)	0.06 (0.04 - 0.07)	0.34 (0.31 - 0.37)
Melanoma skin malignancy	N events	10	4	20	2	0
	Follow-up (person-years)	15593	13948	67913	10269	7657
	IR (95% CI)	0.06 (0.03 - 0.12)	0.03 (0.01 - 0.08)	0.03 (0.02 - 0.05)	0.02 (0 - 0.08)	0 (0 - 0.05)
	SIR (95% CI)	0.06 (0.05 - 0.08)	0.02 (0.02 - 0.04)	0.03 (0.02 - 0.04)	0.02 (0.01 - 0.03)	0 (0 - 0)
Non-melanoma skin cancer	N events	31	7	15	18	4
	Follow-up (person-years)	15545	13944	67913	10252	7645
	IR (95% CI)	0.20 (0.14 - 0.28)	0.05 (0.02 - 0.11)	0.02 (0.01 - 0.04)	0.18 (0.11 - 0.28)	0.05 (0.02 - 0.14)
	SIR (95% CI)	0.17 (0.15 - 0.20)	0.06 (0.04 - 0.07)	0.02 (0.02 - 0.03)	0.16 (0.14 - 0.19)	0.06 (0.05 - 0.07)

CI = Confidence Interval, IR = Incidence Rate, SIR = Standardized Incidence Rate for Sex and Age distribution
*National healthcare databases used for Denmark and Sweden

Table 8. Incidence Rate Ratios (IRR) of malignancy overall and by subgroup for Denmark, France, Italy and MSBase compared to Sweden.

Outcomes		***Denmark***	***France***	***Italy***	***MSBase***
Malignancy overall	IRR (95% CI) p-value	1.31 (1.14 – 1.49) p < 0.001	0.94 (0.81 – 1.08) p = 0.39	0.59 (0.51 – 0.70) p < 0.001	1.18 (1.03 – 1.35) p = 0.02
Haematological malignancy	IRR (95% CI) p-value	0.41 (0.24 – 0.70) p < 0.001	0.14 (0.06 – 0.32) p < 0.001	0.11 (0.04 – 0.27) p < 0.001	0.47 (0.28 - 0.78) p = 0.003
Non-haematological malignancy	IRR (95% CI) p-value	1.31 (1.15 – 1.49) p < 0.001	0.92 (0.80 – 1.06) p = 0.26	0.58 (0.49 – 0.69) p < 0.001	0.17 (0.13 – 0.22) p < 0.001
Melanoma skin malignancy	IRR (95% CI) p-value	-	-	-	-

Non-melanoma skin cancer	IRR (95% CI) p-value	2.94 (2.24 – 3.89) p < 0.001	0.94 (0.67 – 1.32) p = 0.73	0.39 (0.25 – 0.61) p < 0.001	2.76 (2.09 – 3.64) p < 0.001

IRR = Incidence Rate Ratio, CI = Confidence Interval, IRR calculated as SIR BMSD / SIR Sweden

Denmark consistently had the highest malignancy burden, with significantly elevated rates for overall, non-haematological, and skin cancers compared to Sweden, a pattern matching that reported by Ferlay et al (2018) probably due to differences in the recording strategies of the respective cancer registries and other environmental factors. Italy exhibited the lowest malignancy rates, across all categories supporting the notion that this is caused mainly by the change of reporting format in the RISM system. MSBase had generally comparable rates or even elevated rates for skin cancers, but markedly lower rates for non-haematological malignancies overall. France tended to be closer to the Swedish levels across most malignancy categories.

Serious infections

Standardized incidence rates for serious infections overall ranged from 1.32 (France 95% CI 1.24 - 1.41) to 3.75 (Denmark 95% CI 3.61 - 3.90) per 100 person-years (Table 9). Denmark's SIR was comparable to Sweden's with an IRR of 1.06 (95% CI: 1.00 – 1.12; p = 0.042) (Table 10). France, Italy, and MSBase all had significantly lower IRRs (0.37 (95% CI 0.35 – 0.40), 0.80 (95% CI 0.75 – 0.84), and 0.42 (95% CI 0.39 – 0.45) respectively; all p < 0.001).

Looking into the subtypes of infections, all registries reported higher numbers of potential opportunistic infections than Sweden, with Denmark and France having the highest SIR (0.25 (95% CI 0.22 – 0.29) and 0.12 (95% CI 0.10 – 0.15) per 100 person-years respectively) and the highest IRR 4.19 for Denmark (95% CI 3.02 - 5.83; p < 0.001) and 1.99 for France (95% CI 1.39 - 2.87; p < 0.001) respectively. Italy and MSBase were more comparable to Sweden with non-significant IRRs (1.21 (95% CI 0.81 – 1.81, p = 0.347) and 1.31 (95% CI 0.89 – 1.95, p = 0.172) respectively). The low number of events in Sweden was highly influenced by the seriousness proxy criteria applied. As described earlier, in absence of information on the seriousness of the event captured in the national patient registry seriousness proxy rules were created to characterize each event. According to these rules an event was considered serious if it was captured in the hospitalization data or in the emergency outpatient contacts, appeared in the cause of death or was listed in the EMA's important medical event list. Removing the seriousness criteria and including all events as in Denmark, increased the number of opportunistic infection events in Sweden from 3 to 10 and the IR increased to 0.19 per 100 person-years (95% CI 0.16 – 0.23, data not shown), values closer to Denmark's.

In contrast to most outcomes, Italy and MSBase showed higher SIRs (0.33 (95% CI 0.29 – 0.37) and 0.45 (95% CI 0.41 – 0.50) per 100 person-years respectively) for herpetic infections and significantly higher IRRs: 1.32 (95% CI 1.09 – 1.60. p = 0.004) and 1.81 (95% CI 1.51 – 2.17, p < 0.001), respectively, compared to Sweden. France and Denmark reported significantly lower IRRs (0.32 (95% CI 0.24 – 0.43) and 0.20 (95% CI 0.14 – 0.29) respectively; $p < 0.001$), reflecting possible under capture in those registries. Both Italy and MSBase include a specific question regarding herpes infections in their mandatory information gathered during a patients visit (see part 1 description of AEs collection routines for RISM and MSBase) while France's routine includes an overall question and does not include specific categories of infections. The results here indicate that when a doctor asks specifically for a type of AE the rate of capturing these events may increase. The difference observed between Denmark and Sweden is probably due to differences in healthcare systems and practices. It is possible that herpes infection cases are managed in primary care mainly for which data is not available.

Denmark had the highest SIR for urinary tract infections (UTIs) (1.03 per 100 person-years, 95% CI (0.96 – 1.10)) and a significantly elevated IRR of 2.21 (95% CI 1.94 – 2.51; p < 0.001) compared to Sweden. These results are similarly affected by the different approach in classifying events based on seriousness between Sweden and Denmark. Including non-serious UTIs in the Swedish analysis resulted in higher number of events (55) and similar IR as in Denmark (1.04 per 100 person-years (95% CI 0.96 – 1.12), data not shown). The other registries showed significant lower rates compared to Sweden (France: IRR 0.22; 95% CI 0.17 - 0.29, Italy: IRR 0.23; 95% CI 0.18 - 0.23, MSBase: IRR 0.67; 95% CI 0.57 - 0.79, all p < 0.001), with SIRs ranging between 0.31 per 100 person-years (MSBase, 95% CI 0.27 - 0.35) and 0.10 per 100 person-years (France, 95% CI 0.08 - 0.13) indicating possible underreporting. Nonetheless, reported incidence rates of UTIs from observational studies vary largely. Luna et al (2020) reported an IR of 0.03 per 100 person-years (95% CI 0.01 – 0.07) in a large Swedish MS cohort of more than 6,000 patients while a smaller study of 225 MS patients from Italy reported an IR of 2.89 per 100 person-years (95% CI 1.68 – 4.98, Manni et al 2017) while a French study of 50 MS patients reported an IR of 1.82 per 100 person-years (95% CI 0.26 – 12.9, Durozard et al, 2019).

Sweden consistently showed the highest SIRs for both lower (0.98, 95% CI 0.91 - 1.05) and upper respiratory tract infections (RTIs) (0.76, 95% CI 0.70 - 0.82). France had high SIRs for lower RTIs (0.81, 95% CI 0.75 - 0.88), very closely comparable to Sweden (RR 0.83; 95% CI 0.74-0.92. p < 0.001) but low rates for upper RTIs (SIR 0.03 per 100 person-years, 95% CI 0.02 - 0.05), indicating possible inconsistency in reporting by infection type. Italy consistently showed low SIRs for both lower and upper RTIs (SIR 0.10 per 100 person-years; 95% CI 0.08 - 0.12 and SIR 0.08 per 100 person-years; 95% CI 0.06 - 0.10, respectively) while MSBase had low-to-moderate rates compared to Sweden (lower RTIs IRR 0.12; 95% CI 0.09 - 0.15, p < 0.001 and upper RTIs IRR 0.33; 95% CI 0.28 - 0.39, p < 0.001). Butzkueven et al (2014) reported pneumonia IRs of 0.15 per 100 person-years (95% CI 0.09 – 0.25) in an international cohort of 4,821 MS patients, values like the MSBase result for lower RTIs in this analysis (0.12, 95% CI 0.09 - 0.14). Similarly, Ragonese et al (2017) and Sangalli et al (2011) reported IRs of pneumonia in 2 cohorts of 264 and 285 Italian MS patients of 0,10 (95% CI 0.02 – 0.38) and 0.27 per 100 person-years (95% CI 0.04 – 1.93), respectively.

Table 9. Crude incidence rates (IR) and standardized incidence rates (SIR) for age and sex distribution of serious infections overall and by subgroup for all registries.

Outcome		*Denmark*	*France*	*Italy*	*MSBase*	*Sweden*
Serious infections overall	N events	367	168	1041	125	180
	Follow-up (person-years)	9963	12712	36766	7895	5194
	IR (95% CI)	3.68 (3.33 - 4.08)	1.32 (1.14 - 1.54)	2.83 (2.66 - 3.01)	1.58 (1.33 - 1.89)	3.47 (2.99 - 4.01)
	SIR (95% CI)	**3.75** (3.61 - 3.90)	**1.32** (1.24 - 1.41)	**2.82** (2.70 - 2.95)	**1.49** (1.41 - 1.59)	**3.54** (3.41 - 3.68)
Potential opportunistic infections	N events	26	15	25	6	3
	Follow-up (person-years)	10475	12875	36766	8067	5504
	IR (95% CI)	0.25 (0.17 - 0.36)	0.12 (0.07 - 0.19)	0.07 (0.05 - 0.10)	0.07 (0.03 - 0.17)	0.05 (0.02 - 0.17)
	SIR (95% CI)	0.25 (0.22 - 0.29)	0.12 (0.10 - 0.15)	0.07 (0.06 - 0.09)	0.08 (0.06 - 0.10)	0.06 (0.04 - 0.08)
Herpetic infections	N events	6	10	121	38	13
	Follow-up (person-years)	10499	12878	36766	8022	5496
	IR	0.06	0.08	0.33	0.47	0.24

	(95% CI)	(0.03 - 0.13)	(0.04 - 0.14)	(0.28 - 0.39)	(0.34 - 0.65)	(0.14 - 0.41)
	SIR	0.05	0.08	0.33	0.45	0.25
	(95% CI)	(0.04 - 0.07)	(0.06 - 0.10)	(0.29 - 0.37)	(0.41 - 0.50)	(0.22 - 0.29)
Urinary tract infections	N events	105	13	38	27	25
	Follow-up (person-years)	10366	12880	36766	8046	5460
	IR	1.01	0.10	0.10	0.34	0.46
	(95% CI)	(0.84 - 1.23)	(0.06 - 0.17)	(0.08 - 0.14)	(0.23 - 0.49)	(0.31 - 0.68)
	SIR	1.03	0.10	0.11	0.31	0.46
	(95% CI)	(0.96 - 1.10)	(0.08 - 0.13)	(0.08 - 0.13)	(0.27 - 0.35)	(0.42 - 0.52)
Lower RTIs	N events	44	104	34	11	52
	Follow-up (person-years)	10436	12782	36766	8063	5433
	IR	0.42	0.81	0.09	0.14	0.96
	(95% CI)	(0.31 - 0.57)	(0.67 - 0.99)	(0.07 - 0.13)	(0.08 - 0.25)	(0.73 - 1.26)
	SIR	0.39	0.81	0.10	0.12	0.98
	(95% CI)	(0.35 - 0.44)	(0.75 - 0.88)	(0.08 - 0.12)	(0.09 - 0.14)	(0.91 - 1.05)
Upper RTIs	N events	77	4	31	21	40
	Follow-up (person-years)	10376	12886	36766	8054	5445
	IR	0.74	0.03	0.08	0.26	0.73
	(95% CI)	(0.59 - 0.93)	(0.01 - 0.08)	(0.06 - 0.12)	(0.17 - 0.40)	(0.54 – 1.00)
	SIR	0.79	0.03	0.08	0.25	0.76
	(95% CI)	(0.73 - 0.86)	(0.02 - 0.05)	(0.06 - 0.10)	(0.22 - 0.29)	(0.70 - 0.82)

CI = Confidence Interval, IR = Incidence Rate, SIR = Standardized Incidence Rate for Sex and Age distribution, RTIs = Respiratory tract infections

*National healthcare databases used for Denmark and Sweden

Table 10. Incidence Rate Ratios (IRR) of serious infections overall and by subgroup for Denmark, France, Italy and MSBase compared to Sweden.

Outcomes		***Denmark***	***France***	***Italy***	***MSBase***
Serious infections overall	IRR	1.06	0.37	0.80	0.42
	(95% CI)	(1.00 – 1.12)	(0.35 – 0.40)	(0.75 – 0.84)	(0.39 – 0.45)
	p-value	p = 0.042	p < 0.001	p < 0.001	p < 0.001
Potential opportunistic infections	IRR	4.19	1.99	1.21	1.31
	(95% CI)	(3.02 – 5.83)	(1.39 – 2.87)	(0.81 – 1.81)	(0.89 – 1.95)
	p-value	p < 0.001	p < 0.001	p = 0.347	p = 0.172
Herpetic infections	IRR	0.20	0.32	1.32	1.81
	(95% CI)	(0.14 – 0.29)	(0.24 – 0.43)	(1.09 – 1.60)	(1.51 – 2.17)
	p-value	p < 0.001	p < 0.001	p = 0.004	p < 0.001
Urinary tract infections	IRR	2.21	0.22	0.23	0.67
	(95% CI)	(1.94 – 2.51)	(0.17 – 0.29)	(0.18 – 0.29)	(0.57 – 0.79)
	p-value	p < 0.001	p < 0.001	p < 0.001	p < 0.001
Lower RTIs	IRR	0.40	0.83	0.10	0.12
	(95% CI)	(0.35 – 0.46)	(0.74 – 0.92)	(0.08 – 0.13)	(0.09 – 0.15)
	p-value	p < 0.001	p < 0.001	p < 0.001	p < 0.001
Upper RTIs	IRR	1.04	0.04	0.11	0.33
	(95% CI)	(0.93 – 1.17)	(0.03 – 0.06)	(0.08 – 0.14)	(0.28 – 0.39)
	p-value	p = 0.489	p < 0.001	p < 0.001	p < 0.001

IRR = Incidence Rate Ratio, CI = Confidence Interval, RTIs = Respiratory tract infections, IRR calculated as SIR BMSD / SIR Sweden

These results show that the rate of capture of serious infections in the different registries is quite variable and depends on the type of infection but several of them perform robustly enough to support their use in a PASS context. France, while showing lower rates for some outcomes, still captures a significant number of serious infections overall and opportunistic infections (IRRs: 0.37 and 1.99, respectively; both $p < 0.001$), indicating effective identification of key safety events. MSBase also captures adverse events at meaningful levels, with significantly elevated detection of herpetic infections (IRR: 1.81; $p < 0.001$) and moderate rates for other outcomes. Italy, though reporting slightly lower rates for some events, still identifies elevated herpetic infections (IRR: 1.32; $p = 0.004$) and performs comparably to MSBase and France for opportunistic infections. The relatively recent update of the RIMS reporting system from free text to MedDRA (2020) may be partially responsible for the relatively lower SIRs in Italy presented here, as the events captured from the study start (January 2018) until the update (2020) are only available in free text and not MedDRA coding. This makes their use in any analysis much more complicated and cumbersome resulting in excluding these events from the analysis all together. Nonetheless, Italy is working actively on recoding older AE reports in their registry to MedDRA terms. Overall, these findings suggest that the participating registries are capturing adverse events at levels sufficient to support their use in post-marketing safety surveillance, particularly when considering real-world data heterogeneity across settings.

B. Results from the analysis of the data used in the ECCS feasibility study

The results of the comparison based on the data used in the ECCS feasibility study are presented in tables 11 (for incidence rates) and 12 (for incidence rate ratios). Czechia and Sweden reported comparable standardized incidence rates of malignancies overall excluding non-melanoma skin cancer (Czechia: 0.72 per 100 person-years (95% CI 0.65-0.79) and Sweden: 0.69 per 100 person-years (95% CI 0.62-0.75) yielding an IRR of 1.05 (95% CI 0.92 – 1.19, p = 0.49), indicating no significant difference. Pehalova et al (2021) in their study reported an average of 59,559 new malignancy cases (excluding non-melanoma skin cancer) per year between 2016 and 2018 based on data recorded in the Czech National Cancer Registry, yielding a crude incidence rate of 0.56 per 100 person-years, while the age standardized rate (ASR) based on the European population was 0.70 and 0.48 per 100 person-years for males and females, respectively, supporting our results and showing that the collection of adverse event related to malignancy is adequate in the Czech MS registry. Denmark reported a lower malignancy SIR of 0.41 per 100 person-years (95% CI 0.36 - 0.46), and a low IRR of 0.60 (95% CI: 0.51 – 0.70; $p < 0.001$) compared to Sweden. Both the Swedish and Danish IRs were calculated based on data from the respective national cancer registries, which have a very high nation-wide coverage (Pukkala et al 2018). Therefore, the results here reflect differences in incidence of malignancies particular to the specific cohort of MS patient included in this analysis rather than underreporting in the Danish national cancer registry.

Regarding serious infections overall including opportunistic infections Czechia reported a SIR of 1.33 per 100 person-years (95% CI 1.24 - 1.42), very similar to Sweden, with an IRR of 1.04 (95% CI 0.94 – 1.14, p = 0.45), indicating no meaningful difference. Denmark's SIR was higher, at 1.73 per 100 person-years (95% CI 1.63 - 1.84), compared to 1.28 per 100 person-years (95% CI 1.19 - 1.37) in Sweden, and showed an elevated IRR of 1.36 (95% CI: 1.24 - 1.49; $p < 0.001$). A small study of 240 pwMS in Czechia followed the patients for a year with 3-monthly visits and reported a serious infection IR of 0.42 per 100 person-years (95% CI 0.06 – 2.96, Ticha et al. 2017). Moreover, several observational studies based on European cohorts of at least 100 pwMS have reported incidence rates of serious infections that ranged from 0.03 per 100 person-years (95% CI 0.004 – 0.20, Tedeschi et al 2009) to 2.86 per 100 person-years (95% CI 0.92 – 8.86, Rasenack et al 2016) confirming the validity of our findings.

These results suggest that Czechia captures both malignancies and serious infections at levels comparable to the Swedish national healthcare databases, supporting its use in post-marketing surveillance.

Table 11. Crude incidence rates (IR) and standardized incidence rates (SIR) for age and sex distribution, of malignancies and serious infections based on data used in the ECCS feasibility study

Outcome		***Czechia***	***Denmark***	***Sweden***
Malignancies	N events	21	80	281
	Follow-up (person-years)	3132	20474	39780
	IR (95% CI)	0.67 (0.44 – 1.03)	0.39 (0.31 – 0.49)	0.71 (0.63 – 0.79)
	SIR (95% CI)	0.72 (0.65 – 0.79)	0.41 (0.36 – 0.46)	0.69 (0.62 – 0.75)
Serious Infections	N events	38	335	506
	Follow-up (person-years)	3079	19841	38873
	IR (95% CI)	1.23 (0.90 – 1.70)	1.69 (1.52 – 1.88)	1.30 (1.19 – 1.42)
	SIR (95% CI)	1.33 (1.24 – 1.42)	1.73 (1.63 – 1.84)	1.28 (1.19 – 1.37)

Table 12. Incidence Rate Ratios (IRR) of malignancies and serious infections for Denmark and Czechia compared to Sweden.

Outcomes		***Czechia***	***Denmark***
Malignancies	IRR (95% CI) p-value	1.05 (0.92 – 1.19) p = 0.49	0.60 (0.51 – 0.70) p < 0.001
Serious infections	IRR (95% CI) p-value	1.04 (0.94 – 1.14) p = 0.45	1.36 (1.24 – 1.49) p < 0.001

IRR = Incidence Rate Ratio, CI = Confidence Interval, IRR calculated as SIR BMSD / SIR Sweden

Conclusions

This study shows that SAE information can effectively be collected for patients in all six participating registries, either directly by the registry IT platforms (for Czechia, France, Italy and MSBase) or indirectly by linking to national patient registries (for Denmark and Sweden). Moreover, with this approach, SAE incidence rates between the BMSD registries are similar if not identical, although data collection procedures are somewhat differently organized. We believe this adds confidence in the SAE incidence rates reported by BMSD registries in the context of PASSs and provides evidence for “fitness-of-purpose”.

In all BMSD countries, neurologists, when seeing patients, are required to inquire about and document serious or unexpected adverse event in connection to their treatment. The BMSD registries offer structured, robust and well-integrated IT interfaces to facilitate the AEs collection, ensuring consistency and completeness, and the reporting to the authorities responsible for pharmacovigilance. Nowadays, the coding system is based mainly on MedDRA terminology and ICD-10 codes which facilitates the use of this data for large safety studies while efforts are underway to update historical data to the modern standards.

In addition, the study demonstrates an innovative approach to effective pharmacovigilance, which is generally assumed to be a challenge, by using data from large national healthcare databases, available mainly in the Nordic countries. Our results show that these offer valuable data on medical conditions of interest to safety studies and can be used to compensate for any underreporting in the MS registries as in the case of Sweden and Denmark although these sources are not designed for pharmacovigilance. Therefore, there is a lack of important information such as seriousness of the event, action taken regarding treatment, outcome, etc. Adequate strategies of handling these data for safety studies are indeed being developed in ongoing PASS to ensure correct and comparable estimates between different countries.

Our results show that the registries that rely on their own data collection and do not have access to national healthcare databases seem to have less underreporting compared to the Swedish and Danish MS registries and are comparable to the Nordic national databases for many of the outcomes studied here indicating a good capture of several categories of AEs, while highlighting areas where the registries could work on improvement.

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