Federal Institute
for Drugs
and Medical Devices

Workshop on the draft guideline on registry-based studies

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Session 2: Regulator´s example - MS Registry

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Disclaimer

- No CoI
- The opinions expressed in this presentation are solely those of the presenter and do not necessarily reflect the official views of the Federal Institute of Drugs and Medical Devices (BfArM) or the European Medicines Agency (EMA).
- All information discussed is included in the Draft Guideline on registry-based studies **(EMA/502388/2020, 24 September 2020)** or publically available.

Registries as basis for registry-based studies

Pharmacoepidemiology studies, e.g.

- Drug utilisation studies
- PASS
- PAES

Examples

- Qualification Opinion on The European Cystic Fibrosis Society Patient Registry (ECFSPR) and CF Pharmaco-epidemiology Studies (EMA/CHMP/SAWP/622564/2018)
- Qualification opinion on Cellular therapy module of the European Society for Blood & Marrow Transplantation (EBMT) Registry (EMA/CHMP/SAWP/792574/2018)
- Multiple Sclerosis (MS) with ongoing and upcoming qualification procedures

Population characteristics in MS

- MS is a chronic, inflammatory, demyelinating CNS disease
- Affects approx. 2.3 million people worldwide

How can representativeness be ensured – benchmarking?

What needs to be shown:

- MS registry data are constantly covering the whole range of demographic and clinical characteristics in each of the MS subtypes and inclusion of all DMTs (disease modifying therapies) available
- Does comparison to national social security systems help?

Difficult

National registries versus Big Data networks

- Each registry is developed within a unique ecosystem with specified structures and resources, but also different missions.
- Representativeness could be enhanced by cooperation with other registries especially for the dataset to be maximally useful for regulatory purposes across different countries.
- Key factor of understanding treatment practices and outcomes across the EU

Example MSBase; Big MS Data (BMSD)

Population characteristics in MS –BIG MS Data network

http://www.ofsep.org/ECTRIMS/2017/P738_BIG%20MS%20DATA_poster1.pdf

Table 1. Main characteristics of the cohort extracted stratified by registry.

	Italy	Sweden	Denmark	OFSEP	MSBase **	Total
Total cohort *	38,433	16,502	8,991	54,066	31,644	149,636
Patients with ≥ 10 years follow-up + at least 3 EDSS evaluations	9,133	1,623	1,894	4,941	3,819	21,410
Treated patients	8,217	1,487	1,894	3,225	3,452	18,275
Untreated patients	916	136	0	1,716	367	3,135
Total number of EDSS score evaluations	230,401	20,795	40,925	87,126	93,076	472,323
mean (SD)	25.2 (17.0)	12.8 (6.6)	21.6 (6.9)	17.6 (13.4)	24.4 (17.6)	
median (min - max)	21 (3-109)	11 (3-46)	21 (4-52)	15 (3-127)	18 (3-162)	

* As reported ar September 2016; ** Excluding Italian Participating Centers

Report on Muliple Sclerosis Registries – Workshop July 2017

EMA/548474/2017

Recommendation that registry holders should agree on a common core data set

- Patient specific data (Date of birth, death, gender, country and residence, employment status)
- Disease specific information (Date of diagnosis, onset, MS type: RRMS including CIS, SPMS, PPMS, EDSS, relapse, QoL, hospitalisation)
- Para-clinical investigations (MRI, CSF, lymphocytes, liver enzymes)
- Co-morbidities
- Treatment (MS therapy including symptomatic therapy, other)
- Serious suspected adverse events
- Pregnancy

Critical recommendation on socio-economic background

Working environment e.g. employment opportunities and amount of income:

It is not a natural part of the patient-physician relationship. Open discussion on income is embarrassing and not justified without good reason.

Scientific/Regulatory adequacy of the datasets1:

- Are the EMA MS workshop recommendations followed?
- Criteria for a relapse or the grading of severity of relapse should be clearly defined based on the current medical knowledge at the time of documentation including McDonald diagnostic criteria in MS.
- Regular trainings and discussions in web-based seminars

Scientific/Regulatory adequacy of the datasets2:

- For AEs reporting recommendation to implement the use of MedDRA terms
- Can we ask to develop an eCRF (electronic case report form) enabling the user to generate a CIOMS-like form for ADR reporting as well ?
  - (reference to ICH E2B on electronic transmission of individual case safety reports (ICSRs) - data elements and message specification - implementation guide; EMA/CHMP/ICH/287/1995)
  - might be especially important for e.g. imposed PASS studies

Challenging aspect of aligning regulatory needs with “real world” registry practice

Technical and QA-related adequacy of the datasets and the data capturing system

- Compliance with GCP
- Information needed on
  - computerised system validation strategy,
  - the change control process,
  - a version history of the MS registry system
  - audit trail functionality as well as an edit check specification document
- Information on the technical adequacy of the datasets and data entry forms e.g. the sample CRFs (including ePRO) should be provided
- Definition of minimum data sets, mandatory data entry fields and positive missing data confirmation should be provided to evaluate data completeness
- Data audit trail should be incorporated

Summary of difficulties encountered

- Representativeness of the population and generalisability of results derived solely from national registries (DUS, PAES, HTA purposes)
- Common data elements (nice-to have vs. need-to have)
- ADR collection and reporting
- Technical validation (GCP, validated computerised systems to ensure data integrity)

What can be offered?

- Early involvement of SAWP for **Scientific advice**
- **CHMP Qualification Opinion** on the acceptability of a specific use of the proposed method (e.g. a registry based study) in a research and development (R&D) context (registry), based on the assessment of submitted data.
- **CHMP Qualification Advice on future protocols and methods for further method development towards qualification**, based on the evaluation of the scientific rationale and on preliminary data submitted.

Thank you very much for your attention!

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