Supplementary material

Collection of data on adverse events related to medicinal products: a survey among registries in the ENCePP Resources database – Drug Safety

Kelly Plueschke[1]

Carla Jonker[1, 2]

Valerie Strassmann[1]

Xavier Kurz[1]

1 Data Analytics and Methods Task Force, European Medicines Agency, Amsterdam, The Netherlands

2 Medicines Evaluation Board, The Netherlands

Corresponding author: Kelly Plueschke[1]

e-mail: Kelly.plueschke@ema.europa.eu

Address: European Medicines Agency, Domenico Scarlattilaan 6, 1083 HS Amsterdam, The Netherlands

Telephone: +31 (0)88 781 8000

Table 1 - List of respondent patient registries

The information included in the table below have been retrieved from the ENCePP Resources database in September 2020

Name of the patient registry	Countries	Scope	Link
BIKER	AT, DE	Children rheumatology	Data Source (encepp.eu)
BIOREG	AT	Registry for Biologic Agents	Data Source (encepp.eu)
chILD-EU	EEA (AT, BE, DK, FR, DE, IT, NL, PL, PT, RO, ES, UK) + Switzerland, Middle East, Africa	European Management Platform for Childhood Interstitial Lung Diseases	Data Source (encepp.eu)
Danish Registries (access/analysis)	DK	Danish national population registries (administered by Danish authorities and accessed by researchers on project basis)	Data Source (encepp.eu)
Deutsches Hämophilieregister (DHR)	DE	Haemophilia	Data Source (encepp.eu)
EBMT	EEA + Non EEA Europe (excluding Russia & former Soviet Republics), Russia & former Soviet Republics, Middle East, Asia, North America, South America, Africa, Australia & Oceania	European Society for Blood and Marrow Transplantation	Data Source (encepp.eu)
EHDN - REGISTRY	EEA (AT, BE, CZ, DK, FI, FR, DE, IT, NL, NO, PL, PT, ES, SE, UK) + Switzerland, Russia & former Soviet Republics	Huntington's Disease	Data Source (encepp.eu)
Enroll-HD	EEA (AT, BE, DK, FR, DE, IE, IT, NL, PL, ES, UK) + Switzerland, North America, Central America & Caribbean,	Huntington's Disease	Data Source (encepp.eu)

Name of the patient registry	Countries	Scope	Link
	South America, Australia & Oceania		
ESID Registry	EEA (AT, BE, HR, CZ, EE, FR, DE, GR, HU, IE, IT, LT, NL, PL, PT, RO, SK, SI, ES, SE, UK) + Switzerland, Russia & former Soviet Republics	Immunodeficiencies	Data Source (encepp.eu)
EURAP-Epilepsy and pregnancy	EEA + Non EEA Europe (excluding Russia & former Soviet Republics), Asia, South America, Australia & Oceania	International Registry of Antiepileptic Drugs and Pregnancy	Data Source (encepp.eu)
EUROmediCAT	EEA (BE, HR, DK, FR, DE, IE, IT, MT, NL, NO, PL, ES, UK) + Switzerland, Non EEA Europe (excluding Russia & former Soviet Republics)	Central database of congenital anomaly registries	Data Source (encepp.eu)
European Porphyria Registry (EPR)	EEA + Africa	Porphyria, Inherited blood disorders	Data Source (encepp.eu)
FranceCoag	FR	Haemophilia	Data Source (encepp.eu)
German AD Registry TREATgermany	DE	Atopic Dermatitis	Data Source (encepp.eu)
German MS-Register	DE	Multiple sclerosis	Data Source (encepp.eu)
Global FKRP Registry - LGMDR9	EEA (all MSs) + Switzerland, Russia & former Soviet Republics, Middle East, Asia, North America, Central America & Caribbean, South America, Africa, Australia & Oceania	Global Fukutin-Related Protein disease	Data Source (encepp.eu)
HemoNED - Haemophilia	NL	Haemophilia	Data Source (encepp.eu)

Name of the patient registry	Countries	Scope	Link
ICRS	FR, DE, IT, NL, ES + Asia	Cartilage Damage (International Cartilage Repair Society Patient Registry)	Data Source (encepp.eu)
MappHemo	Information cannot be found in ENCePP	Information cannot be found in ENCePP	Information cannot be found in ENCePP
PedNet	EEA (AT, BE, DK, FI, FR, DE, GR, IR, IT, NL, NO, PT, ES, SE, UK) + Switzerland, Middle East, North America	Haemophilia	Data Source (encepp.eu)
Pharmachild	IT + Russia & former Soviet Republics, Middle East, South America	Juvenile idiopathic arthritis (JIA)	Data Source (encepp.eu)
PROGNOSIS	EEA	The PROspective German NOn-CF BronchiectaSIS Patient Registry	Data Source (encepp.eu)
Registry of children with neuromuscular diseases	Information cannot be found in ENCePP	Information cannot be found in ENCePP	Information cannot be found in ENCePP
R-LIVER rare liver disease registry	EEA (DK, DE, HU, LT, NL, PL, ES) + Switzerland	Rare liver diseases	Data Source (encepp.eu)
RORENO - Oncology	PT	Oncology	Data Source (encepp.eu)
SMArtCARE	AT, DE + Switzerland Non EEA Europe excluding Russia & former Soviet Republics)	Spinal Muscular Atrophy	Data Source (encepp.eu)
The Danish Prescription Registry linked to the Patient Registry	DK	Information cannot be found in ENCePP	Information cannot be found in ENCePP
UK CF Registry	UK	Cystic Fibrosis	Data Source (encepp.eu)
UK Myotonic Dystrophy Patient Registry	UK	Myotonic Dystrophy	Data Source (encepp.eu)

Name of the patient registry	Countries	Scope	Link
UK SMA Patient Registry	UK	Spinal Muscular Atrophy	Data Source (encepp.eu)
World Bleeding Disorders Registry	EEA + International	Bleeding Disorders	Data Source (encepp.eu)

Table 2 - Aggregated responses

Questions	Responses	% from respondents	Summary of comments received
Does your registry routinely collect information on medicines taken by each patient enrolled in the registry?	Total: 31 Yes: 29 No: 2	Yes: 93%	• Datasets recently expanded by some of the registries to capture information on (some of the) medicines • Data routinely updated (e.g. during annual visits) • Some registries also collect data on medicines taken prior, concomitantly or after the treatment of interest • - 2 "NOs": No information on whether the data can be collected upon request from regulatory authorities and/or pharmaceutical companies
Does your registry routinely collect information on adverse events experienced by patients taking medicines?	Total: 29 Yes: 19 No: 10	Yes: 65%	YES: • Subset of centres only (roll-out in phases) • Subset of AESI/ADRs according to specific timepoints • Patients report AEs they experience but no further details asked NO: • Subset of patients in dedicated studies only • Field exist but rarely used
Which information on adverse events experienced by patients taking medicines does your registry routinely collect? Total: 19 responses			
Serious[1] adverse events[2] only	Yes: 4 No: 15	Yes: 21%	• Patient-reported data for some registries • Only targeted events/reactions or according to study protocols accepted by centres • AEs/ADRs recorded but registries not designed for pharmacovigilance purposes (i.e. no ICSR reporting) • Causality assessment and seriousness not systematically collected *NOTE: Respondents could tick several options*
All serious and non-serious adverse events	Yes: 14 No: 5	Yes: 74%	
Serious suspected adverse drug reactions only	Yes: 2 No: 17	Yes: 10%	
All serious and non-serious adverse drug reactions[3]	Yes: 11 No: 8	Yes: 58%	
Adverse events of special interest[4] (defined a priori)	Yes: 11	Yes: 58%	

[1] Resulting in death, life-threatening, requiring in-patient hospitalisation or prolongation of existing hospitalisation, resulting in persistent or significant disability or incapacity, or is a congenital anomaly/birth defect
[2] Any untoward medical occurrence in a patient administered a medicine and which does not necessarily have a causal relationship with this treatment. An adverse event can therefore be any symptom, sign or disease temporally event associated with the use of a medicine, whether considered related to the medicine or not
[3] Synonyms: "adverse reaction" or "adverse drug reactions, "adverse effect", "undesirable effect": response to a medicinal product which is noxious and unintended, and for which a causal relationship between a medicine and the occurrence is suspected
[4] A noteworthy event for the particular product or class of products that is monitored. It could be serious or non-serious. Such events should be described in study protocols and instructions provided for investigators as to how and when they should be reported

Questions	Responses	% from respondents	Summary of comments received
	No: 8		
Information on spontaneous reports related to patients included in the registry that have also been sent to national competent authorities or marketing authorisation holders	Yes: 6 No: 12 Do not know: 1	Yes: 31%	
At which frequency is the data on adverse events collected centrally?	19 responses: • Collected at each patients' visit (depends on frequency of FU visits by local practices or centres' set data upload): 6 • At least once a year: 5 • Every 6 months: 3 • Between 3 to 6 months: 3 • Continuously: 1 • Specific timepoints (e.g. baseline, 100 days, 6 months and then yearly): 1		
Is information available to explain the current practice and processes in place for the collection of data on adverse events?	Total: 19 Yes: 12 No: 7	Yes: 63%	• The complete data set recorded in the registry / study protocol / data collection forms can be downloaded from some of the registries' websites • Available upon request
Does your registry provide to other organisations data on adverse events experienced by patients taking medicines?	Total: 19 Yes: 13 No: 6	Yes: 68%	• YES: Publication of (bi-)annual reports; upon requests according to agreed timelines • No: Only for scientific publications • To pharmaceutical companies: 11 • To regulatory/national competent authorities: 9 • Others (researchers, PV programme): 2
What is the time lag between the collection of data on adverse events at a central level and the date of sharing of these data with other organisations?	13 responses: • Immediately (e.g. automatic link to authorities): 3 • 3 to 6 months: 2 • 1 year and more: 1 • Up to 1 month: 1 • Do not know/Not enough experience: 2 • Depends on request and stakeholder: 4		
Can your registry collect additional data elements related to adverse events experienced by patients taking medicines upon requests from pharmaceutical companies and/or regulatory authorities?	Total: 31 Yes: 22 No: 6 Do not know: 3	Yes: 71%	• Possible implementation upon financial support, e.g. for registry-based studies • May require steering committee/ethics approval to change the registry platform • Possibility to go back to the site(s) and ask for additional information on cases • To pharmaceutical companies: 18 • To regulatory/national competent authorities: 18

Questions	Responses	% from respondents	Summary of comments received
			• Others (patient organisations, researchers, PV programme): 5
Has your registry developed a policy for collaboration with other organisations for the monitoring of medicines?	Total: 22 Yes: 8 No: 12 Do not know: 2	Yes: 36%	• Examples provided: Protocols for data sharing; Governance documents for data linkage program; Data application procedures
Does your registry analyse internally data on adverse events to medicines requested by pharmaceutical companies and/or regulatory competent authorities and is the result of this analysis shared with the requester?	Total: 22 Yes: 11 No: 10 Do not know: 1	Yes: 50%	Time lag between data collection and sharing of analysis: • Up to 1 month: 3 • 3 to 6 months: 4 • 1 year and more: 1 • Other (Do not know / not enough experience / depends on timing of requests): 3 Other comments: • According to agreements with stakeholders in place • AEs are analysed centrally and reported at least annually in a report • Specific projects on medications of interest are published
What are important obstacles for the collection and provision of data on adverse events to pharmaceutical companies and/or regulatory competent authorities? *Total: 22*	Data collection process • Lack of harmonisation of data collection forms – time consuming to map/adapt • Staff training at centres and registries' levels (e.g. for MedDRA-Coding and follow-up on AEs) • Data reported by patients (possible impact on data quality) • Non-compliance of physicians in reporting AEs in a timely manner • Voluntary contribution of centres to the registries • Lack of data linkage with other healthcare databases • Long term follow-up of patients that might be moving between centres and countries • Possible bias in (non)reporting AEs for certain products • Collection of Patient Reported Outcomes from patients Data sharing/reporting • Time lag between the event, registry data entry, and subsequent analysis and reporting • Need for more formal and harmonised process to collect, share and use the data • Pressure on centres and registries: Increasing demands from MAHs for conducting a PAS in existing registry and request centres to submit additional data to allow MAHs to comply with their reporting obligations • Limitations to data sharing: Ethical laws, GDPR, informed consent, national obligations		

Questions	Responses	% from respondents	Summary of comments received
	Governance • Funding/resources: need for compensation/incentives for the centres to ensure data collection and quality management • Collection of AEs not the registry's purpose (HCPs reports AEs/ADRs as they occur outside routine data collection) • Registry maintained by the regulatory authority • Lack of EU regulatory framework for conducting a PAS in existing registry, lack of guidance • Communication between stakeholders • Role of academia in collecting and sharing AEs on rare diseases should be better described and emphasized		
Important factors facilitating the collection and provision of data on adverse events to pharmaceutical companies and/or regulatory competent authorities? *Total: 29*	Operational aspects • More guidance on use of real-world data from Registries in regulatory frameworks • Standardisation of data fields • Harmonisation of requirements, e.g. through a CDM or a common protocol • Unique patient numbers in the EU • Quality-assured reporting procedures for safety data • Registries' flexibility on alternative time periods for data sharing and additional collection of events • Ability to report only de-identified dataset (aggregated data) • Quick access to data for analysis • Easy to capture data and add fields to the registry • More regular contacts between registries and regulatory authorities to align expectations, highlighting issues Governance • Funding/sponsors to allow for additional resources • Clear contractual agreements and responsibilities • Collaboration with academia • Involvement of the registry steering committee before data sharing • Registry maintained by the regulatory authority • Data confidentiality • Legal obligation for centres and patients to share data		