



Collection of Data on Adverse Events Related to Medicinal Products: A Survey Among Registries in the ENCePP Resources Database

Kelly Plueschke¹ · Carla Jonker^{1,2} · Valerie Strassmann¹ · Xavier Kurz¹

Accepted: 10 May 2022 / Published online: 21 June 2022
© The Author(s) 2022

Abstract

Introduction As patient registries are not subject to regulatory requirements on the collection of adverse events (AEs) related to medicinal products, they may not have foreseen the collection of such information on a routine basis or as part of specific data collection schemes.

Objective The European Medicines Agency conducted a survey among registries to better understand their approach towards the collection, management and reporting of AEs related to medicines.

Method An online survey composed of 15 questions was distributed in May 2020 to registries listed in the European Network of Centres in Pharmacoepidemiology and Pharmacovigilance (ENCEPP) resources database for completion by August 2020. Aggregated results are presented in this paper.

Results One third of the registries completed the survey (31/85; 36.5%). Most of the respondents routinely collect information on medicines (29/31; 93.5%), out of which 65.5% (19/29) also collect data on AEs and adverse drug reactions (ADRs). Frequencies and timelines for collecting and reporting AEs/ADRs vary widely across registries, as does their level of experience in providing data to third parties for regulatory purposes.

Conclusions The low response rate may indicate little interest in this topic or that registries were not originally developed for routine data collection on AEs/ADRs and, ultimately, monitoring of the safety of medicines. Results indicate that clear guidance on the collection and use of real-world data in regulatory frameworks and strengthened collaboration between registry holders, academia, regulators and medicines developers are needed to achieve comprehensive and high levels of quality of safety data captured by registries to support regulatory decision making. These will hopefully be enabled by the European Medicines Regulatory Network strategy to 2025.

1 Introduction

Patient registries are organised systems that collect uniform data (clinical and other) to identify specified outcomes for a population defined by a particular disease, condition or exposure [1]. The term ‘patient’ highlights the focus of the registry on health information. It is broadly defined and may include patients with a certain disease, pregnant or lactating women or individuals presenting with another condition such as a birth defect or a molecular or genomic feature. Such registries constitute valuable data sources to support

regulatory decision making on medicinal products by providing evidence on the efficacy/effectiveness and safety of medicinal products in the frame of clinical trials and non-interventional studies [2] in both pre- and post-authorisation phases [3–6]. This paper focuses on the use of patient registries to generate evidence on the safety of medicinal products [7–9].

Independent registries established for epidemiological or academical research purposes by entities other than marketing authorisation holders (MAHs) must follow national reporting requirements on safety data (mainly spontaneous reporting of adverse drug reactions [ADRs] by treating physicians to national competent authorities or MAHs), but are not subject to the regulatory requirements applicable to MAHs on the collection of data on adverse events (AEs) related to medicinal products [10]. Therefore, these registries may not have foreseen the collection of such data on a routine basis or as part of specific data collection schemes.

✉ Kelly Plueschke
Kelly.plueschke@ema.europa.eu

¹ Data Analytics and Methods Task Force, European Medicines Agency, Domenico Scarlattilaan 6, 1083 HS Amsterdam, The Netherlands

² Medicines Evaluation Board, Utrecht, The Netherlands

Key Points

While patient registries constitute valuable data sources to support regulatory decision making on medicinal products, not all of them routinely and standardly collect data on adverse events and adverse drug reactions linked to medicinal products.

A survey conducted by the European Medicines Agency among registries in the European Network of Centres in Pharmacoepidemiology and Pharmacovigilance (ENCePP) resources database revealed heterogeneous policies on the capture and sharing of these data, including on the type of information (serious versus non-serious) and frequency of collection and reporting due to various challenges.

Several key European initiatives are presented, describing regulators' needs as to the type and quality of data, as well as objectives to leverage the use of registries to generate real-world evidence contributing to regulatory assessment on the efficacy/effectiveness and safety profiles of medicinal products.

Unfortunately, it is currently difficult to identify, based on published information, which of these registries do routinely undertake collection and reporting of AEs/ADRs linked to medicinal products. This aspect is, however, critical to know in order to assess the suitability of registries to support generation of evidence on medicines' safety [1].

In order to better understand the approach of patient registries towards the collection and reporting of AEs/ADRs, the European Medicines Agency (EMA) conducted a survey among registries registered in the European Network of Centres in Pharmacoepidemiology and Pharmacovigilance (ENCePP) resources database [11]. The aggregated results, data gaps and opportunities are presented in this paper.

2 Methodology

2.1 Data Source

The data source selected for this study is the ENCePP resources database, an electronic catalogue coordinated by EMA of available EU research organisations, networks and data sources in the field of pharmacoepidemiology and pharmacovigilance [11]. It is a key component of the ENCePP web portal as it allows identification of organisations and data sources potentially relevant for specific pharmacoepidemiology and pharmacovigilance studies in Europe. All

information is provided and maintained by the listed organisations, data providers or registry holders. This database is not limited to a specific group of diseases, and contains a function that easily allows searching across three types of resources: 'Centre', 'Network' and 'Data Source'. Upon selection of a resource, users are brought to a form composed of several specific variables that can be completed in order to refine the search.

2.2 Identification of Patient Registries

In April 2020, the ENCePP resources database was searched for all 'Data Sources' classified as 'Disease/Case registry', 'Routine primary care electronic primary care registry', 'Exposure registry' and 'Other'. The results were independently screened by two reviewers to identify the data sources meeting the definition of patient registries as included in the introduction. In case of any doubts on whether a data source was actually a patient registry based on the information available in the ENCePP resources database, the reviewers consulted the website of the organisation and/or the data source itself if any. A third reviewer was consulted in the event of selection disparities between the two independent reviewers.

2.3 Survey

An online survey in English was developed in the EUSurvey tool [12] to investigate (1) patient registries' process(es) for the collection of data elements on AEs/ADRs related to medicinal products; (2) their governance for accessing and sharing such data; and (3) their abilities to implement additional data collection on AEs/ADRs.

The survey was composed of 15 structured or open questions drafted in consultation with the EMA Registries Task Force [13] and some members of the Pharmacovigilance Risk Assessment Committee (PRAC) [14]. It is available in the EU PAS Register [15]. The first set of questions aimed at asking registries if they routinely collect information on medicines taken by each patient enrolled and on experienced AEs. Respondents had to select the type of safety information they do collect and at which frequency, e.g. AEs (any untoward medical occurrences in a patient administered a medicine and which do not necessarily have a causal relationship with the treatment) characterised as serious (resulting in death, life-threatening, requiring in-patient hospitalisation or prolongation of existing hospitalisation, resulting in persistent or significant disability or incapacity, or congenital anomaly/birth defect) or non-serious AEs or serious or non-serious ADRs (responses to a medicinal product that are noxious and unintended and for which a causal relationship between a medicine and the occurrence is suspected), as well as serious or non-serious AEs of special interest (AESI)

(noteworthy events for the particular product or class of products that is monitored). Another set of questions covered processes for sharing the different type(s) of safety information collected, with which organisations (e.g. pharmaceutical companies, regulatory/national competent authorities or others), at which frequency and in which format. Registries were also asked about their capacity to collect additional data elements upon request, about the development of policy for collaboration and about their processes for data analysis as applicable. Finally, two open questions intended to collect feedback on important obstacles and facilitating factors for the collection and provision of data on AEs to pharmaceutical companies and/or regulatory competent authorities.

The link was first sent to five of the patient registries identified in the database with which the EMA had had recent interactions to make sure the questions were clear. These five registries provided their responses to the survey within 2 weeks. As none of them raised comments on the clarity of the questions, no changes to the survey were deemed required and the link was sent in May 2020 to all the contact points of the patient registries identified in the ENCePP resources database. In the absence of response within the set deadline, a first reminder was sent, followed by a second as applicable. In addition, other registries' contact points identified on the internet and dedicated websites were contacted in parallel. The survey was closed on 31 August 2020. Registries for which no response was provided by this date were considered as non-respondents. Upon survey closure, all responses were compiled and evaluated in an aggregated and anonymous format.

The geographical coverage, defined as the number of countries (including Member States of the European Economic Area [EEA]) contributing data to a registry as specified in the ENCePP resources database, was collected for all registries invited to complete the survey, and was then compared between the respondents and non-respondents to help contextualise the results.

3 Results

Eighty-five patient registries were identified in the ENCePP resources database, all of which were sent the survey link via the registered contact point. Responses were received from 31 of these registries (31/85; 36.5%) [Supplementary Material Table 1; see the electronic supplementary material]. An aggregated summary of the answers is provided in Supplementary Material Table 2.

3.1 Geographical Coverage

Table 1 presents the geographical coverage of both respondent and non-respondent registries as recorded in the ENCePP resources database. Fourteen of the 31 respondent registries (14/31; 45.2%) covered five or more (up to 28) EEA Member States as well as countries outside the EEA, whilst 12 (12/31; 38.7%) were national registries covering a single EEA Member State. Five (5/31; 16.1%) covered two to four ($n = 3$) or an unknown number of countries ($n = 2$). Of the non-respondent registries, 31 (57.4%) covered at least five Member States, while 21 (38.9%) covered a single country. The United Kingdom was considered in this study as an EEA Member State since the data was collected prior to 1 January 2021.

3.2 Routine Collection on Medicines and Types of AEs/ADRs

Figure 1 shows the breakdown of registries invited to the survey ($n = 85$) that did provide a response (31/85; 36.5%) indicating they do routinely collect information on medicines taken by each patient enrolled (29/31; 93.5%, while two stated they do not) and, out of those, the number that routinely collect safety information related to medicines (19/29; 65.5%).

The most common types of safety information collected were 'serious and non-serious AEs' (14/19; 73.7%), followed by 'serious and non-serious ADRs' (11/19; 57.9%) and AESI defined a priori (11/19; 57.9%). Most of the registries collected a combination of safety information, as described in Fig. 2. Three of them (3/19; 15.8%) indicated

Table 1 Geographical coverage of registries registered in the ENCePP resources database invited to complete the survey

	EEA member states		
	Five or more (n ; %)	One (n ; %)	Between 2 and 4 or unknown (n ; %)
Respondent registries (31/85 = 36.5%)	14; 45.2%	12; 38.7%	5; 16.1%
Non-Respondent registries (54/85 = 63.5%)	31; 57.4%	21; 38.9%	2; 3.7%

EEA European Economic Area, ENCePP European Network of Centres in Pharmacoepidemiology and Pharmacovigilance

that they routinely capture all types listed in the survey, i.e. serious and non-serious AEs and ADRs, AESI and information on spontaneous reports related to patients included in the registry that were also sent to national competent authorities or MAHs.

The data are collected at various frequencies across registries depending on the patients' scheduled visits, which may differ across centres or countries between 'every 3–6 months' (6/19; 31.6%), 'at least once a year' (5/19; 26.3%), 'at each patients' visit' (6/19; 31.6%), 'continuously' (1/19; 5.3%) or 'at specific timepoints' (1/19; 5.3%) as reported by the respondents in the survey's free-text field. Details on the processes in place for the collection of AEs/ADRs were published by 63.2% of them (12/19; 63.2%).

3.3 Sharing of Safety Information on Medicines

Thirteen of 19 registries (68.4%) provided data on AEs/ADRs either to pharmaceutical companies (11/19; 57.9%), regulatory/national competent authorities (9/19; 47.4%) and/or other entities (2/19; 10.5%, e.g. researchers, specific pharmacovigilance programmes) in the form of regular publications or upon requests according to agreed timelines.

The same 13 registries (13/19; 68.4%) fed-back on the time lag between data collection of AEs/ADRs at the central level and data sharing. The majority indicated that time lag depends on various factors like type of data to be shared, specific registry-based study timelines and/or agreement with recipient stakeholders (5/13; 38.5%). Others provided more specific timeframes, e.g. 'immediately' (3/13; 23.1%), '3 to 6 months' (2/13; 15.4%) and '1 month' (1/13; 7.7%). Two registries responded that they do not know or do not have enough experience at this stage to answer the question (2/13; 15.4%).

Additional data elements on AEs/ADRs may be collected upon requests from regulatory authorities (18/31; 58.1%), pharmaceutical companies (18/31; 58.1%) and others (5/31; 16.1%, e.g. patient organisations, researchers, pharmacovigilance programme).

Eleven of 22 respondents (11/22; 50.0%) indicated that they analyse internally data on AEs/ADRs requested by pharmaceutical companies and/or regulatory competent authorities, and that results are shared in an aggregated form according to agreements in place with requesters.

A policy for collaboration with other organisations on the monitoring of medicines has formally been developed by eight registries of the 22 that responded to this question (8/22; 36.4%) in the form of protocols for data sharing, governance documents for data linkage programs and data application procedures.

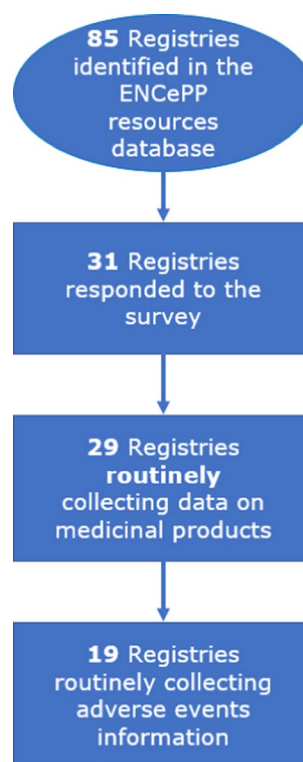


Fig. 1 Overview of registries in the ENCePP resources database collecting data on medicines and adverse events. Out of 85 registries identified in the ENCePP resources database, 31 responded to the survey and 29 indicated they routinely collect data on medicinal products, out of which, 19 routinely collect information on adverse events. *ENCePP* European Network of Centres in Pharmacoepidemiology and Pharmacovigilance

3.4 Obstacles and Facilitating Factors for the Collection and Sharing of Safety Information on Medicines

Obstacles highlighted by registries are well known [7, 9] and touch upon data collection (e.g. lack of harmonisation of data collection forms, non-compliance in reporting AEs in a timely manner), data sharing (e.g. General Data Protection Regulation (GDPR), national requirements), reporting processes (e.g. time lags), as well as governance aspects (limited or lack of funding/financial compensation/incentives for the centres to ensure data collection and quality management). The respondents provided their views on important factors that could help overcome these difficulties. These included the need for appropriate funding to allow sustainability of registries, strengthened communication between regulators, academia, the pharmaceutical industry and registry holders to clarify expectations, and guidance on use of real-world data from registries in regulatory frameworks.

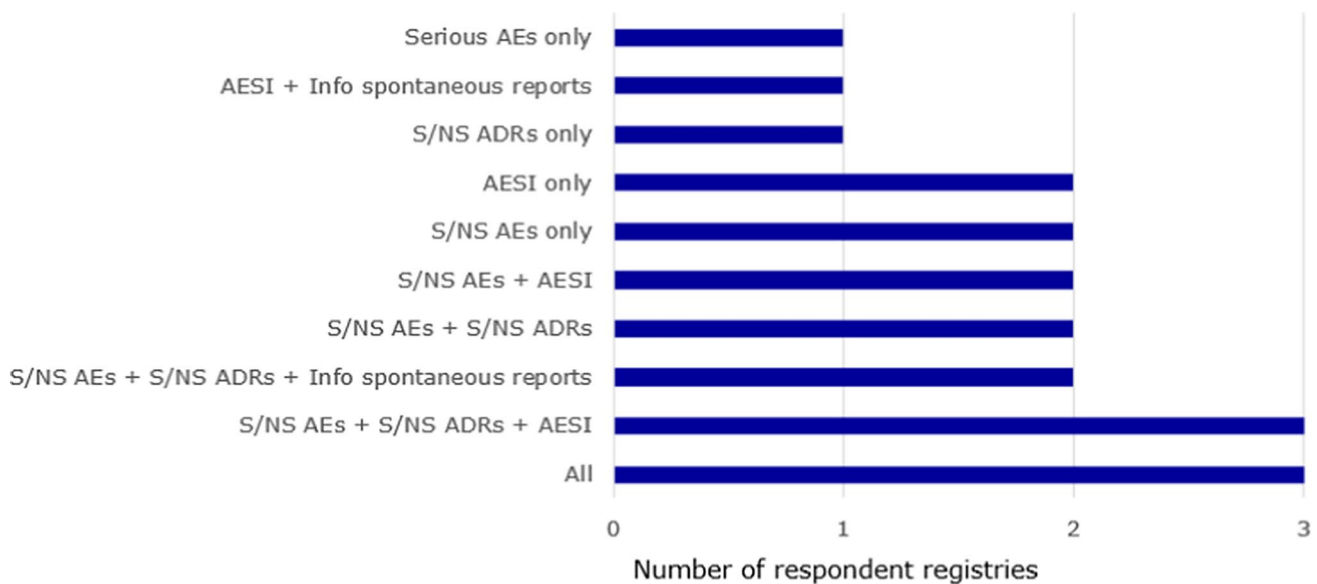


Fig. 2 Number of registries collecting each type of safety information described in the survey. *ADR* adverse drug reaction, *AE* adverse event, *AESI* adverse events of special interest, *Info spontaneous*

reports information on spontaneous reports reported to competent authorities, *NS* non-serious, *S* serious

4 Discussion

To our knowledge, this is the first survey on the collection of AEs related to medicinal products in registries. Only one third of the registries recorded in the ENCePP resources database responded to this questionnaire.

While 93.5% (29/31) of the respondents do routinely collect information on medicines taken by each patient enrolled, 65.5% (19/29) of those also collect AEs/ADRs. These were reported to cover both serious and non-serious cases instead of one type or the other. This should be interpreted with caution as it does not provide a precise indication of what information is actually collected (all or only a subset of AEs/ADRs/AESI), how detailed it is (causality assessment and seriousness not systematically reported) and who collects it (clinician- or patient-reported data). This raises questions on the quality of the data and on their usability beyond the purpose for which the information is originally collected. Ideally, collection of data should come directly from the healthcare system, within which registries should be fully integrated.

Registries reported heterogeneous frequencies for collection and reporting of AEs/ADRs. This can be explained by the individual registries' scope of disease(s) impacting on the frequency of patients visits and the extent of variables collected, by the primary purpose for which registries have been created (other than pharmacovigilance) and by any contracts in place with third parties for data sharing. Nevertheless, 71.0% (22/31) of the registries highlighted the possibility to collect additional data elements related to

AEs experienced by patients taking medicines upon requests from pharmaceutical companies and/or regulatory authorities. Of these, 36.4% (8/22) have already developed policies for collaboration with these organisations for medicines' safety monitoring. Questions remain as to the suitability of these registries for use in regulatory contexts. This needs to be evaluated case by case based on specific research questions through a feasibility analysis, taking into account the data elements collected, opportunities to capture additional information on individual patients, e.g. through data linkage with other healthcare databases or through amendments of the primary data collection forms, their operational processes and the governance in place [1].

4.1 Limitations

Only one third of the 85 contacted registries responded to the survey, which is not considered representative of all registries registered in the ENCePP resources database, let alone all registries existing across the EEA. Reasons for the limited response rate may be, besides possibly outdated information on contact details, a low interest in the topic, or the fact that registries were not originally developed for the purpose of routine data collection on AEs/ADRs. It might also be that some registries are no longer active and that the ENCePP resources database has not been updated accordingly.

The geographical coverage between respondents and non-respondents (Table 1) was similar in the way that both groups had their majority of registries covering five EEA

Member States or more (45.2% and 57.4% respectively), as well as comparable proportions of registries covering a single country (38.7% and 38.9%). These distributions may guide readers towards the assumption that the survey results could be generalised, i.e. that most registries do routinely collect data on AE/ADRs. However, such a conclusion cannot be validated in the absence of further details on each registry's characteristics beyond geographical coverage (e.g. original purpose of creation and funding), as well as knowledge of the reasons why the 54 registries did not respond to the survey. Information on sources of funding would have been useful to understand how this aspect might influence collection of AE/ADRs, and whether registries could be more prompt to collect such data if they are funded by pharmaceutical companies. Unfortunately, public information on funding is rather scarce, and not always systematically or clearly reported on registries' websites to allow for a fair comparison. It was therefore not captured in this study.

The search for identification of registries that could take part in the survey was limited to the ENCePP resources database. Enlarging the scope to other data sources such as, for example, Orphanet [16] and RD-Connect [17], could have increased the number of respondents and response rates.

The input received on the type of AEs/ADRs collected ('All *serious and non-serious AEs/ADRs and AESI*') widely differs from the feedback that was provided during the registry workshops held at the EMA in 2016 [18]. It is possible that the way questions were phrased and the fact that the survey was only available in English could have led to misunderstanding, despite the review by five registries prior to the survey launch. A greater level of automatic structuring, including conditional questions, pre-defined drop-down lists and prompts to give more detailed pieces of information, would have provided a better understanding of the registries' responses (e.g. underlying reasons for each registry to collect AEs/ADRs or not, which type and to what extent, how these are routinely collected, what measures are required to be put in place to allow capture of such elements, and implications these would have on data processing and sharing).

The results may have been influenced by different factors, such as the national healthcare systems of the respondent registries and their attitude towards the integration of registries into clinical practices as well as linkage with databases that collect safety data.

4.2 Real-World Evidence Initiatives to Support and Leverage the Use of Registries in Regulatory Decision Making

In 2015, EMA launched an initiative aimed at promoting the use of patient registries by introducing and supporting a systematic and standardised approach to their contribution to the benefit–risk evaluation of medicines within the EEA

[13]. Five multi-stakeholder workshops have taken place since 2017 to better understand the barriers and facilitators to collaboration between stakeholders [19–23]. The experience acquired during these dialogues contributed to the development of the Committee for Medicinal Products for Human use (CHMP) guideline on registry-based studies [1], which sets out regulators needs and expectations as to the quality and representativeness of registries in order for them to be considered suitable to answer specific study questions on medicinal products. This includes registries' capacity to provide data on AEs/ADRs (whether this is through routine primary collection or via linkage to other databases). The guideline will hopefully influence the way new registries are set up and possibly the way existing registries are further developed in regards to the collection of safety information on medicines that can then constitute useful evidence for regulatory assessment. A successful example of a registry's integration into regulatory evaluation is the European Cystic Fibrosis Society Patient Registry (ECFSPR), which was qualified in July 2018, by the CHMP for its contributions to pharmacoepidemiology studies. Such qualification increases regulators' confidence in the quality of the data derived from this registry when used in specific regulatory activities [24].

The European Medicines Regulatory Network (EMRN) has outlined a vision that by 2025, the use of real-world evidence will have been established across the spectrum of regulatory use cases [25, 26]. The EU-wide distributed network of real-world data named Data Analytics and Real World Interrogation Network (DARWIN EU) [27], which is part of the Heads of Medicines Agencies HMA-EMA joint Big Data Steering Group (BDSG) 2021–2023 workplan [28], was launched in early 2022 with the establishment of its coordination centre to on-board data partners, including registries, and to drive the conduct of studies requested by medicines regulators and other stakeholders. This programme will leverage the capacity of registries to deliver high-quality data across the lifecycle of medicines, from disease epidemiology that supports decisions on the development of products, to safety studies for products on the market, allowing rapid and robust evaluation of safety signals.

5 Conclusion

About one third of the registries recorded in the ENCePP resources database responded to an EMA survey on the collection of AEs related to medicinal products. Despite a relatively low response rate, the results indicate the heterogeneity of approaches towards collection of such data across registries in terms of their type (serious versus non-serious) and frequency of collection and reporting. More surveys are needed to better understand if and how AEs/

ADRs are currently collected, and how their collection can be improved to support medicines' safety monitoring. Multiple factors have been highlighted to describe the challenges currently faced by registries in the provision of data to third-party organisations. More regulatory guidance and funding are needed to achieve the levels of data quality and quantity required to support regulatory decision making. Collaboration of registry holders with other stakeholders including the EMRN within the multiple ongoing initiatives outlined in the BDSG workplan will strengthen the usefulness and place of patient registries in the generation of relevant evidence on medicinal products to support better care for patients.

Supplementary Information The online version contains supplementary material available at <https://doi.org/10.1007/s40264-022-01188-x>.

Acknowledgements The authors thank the PRAC members Sabine Straus and Menno van der Elst (Medicines Evaluation Board, The Netherlands), Ulla Wändel Liminga (Medical Products Agency, Sweden) and Martin Huber (Federal Institute for Drugs and Medical Devices, Germany) for their feedback on the survey questions. All have provided written consent to be named in this section. The authors also thank the peer-reviewers of this article.

Declarations

Funding No sources of funding were used to assist in the preparation of this study.

Competing interests The authors Kelly Plueschke, Carla Jonker, Valerie Strassmann and Xavier Kurz declared no competing interests for this work. The views expressed in this article are the personal views of the authors and may not be understood or quoted as being made on behalf of or reflecting the position of the European Medicines Agency or one of its committees or working parties.

Ethics approval Not applicable.

Consent to participate Not applicable.

Consent for publication Not applicable.

Availability of data and material (data transparency) Data sharing is not applicable to this article as no datasets were generated or analysed during the current study.

Code availability Not applicable.

Author contributions KP developed the survey questions, compiled the responses and drafted the manuscript. CJ contributed to the drafting of the manuscript. VS developed the survey questions and contributed to the drafting of the manuscript. XK led and supervised the study. All authors read and approved the final version.

Open Access This article is licensed under a Creative Commons Attribution-NonCommercial 4.0 International License, which permits any non-commercial use, sharing, adaptation, distribution and reproduction in any medium or format, as long as you give appropriate credit to the original author(s) and the source, provide a link to the Creative Commons licence, and indicate if changes were made. The images or other third party material in this article are included in the article's Creative

Commons licence, unless indicated otherwise in a credit line to the material. If material is not included in the article's Creative Commons licence and your intended use is not permitted by statutory regulation or exceeds the permitted use, you will need to obtain permission directly from the copyright holder. To view a copy of this licence, visit <http://creativecommons.org/licenses/by-nc/4.0/>.

References

1. CHMP Guideline on registry-based studies. https://www.ema.europa.eu/en/documents/scientific-guideline/guideline-registry-based-studies_en-0.pdf. Accessed 3 May 2022.
2. Regulation (EU) No 536/2014 of the European Parliament and of the Council of 16 April 2014 on clinical trials on medicinal products for human use, and repealing Directive 2001/20/EC. Accessed 3 May 2022.
3. Blake KV, de Vries CS, Arlett P, et al. Increasing scientific standards, independence and transparency in post-authorisation studies: the role of the European Network of Centres for Pharmacoepidemiology and Pharmacovigilance: ENCePP AND POST-AUTHORISATION MEDICINE RESEARCH. *Pharmacoepidemiol Drug Saf.* 2012;21:690–6. <https://doi.org/10.1002/pds.3281>.
4. McGettigan P, Alonso Olmo C, Plueschke K, et al. Patient registries: an underused resource for medicines evaluation: operational proposals for increasing the use of patient registries in regulatory assessments. *Drug Saf.* 2019;42:1343–51. <https://doi.org/10.1007/s40264-019-00848-9>.
5. Jonker CJ, Kwa MSG, van den Berg HM, et al. Drug registries and approval of drugs: promises, placebo, or a real success? *Clin Ther.* 2018;40:768–73. <https://doi.org/10.1016/j.clinthera.2018.04.005>.
6. Jonker CJ, van den Berg HM, Kwa MSG, et al. Registries supporting new drug applications. *Pharmacoepidemiol Drug Saf.* 2017;26:1451–7. <https://doi.org/10.1002/pds.4332>.
7. Cave A, Kurz X, Arlett P. Real-world data for regulatory decision making: challenges and possible solutions for Europe. *Clin Pharmacol Ther.* 2019;106:36–9. <https://doi.org/10.1002/cpt.1426>.
8. Santoro A, Genov G, Spooner A, et al. Promoting and protecting public health: how the European Union pharmacovigilance system works. *Drug Saf.* 2017;40:855–69. <https://doi.org/10.1007/s40264-017-0572-8>.
9. Olmo CA, McGettigan P, Kurz X. Barriers and opportunities for use of patient registries in medicines regulation. *Clin Pharmacol Ther.* 2019;106:39–42. <https://doi.org/10.1002/cpt.1414>.
10. European Medicines Agency. Guideline on good pharmacovigilance practices (GVP): module VI: Collection, management and submission of reports of suspected adverse reactions to medicinal products (Rev 2). https://www.ema.europa.eu/en/documents/regulatory-procedural-guideline/guideline-good-pharmacovigilance-practices-gvp-module-vi-collection-management-submission-reports_en.pdf. 2017. Accessed 3 May 2022.
11. ENCePP Resources Database. <https://www.encepp.eu/encepp/resourcesDatabase.jsp>. Accessed 3 May 2022.
12. EUSurvey Tool - <https://ec.europa.eu/eusurvey/home/welcome>. Accessed 3 May 2022.
13. EMA Patient Registries initiative. <https://www.ema.europa.eu/en/human-regulatory/post-authorisation/patient-registries>. Accessed 3 May 2022.
14. Pharmacovigilance Risk Assessment Committee (PRAC). <https://www.ema.europa.eu/en/committees/pharmacovigilance-risk-assessment-committee-prac>. Accessed 3 May 2022.
15. Survey on the collection of data on adverse events related to medicinal products through registries—EUPAS35474. <http://>

- www.encepp.eu/encepp/viewResource.htm?id=37195. Accessed 3 May 2022.
16. Orphanet. <https://www.orpha.net/consor/cgi-bin/ResearchTrials.php?lng=EN>. Accessed 3 May 2022.
 17. RD-Connect. <https://rd-connect.eu/>. Accessed 3 May 2022.
 18. Patient registries workshop: observations and recommendations. https://www.ema.europa.eu/en/documents/report/report-patient-registries-workshop_en.pdf. Accessed 3 May 2022.
 19. Report on cystic fibrosis registries workshop. 2017. https://www.ema.europa.eu/documents/report/report-cystic-fibrosis-registries_en.pdf. Accessed 3 May 2022.
 20. Report on multiple sclerosis registries workshop. 2017. https://www.ema.europa.eu/documents/report/report-multiple-sclerosis-registries_en.pdf. Accessed 3 May 2022.
 21. Report on CAR-T cell therapy registries workshop. 2018. https://www.ema.europa.eu/documents/report/report-car-t-cell-therapy-registries-workshop_en.pdf. Accessed 3 May 2022.
 22. Report on haemophilia registries workshop. 2018. https://www.ema.europa.eu/documents/report/report-haemophilia-registries-workshop_en.pdf. Accessed 3 May 2022.
 23. Report on Workshop on the role of registries in the monitoring of cancer therapies based on genetic and molecular features. 2019. https://www.ema.europa.eu/documents/report/report-workshop-use-registries-monitoring-cancer-therapies-based-tumours-genetic-molecular-features_en.pdf. Accessed 3 May 2022.
 24. CHMP Qualification Opinion on The European Cystic Fibrosis Society Patient Registry (ECFSPR) and CF Pharmacoepidemiology Studies. https://www.ema.europa.eu/documents/regulatory-procedural-guideline/qualification-opinion-european-cystic-fibrosis-society-patient-registry-ecfspr-cf-pharmaco_en.pdf. Accessed 3 May 2022.
 25. Peter Arlett, Jesper Kjær, Karl Broich, Emer Cooke. Real-world evidence in EU Medicines Regulation: enabling use and establishing value. 19 November 2021. <https://doi.org/10.1002/cpt.2479>
 26. EMRN Regulatory Science Strategy to 2025. <https://www.ema.europa.eu/en/about-us/how-we-work/regulatory-science-strategy>. Accessed 3 May 2022.
 27. Data Analysis and Real World Interrogation Network (DARWIN EU). <https://www.ema.europa.eu/en/about-us/how-we-work/big-data/data-analysis-real-world-interrogation-network-darwin-eu>. Accessed 3 May 2022.
 28. 2021-2023 HMA-EMA joint Big Data Steering Group (BDSG) workplan. https://www.ema.europa.eu/en/documents/work-programme/workplan-2021-2023-hma-ema-joint-big-data-steering-group_en.pdf. Accessed 3 May 2022.