EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

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Survey on the collection of data on adverse events related to medicinal products through registries

Draft protocol version 2.1

Roles and responsibilities

Role	Responsibility
Lead investigator	Valerie Strassmann
Investigator	Kelly Plueschke
Review	Xavier Kurz
Consultation	Peter Mol, Sabine Straus, Peter Arlett
Sign-off	Xavier Kurz

Milestones

Milestone	Planned	Actual
Finalisation of draft questionnaire	02/2020	02/2020
Begin of pilot	03/2020	03/2020
End of pilot	03/2020	03/2020
Amended questionnaire and survey protocol based on pilot	03/2020	03/2020
Start of survey	04/2020	04/2020
Date of reminders	1st: start + 2 weeks 2nd: date 1st reminder + 2 weeks	
End of survey	06/2020	

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Internal report	07/2020	
Presentation to Task Force	TBD (Q3 or Q4/2020)	
Presentation to Committees	TBD (Q3 or Q4/2020)	

Objectives

The objective of the survey is to gather information on the current practice and capability of registries registered in the ENCePP database[1] to collect, manage and share data on adverse events related to medicines. The responses will provide to stakeholders of the regulatory network key information on the use of registry data as part of post authorisation safety studies.

Background

Patient registries are potentially valuable sources of data to support regulatory decision-making on medicinal products, as well as to generate safety data as part of the post marketing surveillance (Blake K et al. 2012, Jonker CJ et al. 2017, Jonker CJ et al. 2018, Mc Gettigan P et al. 2019). The collection of data on adverse events related to medicines from real-world data sources is one of the main components of pharmacovigilance allowing to generate evidence on safety in broad populations (Santoro A et al., Cave A et al. 2019, Olmo CA et al. 2019).

Registries can be used as data sources for conducting post authorisation safety studies (PASS) that aim to identify, characterise or quantify a safety hazard, aim to confirm the safety profile of a medicine or measure the effectiveness of risk-management measures. Those registry-based studies may be initiated, managed or funded by the marketing authorisation holder (MAH). In that case, the MAH must comply with regulatory and legal provisions to collect and record data on adverse events, if not provided otherwise as part of the study protocol. The protocol allows to further define the approach towards data collection, including targeted data collection for adverse events of special interest identified a priori (Guideline on good pharmacovigilance practices (GVP) Module VI and Module VIII).

The general regulatory requirements related to the collection of data on adverse events related to medicinal products are however not mandatory for independent registries and registry-based observational studies that do not involve MAHs. Instead, national reporting requirements on safety data (that mostly relate to spontaneous reporting of adverse drug reactions by treating physicians to national competent authorities or MAHs) apply to those independent registries and studies. Besides, such registries might however foresee the collection of adverse events data either routinely or as part of data collection schemes or study protocols independent from legal or regulatory requirements.

The approach towards routine recording and reporting of safety data might therefore vary across registries depending on the scheme of data collection. There is limited information on how many registries undertake routine collection and documentation of adverse events or adverse drug reactions occurring on patients taking a specific medicinal product and enrolled in the registry, or whether they instead rely on adverse events collection through national reporting systems without data collection on reported reactions as part of the registry. This information is however key to assess the ability of a registry to meet potential regulatory requirements for collection of data on adverse events related to medicinal products as part of post approval regulatory requirements. Prior to involving a registry in observational safety studies, it is therefore important to evaluate its ability to meet regulatory

[1] ENCePP Resources Database: http://www.encepp.eu/encepp/resourcesDatabase.jsp, Kurz X et al. 2018

requirements for collection and sharing of safety data with external stakeholders linked to the investigated medicinal product.

In order to better understand the approach of registries towards the collection and reporting of adverse events related to medicines, the EMA will conduct a survey among registries registered within the ENCePP Resources database[1].

Method

Data source

The ENCePP Resources database[1] is an electronic index of available EU research organisations, networks and data sources in the field of pharmacoepidemiology and pharmacovigilance. It is a key component of the ENCePP web portal as it allows to identify organisations and data sets potentially relevant for conducting specific pharmacoepidemiology and pharmacovigilance studies in Europe, including registries.

Identification of the registries

The database will be searched for all data sources entered as “disease/case registry”, “routine primary care electronic primary care registry”, “exposure registry”, “other”. The research results will be reviewed manually by 2 independent reviewers to identify registries as part of the data sources. If the data retrieved from and available in the ENCePP database are not sufficient to judge on whether a listed data source should be considered as a registry, the website of this data source will be consulted in addition (if available). In case of disparities, a 3rd reviewer will evaluate the data source and provide guidance on whether it should be considered as a registry.

EUSurvey tool and questionnaire

An online questionnaire in English language has been developed in the EUSurvey tool[2] to cover the following aspects:

- Current approach regarding the collection of data elements on adverse events/reactions related to medicinal products (including type of data and frequency of collection);
- Established governance for accessing and sharing adverse events/reactions data;
- Abilities to implement additional data collection for adverse events/reactions data.

The survey is composed of multiple-choice structured questions as well as open questions with free text fields to give respondents the opportunity to provide additional comments. These questions have been drafted in consultation with identified members of the Pharmacovigilance Risk Assessment Committee (PRAC)[3] and the EMA Registries Task Force[4].

The survey will not collect or process any personal data.

Pilot survey

A pilot survey will first be carried out by contacting the 5 registries identified in the database with which the EMA had the most recent interactions. These 5 registries will be sent the link to the questionnaire and will be asked to complete it within 2 weeks. The questionnaire will then be amended as necessary based on their feedback.

[2] EUSurvey is an online survey management tool to create, publish and manage questionnaires and other interactive forms in most web browsers.
[3] https://www.ema.europa.eu/en/committees/pharmacovigilance-risk-assessment-committee-prac
[4] https://www.ema.europa.eu/en/human-regulatory/post-authorisation/patient-registries

Official survey

The revised version of the questionnaire will be sent to all the contact points of the registries identified in the ENCePP database. In case no response is received, a reminder will be sent after 2 weeks. If after further 2 weeks no response is received a second reminder will be sent. In addition, alternative registries' contact points will be explored by scanning available information on the internet and dedicated website if existing. These alternative contacts will be contacted in parallel to sending the 2nd reminder. If no response is received after these attempts, the data source will be considered as non-responder.

Results

Once the deadline for responses will have passed, all the answers will be compiled, evaluated and the results shared in an aggregated and anonymous format.

The EUSurvey tool will be used to analyse/summarise the responses descriptively for each of the individual questions of the survey. The number of respondents and non-respondents will be described.

The approach of registries towards collection and management of safety data will be analysed descriptively taking into account the characteristics of responding registries as entered in the ENCePP Resources database[1].

Graphical displays in form of bar charts, etc. will be used as applicable to visualize the results. The results will be analysed and interpreted in relation to the main research objectives (current approach to safety data collection, governance for accessing and sharing safety data, abilities to implement additional data collection for safety data).

At the end of the study, all participating registry holders will be provided with a link to the results of the survey.

The results of the survey will be presented to and discussed with the EMA Registry Task Force as well as with to the Pharmacovigilance Risk Assessment Committee (PRAC).

The protocol and survey will be entered in the ENCePP EU PAS Register[5] after the end of the pilot testing and at the beginning of the study. The results will be made publicly available as aggregated data after finalisation of the study. They will be used by the EMA as a basis for a publication in a scientific journal.

References

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[5] http://www.encepp.eu/encepp/studiesDatabase.jsp

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Annex: Survey on the collection of data on adverse events related to medicinal products through registries

Introduction

Patient registries are data collection systems that may provide valuable information to support regulatory decisions on medicines. In this context, it is important to know if the adverse events related to medicines experienced by the patients enrolled are recorded and collected centrally in the registry. If this is the case, the types of adverse events on which data are collected, and the delay for the data to become available, are important information to assess the usefulness of the registries for post-authorisation safety studies.

In order to better understand the practice of registries for the collection of data on adverse events, we are conducting a survey among the registries included in the ENCePP Resources database, and this is the reason why we are contacting you. Your answers will give us useful information to develop strategies for optimising the use of registries in the regulatory setting for post authorisation safety studies.

Please note that the EMA does not collect or process any personal data through this survey. Therefore, please do not write your personal name on this form. The data collected in the survey will be analysed statistically and the results will be shared only in aggregated format. As regards the processing of your data by the EUSurvey application, please refer to the specific privacy statement of the EUSurvey tool: https://ec.europa.eu/eusurvey/home/privacystatement.

1. Please indicate the name of your registry: free text

2. Does your registry routinely collect information on medicines taken by each patient enrolled in the registry?
   - o Yes
   - o No – go to question 2.a.
   - o Do not know - go to question 2.a.
   - o Additional information: free text

2.a. Can your registry collect information on medicines taken by each patient enrolled in the registry upon request from upon requests from pharmaceutical companies and/or regulatory authorities?
   - o Yes
   - o No – go to End
   - o Do not know – go to question 9

3. Does your registry routinely collect information on adverse events experienced by patients taking medicines?
   - o Yes
   - o No – go directly to question 9
   - o Do not know - go directly to question 9

4. Which information on adverse events experienced by patients taking medicines does your registry routinely collect? (please respond to all options as several may apply)
   - o All adverse events[6]
     - ▪ Yes:
       - ✓ Serious[7] and Non-serious
       - ✓ Serious[2] only

[6] 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.
[7] 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

        - No
        - Do not know

    - Suspected adverse drug reactions[8]
        - Yes:
            - ✓ Serious[2] and Non-serious
            - ✓ Serious[2] only
        - No
        - Do not know

    - Adverse events of special interest[9] (defined a priori)
        - Yes
        - No
        - Do not know

    - 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
        - No
        - Do not know
        - Additional information: free text

5. At which frequency are the data on adverse events collected centrally?
    - Free text field

6. Is information available to explain the current practice and processes in place for the collection of data on adverse events (e.g. on the registry website, as part of a data collection plan publicly available or another source of information)?
    - Yes
    - No
    - Do not know
    - Additional information: free text

7. Does your registry provide to other organisations data on adverse events experienced by patients taking medicines?
    - Yes:
        - To pharmaceutical companies
        - To regulatory/national competent authorities
        - Others (please specify, free text)
    - No - go directly to question 9
    - Do not know - go directly to question 9

8. 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 (e.g. at the point of data sharing, how “old” would this data be)?
    - Free text field

9. 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?
    - Yes:
        - Upon request from pharmaceutical companies

[8] 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

[9] 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.

        - Upon request from regulatory/national competent authorities
        - Others (please specify, free text)
    - No - go directly to question 13
    - Do not know - go directly to question 13

10. Has your registry developed a policy for collaboration with other organisations for the monitoring of medicines (including e.g. clear framework for data sharing, data analysis and possibly data linkage, information on appropriate scope of projects, potential timeframes and funding principles)?
    - Yes
    - No
    - Do not know
    - Additional information: free text

11. 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?
    - Yes
    - No - go directly to question 13
    - Do not know – go directly to question 13
    - Additional information: free text

12. If your registry analyses / or will analyse data on adverse events requested by pharmaceutical companies and/or regulatory competent authorities, what is / will be the time lag between the collection of the data and the sharing of the results (e.g. at the point of the sharing of the results, how “old” would this data be)?
    - Free text field

13. What are important obstacles for the collection and provision of data on adverse events to pharmaceutical companies and/or regulatory competent authorities?
    - Free text field

14. What are important factors facilitating the collection and provision of data on adverse events to pharmaceutical companies and/or regulatory competent authorities?
    - Free text field

15. Do you have any further comments regarding the collection of data on adverse events to medicines in your registry?
    - Free text