SCOPE Work Package 8
Lifecycle Pharmacovigilance

Identification of Available Data Sources Outside Spontaneous Reports: Recommendations

SCOPE

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Contents

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1. Introduction

1.1 Purpose of the document

The purpose of this document is to provide recommendations emerging from Work Package (WP) 8 – Lifecycle pharmacovigilance, Identification of available data sources outside of spontaneous reports. The WP8 lead is Italy (AIFA), and this topic is led by Italy (AIFA) in collaboration with, Ireland (HPRA), Sweden (MPA), Spain (AEMPS), Portugal (INFARMED), the United Kingdom (MHRA), Norway (NOMA) and Nederland (MEB).

The recommendations include the main findings, principal conclusions and List of Alternative Data Sources useful for pharmacovigilance (PV) assessments.

This document is not intended as a guideline, but it is written to share experiences across the EU PV network. This is a living document, subject to updates whenever new elements to be considered require integration.

The document is intended to offer support to European Union (EU) assessors in identifying suitable data sources, accessible to National Competent Authorities (NCAs), for a better characterisation and understanding of the profile of a medicinal product during a PV procedure. Furthermore, these data sources could be useful in the evaluation of the impact of regulatory measures, in accordance with the current legislation.

Once the availability of Additional Data Sources (ADSs) has been explored and characterised, a useful further purpose of this document could be the promotion of a fruitful cooperation between Member States (MSs). From a common approach point of view, it is envisaged that assessors across Europe are aware of the existence of different ADSs and have access to them in timely manner, promoting a sharing of data between MSs.

1.2 Background

Spontaneous reporting systems (SRS) have been and still are an important method of collecting post-marketing information about the safety of medicines.

The spontaneous reporting system facilitates the reporting and transmission of suspected Adverse Drug Reactions (ADRs) by all concerned parties (healthcare professionals (HCPs), patients and marketing authorisation holders (MAHs).

Marketed medicines can be monitored throughout their whole life cycle with relatively minimal expense and effort. The main challenges in spontaneous reporting are the risks of selective reporting and underreporting. Underreporting and selective reporting could lead to false conclusions and perceptions about a risk.

While valid scientific evidence generated by the MAH remains at the core of regulatory evaluation, such an approach presents potential limitations, as the timing and quality of evidence may be over-reliant on individual MAHs and their resources. It is also not uncommon for the European Union (EU) Regulatory Network to find that the actual studies available to support decision-making either do not address the precise problem or address it in insufficient detail or may simply require some additional contextual information[1].

Consequently, it is beneficial to obtain information on the risks of drugs from a variety of different sources throughout their life cycle. This information is then compiled to obtain a comprehensive overview of the benefit/risk (B/R) profile of a medicine during assessment procedures. Merging different data sources is a challenging task due to differences in the availability, quality, and nature of the data, including the existence of potential biases.

1.3 Context of recommendations

Additional Data Sources (ADSs) could be defined as any tools that allow the detection and collection of additional information on the use of a drug and/or the occurrence of adverse drug events. The identification and selection of the most appropriate data sources may contribute to the identification of new methodologies for assessing the safety profile of a medicinal product throughout their life cycle. Furthermore, the 2010 EU pharmacovigilance (PV) legislation strengthens the planning and legal basis for post-authorisation data collection and regulatory actions[2]. Consequently, the present recommendation is addressed to European PV and clinical assessors involved in procedures evaluating the B/R profile of a medicinal product.

The recommendations set in the context of ongoing proposals on a strategy for best evidence in discussion at the level of groups at the European Medicines Agency (EMA)-National Competent Authorities (NCAs) (PMG2) and the Pharmacovigilance Risk Assessment Committee (PRAC) Organisational, regulatory and methodological matters (ORGAM) and the findings of this Work Package (WP) 8 Topic are linked to other European projects, currently ongoing.

The European Network of Centres for Pharmacoepidemiology and Pharmacovigilance (ENCePP) is aimed at further strengthening the post-authorisation monitoring of medicinal products in Europe by facilitating the conduct of multi-centre, independent, post-authorisation studies, focusing on safety and B/R, using available expertise and research experience across Europe.

[1] Reflection paper on a strategy for best evidence EMA/508487/2014

[2] Arlett P, Portier G, de Lisa R, Blake K, Wathion N, Dogne JM, Spooner A, Raine J, Rasi G. Proactively managing the risk of marketed drugs: experience with the EMA Pharmacovigilance Risk Assessment Committee. Nat Rev Drug Discov. 2014 May;13(5):395-7. http://www.nature.com/nrd/journal/v13/n5/full/nrd3713-c1.html

The European regulatory network has already started to build a system focused on the scientific robustness of post-authorisation evidence and strengthening evidence underpinning decisions on medicines to increase the quality of advice and consistency of elements in European pharmacovigilance assessments. This activity is part of the PRAC Work Plan 2015[3] in a best evidence strategy that supports decision-making by the network.

Funded by the European Commission in 2008, the EU-ADR project, Exploring and Understanding Adverse Drug Reactions, aims to develop an innovative computerised system to detect ADRs, supplementing spontaneous reporting systems.

Another European initiative with an innovative approach to the B/R assessment of medicines is the Pharmacoepidemiological Research on Outcomes of Therapeutics by a European Consortium (PROTECT) external link icon project. It is a public-private partnership for innovative methodologies in PV and pharmacoepidemiology coordinated by the EMA, which has finalised the delivery of two databases that will offer access to important data resources for PV activities and pharmacoepidemiological studies. The first of these two databases is the Drug Consumption Database, which is a comprehensive and structured source of data on drug utilisation in the out- and in-patient healthcare settings. The second database, the PROTECT ADR database, is a listing of all ADRs contained in section 4.8 of the summary of product characteristics (SmPC) of medicinal products centrally authorised in the EU.

1.4 Definitions and abbreviations

Terminology	Description
ADR	Adverse Drug Reaction
ATC	the Anatomical Therapeutic Chemica
ADS	Additional Data Source
B/R	Benefit/Risk
DDD	the defined daily dose
DDIs	Drug-drug Interactions
BIFAP	Base de datos para la Investigacion Farmacoepedemiologica en Atencion Primaria
ENCePP	European Network of Centres for Pharmacoepidemiology and Pharmacovigilance
EMA	European Medicines Agency
EU	European Union
HCP	Healthcare Professional

[3] http://www.ema.europa.eu/docs/en_GB/document_library/Work_programme/2015/07/WC500189287.pdf

Terminology	Description
ICD	the International Classification of Diseases
ICSRs	Individual Case Safety Reports
ISoP	International Society of Pharmacovigilance
JA	Joint Action
MAH	Marketing Authorisation Holders
MA	Marketing Authorisation
MS	Member State
NCA	National Competent Authority
ORGAM	Organisational, regulatory and methodological matters
PMG2	Project and Maintenance Group 2
PRAC	Pharmacovigilance Risk Assessment Committee
PROTECT	Pharmacoepidemiological Research on Outcomes of Therapeutics by a European Consortium
PV	Pharmacovigilance
RPS	Reactions Pharmacovigilance Service
SCOPE	Strengthening Collaboration for Operating Pharmacovigilance in Europe
SmPC	Summary of Product Characteristics
SRS	Spontaneous Reporting System
WHO	World Health Organisation
WP	Work Package
UK	United Kingdom

1.5 Attachments

Ref no.	Document name
Annex 1	List of Alternative Data Sources
Annex 2	Example of Good Experience in ES
Annex 3	Example of Good Experience in IT
Annex 4	Example of Good Experience in UK

2. Recommendation aims

This document aims to provide a list of some ADSs that includes databases, registries and web-based sources of information available or located in Europe. Some of them are used only in certain NCAs and make available data limited to the local area or health system (for example prescription databases or drug sales data). Others could be applied to the whole European setting, but not all NCAs use them routinely. The information about availability and use of ADSs could further support integration of evidence during the assessment of PV procedures. In particular, ADSs could be beneficial in post-marketing regulatory decision-making and for generating scientific evidence on medicine-related issues through:

- Enhancing of pharmacovigilance methodologies (e.g. signal strengthening)
- Support of risk assessment
- Support in conducting drug utilisation and pharmacoepidemiological studies (e.g. pharmacoepidemiological hypothesis testing)
- Evaluation of the impact of risk-minimisation activities
- Closer monitoring of medicinal safety and effectiveness in the early phases of marketing
- Information on the need for further PV actions and/or communications.

In the future, a dedicated webpage intended as a communication and information hub for those interested in the use of ADSs outside of spontaneous reporting in the PV context (e.g. PV and clinical assessors, but also, HCPs, academia, members of the International Society of Pharmacovigilance (ISoP), etc.) could be developed to support the EU PV framework. It could facilitate access to information on good practices concerning ADSs utilisation for PV purposes across the EU.

3. Methodology and recommendations grounds

In the context of the Strengthening Collaboration for Operating Pharmacovigilance in Europe (SCOPE) Joint Action (JA) WP8, a survey was conducted between July and November 2014, in order to collect information regarding the use of ADSs amongst European countries.

In total, 25 NCAs responded and 25 completed the whole questionnaire.

3.1 Recommendations development

This recommendation has been extrapolated from the survey report on WP8 Topic 1 and has been further elaborated on the basis of the comments and discussions raised by participants during the WP8 meetings and consultations.

NCAs' responses to the survey have been analysed in order to create a list of the most useful data sources. From the input of some MSs, it has been agreed within the WP8 to include in the recommendation examples of best practices in the use of ADSs in selected NCAs. Therefore, attached to this document it is possible to consult contributions from IT, ES and the UK regarding their consolidated practice in ADSs. Further effort in WP8 Topic 1 will be made by the end of SCOPE JA activities to obtain additional examples from other participants in the JA. Activities on collection of this data will start in January 2016 and it is foreseen to be concluded by June 2016.

4. Challenges/limits

Among the challenges that could influence the correct interpretation of the survey results and consequently the applicability of this recommendation is the fact that not all European NCAs have been participating in SCOPE project, and also, among those who participated, an incomplete response rate has been registered for all survey questions. Therefore, the present recommendation cannot be considered to reflect the full availability of ADSs within MSs.

5. Recommendations

5.1 The list of useful ADSs

The data sources that MSs reported as useful via the web-based survey conducted amongst EU NCAs have been described and characterised. The information in **Tables 1-3** below is to support assessors in retrieving additional data during routine B/R assessment procedures for a PV purpose.

Table 1. List of useful ADSs: scientific literature

**Publicly (P) or Commercially (C) funded*

Name	Link	P/C*	Aim/brief description
PubMed	http://www.ncbi.nlm.nih.gov/pubmed	P	PubMed comprises citations for biomedical literature from MEDLINE, life science journals, and online books.
Embase	https://www.embase.com/login	C	Embase provides journal and conference coverage for all biomedical information needs. Embase is a useful tool for searching systematic reviews and monitoring the literature in order to make informed decisions on evidence-based medicine or for the purposes of PV and post-market monitoring.
Cochrane Library	http://www.cochrane.org/	P	The Cochrane collaboration is a global independent network of researchers, professionals, patients, carers, and people interested in health. Cochrane contributors from more than 120 countries work together to produce credible, accessible health information that is free from commercial sponsorship and other conflicts of interest.
Micromedex	http://micromedex.com/	C	Evidence-based information from Micromedex. This includes all the unbiased, referenced information about drugs, toxicology, diseases, acute care, and alternative medicine needed to make informed clinical diagnoses and treatment decisions.

Name	Link	P/C*	Aim/brief description
Martindale	http://www.pharmpress.com/product/9780857111395/martindale38	C	Martindale is a reference book published by Pharmaceutical Press, listing drugs and medicines used throughout the world, including details of proprietary preparations. It also includes disease treatment reviews. Martindale contains information on drugs in clinical use worldwide, as well as selected investigational and veterinary drugs, herbal and complementary medicines, pharmaceutical excipients, vitamins and nutritional agents, vaccines, radiopharmaceuticals, contrast media and diagnostic agents, medicinal gases, drugs of abuse and recreational drugs, toxic substances, disinfectants, and pesticides.
LactMed	http://toxnet.nlm.nih.gov/newtoxnet/lactmed.htm	P	The LactMed® database contains information on drugs and other chemicals to which breastfeeding mothers may be exposed. It includes information on the levels of such substances in breast milk and infant blood, and the possible adverse effects in the nursing infant. Suggested therapeutic alternatives to those drugs are provided, where appropriate. All data are derived from the scientific literature and fully referenced. A peer review panel reviews the data to assure scientific validity and currency.
Stockley's Drug Interactions online literature database	Not online open access	C	A source book of interactions, their mechanisms, clinical importance and management

Name	Link	P/C*	Aim/brief description
Adis Reactions Pharmacovigilance Insight	http://www.springer.com/gp/adis/products-services/pharmacovigilance/reactions-pharmacovigilance	C	Reactions Pharmacovigilance Service (RPS) is a literature monitoring service from Adis which identifies published case reports of ADRs (Individual Case Safety Reports (ICSRs)). It includes all relevant international journals (around 8,000 titles), plus companion supplements, proceedings from scientific meetings, newsletters from PV centres participating in the World Health Organisation (WHO) International Drug Monitoring Programme and websites of regulatory agencies and pharmaceutical/generics companies.
Janusinfo	http://www.janusinfo.se/	P	Janusinfo is a non-commercial website providing drug information to support HCPs in their everyday work. The website is the electronic means of communication of the Drug Therapeutic Committee and the Health and Medical Care Administration of the Stockholm County Council, Sweden. Contents and functions of the website should contribute to evidence-based and cost-effective drug treatment.

Table 2. List of useful ADSs: healthcare, prescription and sales data

For main characteristics of different healthcare databases/other data sources identified, please refer to ENCePP web portal http://www.encepp.eu/encepp/search.htm

Name	Link	Link to ENCEPP data source monography	Principal aim
BIFAP database	www.bifap.org	http://www.encepp.eu/encepp/viewResource.htm?id=7154	Electronic database with information provided by primary care doctors from the Spanish Health System who use a computer at work.
Clinical Trial Data			Databases of clinical studies (both pre- and post-approval).
Danish database of interactions	http://www.interaktionsdatabasen.dk/		Danish tool based on published literature and SPC information.
IMS Health MIDAS	www.imshealth.com/	http://www.encepp.eu/encepp/search.htm	This database contains product level data on community and hospital prescriptions.
Primary Care Reimbursement Service			National drug utilisation data.
Prescription databases			These databases contain data about dispensed drugs and are intended for general scientific research purposes, statistical analysis and planning.
Drug sales databases			Sales from national health system.
Clinical Practice Research Datalink	http://www.cprd.com/intro.asp	http://www.encepp.eu/encepp/viewResource.htm?id=12207	Electronic medical healthcare records database, containing longitudinal data on ~8% of United Kingdom (UK) population.

Name	Link	Link to ENCEPP data source monography	Principal aim
Statistics on drug consumption			Generally drug consumption statistics contain the sale of medicinal products on an annual basis. The statistics are grouped according to the active substances (ATC groups) and the consumption results are presented in the number of DDDs per 1000 inhabitants per day (DDD/1000 inhabitants/day).
Mortality data, for misuse of medicines			Analysis of medicines-related deaths.

Table 3. List of useful ADSs: registries

Name	Country(ies)	Principal aim
National prescription registry	SE	All dispensed prescribed medicinal products for individual patients.
Drug Product Registries	IT/NO	Telematic and dynamic tools at national level, placed in the early phases after marketing authorisation (MA) of new drugs or in some cases for 'authorised' off-label use, with a clear purpose, to measure real-world safety and effectiveness.
National patient registry	SE	In-patients and specialised out-patient diagnoses by ICD-codes.
Cause of death registry	SE	Cause of death for deceased persons.
Public health/diseases registries		These registries collect information about individuals, usually focused around a specific diagnosis or condition. Registries can be sponsored by a government agency, non-profit organisation, healthcare facility, or private company.
BIOBADASER	ES	Registry of biologicals for rheumatology.
Disease/quality registers	SE	Clinical data on characteristics for diseases and for some registers interventions.
BIOBADADERM	ES	Registry of biological for dermatology.
Registry of hepatotoxicities	ES	Network of hospitals for the study of idiosyncratic hepatitis. Coordinated by the University of Malaga (http://www.spanishdili.uma.es).
Piel en Red	ES	Registry of Severe cutaneous reactions

5.2 Exchange of information concerning experiences/good practices in use of ADSs

Exchange of information about successful ADR data extrapolation/usage for PV purposes is recommended for fostering of ADSs use in routine PV assessment practices. This could facilitate assessors or other stakeholders in locating information on existing ADSs and their main characteristics, such as descriptions of good PV operating practices (e.g. examples of procedures where the ADS has been successfully used in support of the safety issues assessment, examples of pharmacoepidemiological or studies for evaluation of effectiveness of RMM, new papers concerning ADSs utilisation, etc.).

5.3 Better addressing of possible challenges for ADS information availability

The network's proactive approach in collecting relevant data by using ADSs suitable for generating additional evidence in the context of PV decision-making is strongly recommended. From the work in Topic 1 it emerged that the identification of ADSs alone is not sufficient to ensure the applicability of ADSs in routine PV practices. Therefore, an additional exploration is warranted to better characterise some particular aspects of ADSs' applicability for PV purposes (intended as ADS validation for use in PV procedures assessment), including:

- Accessibility of the ADS and potential barriers to access (e.g. open access or access subject to limitations; direct or indirect access to the ADS)
- Identification of users (public, academic, private)
- Purposes (PV purposes for which the use of the ADS is more feasible)
- Time needed for extrapolation and elaboration of data (e.g. if the proposed times are feasible for agreed procedures timetables, possibility for time reduction for the signal detection)
- Quality of obtained data (e.g. completeness, possible biases, etc.)
- Challenges and limits that could be faced during the extrapolation of data from the ADS (e.g. the possibility to capture medicine identifiers, quantitative vs qualitative results, the type of ADS funding, etc.)
- Strategies to facilitate access to ADSs funded by different stakeholders (e.g. publicly funded or commercial).

Further efforts were made, in the context of WP8, to obtain additional information from NCAs participating in the SCOPE JA on these issues, in order to provide more complete information and advice before the end of the activities of the JA. A second 'call for best practices in the use of ADSs for PV purpose' was sent to NCAs on the 10th May 2016 with the deadline for responses settled on the 30th June 2016.

A training course session specific to this topic has been recognised as a useful tool for increasing awareness in this area of PV.

5.4 Mapping of ADSs

A realisation of a map of ADSs available at MS level is recommended to promote cooperation between assessors in different NCAs when addressing specific safety issues that require access to additional data.

5.5 Grouping of ADSs on the type of safety issue basis

Once a complete picture of the availability of ADSs across the EU is accessible, the classification of ADSs on a safety issue type basis is recommended to make easier the retrieval of information during the assessment. This classification could include different categories, such as pregnancy, breastfeeding, toxicology, prescription appropriateness, DDIs, pharmacogenomics, disease-related sources, etc.

5.6 New strategies for the promotion of innovative methodologies and technologies

New strategies, including innovative methodologies and technologies from collaborative research that could help extrapolation of data useful in support of PV assessments, are warranted (e.g. more advice is needed on how to increase literacy on these topics). Promotion of strategies that can increase awareness of the applicability of new and innovative methodologies/technologies aimed to ensure additional data availability and increase data quality are recommended in order to support system improvements, evidence-based decisions and health promotion and protection.

5.7 Linkage between different European initiatives

To reach the overall objective to fulfil the gap in information and to extend the access to relevant available data in a timely manner, the synergic action between all dedicated projects across Europe (e.g., ENCEPP, PRAC Best Evidence, PROTECT) is recommended. A linkage could be promoted to ensure the best results.

6. Impact assessment (anticipated)

The present recommendation includes a list of useful ADSs that could be considered during a benefit/risk assessment of a medicine. An effort has been made to identify and characterise the most appropriate ADS available in European NCAs in order to share and try to have a common approach regarding their use.

A particular section has been dedicated to the useful experience with three such data sources, as described by ES, IT and the UK, that have been received in the survey regarding their consolidated practice with ADSs.

For consideration in the future, to ensure sharing and promotion of good practice experiences and useful literature, such as to promote and support collaboration between different stakeholders (e.g. assessors from NCAs, academia and ISOP), a dedicated ADSs webpage could be developed at EU level.

The impact expected for the EU PV network mainly concerns the possibility to increase awareness of the utility of ADSs in the context of PV decision-making. It is strictly correlated to PV system improvements, evidence-based decisions and health promotion and protection.

Annexes

Annex 1.Topic 1 Report

Topic 1 Report

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Annex 2. Example of Good Experience in ES

Example of Good Experience in ES

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Example of Good Experience in IT

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Annex 4. Example of Good Experience in the UK

Example of Good Experience in the Uk

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