SCOPE Work Package 4
ADR Collection

IT Systems for ADR Reporting: Best Practice Guide

SCOPE

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ADR Collection:
IT Systems for ADR Reporting: Best Practice Guide

Contents

Acknowledgments

Authors

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1. Introduction

1.1 Purpose of the document

The purpose of the document is to provide guidelines that can be used by MSs to increase knowledge about ADR IT systems. The guidance document will provide insight into ADR IT systems used and into good practice regarding ADR reporting. Materials developed should facilitate improved skills, awareness, education and capability of reporters reporting an ADR to national reporting systems.

1.2 Background

The Strengthening Collaboration for Operating Pharmacovigilance in Europe (SCOPE) Joint Action has been created to support operations of pharmacovigilance (PV) in the European Union (EU) following the requirements introduced by the 2010 European PV legislation[1,2,3]. Information and expertise on how regulators in Member States (MSs) run their national PV systems was gained in order to develop and deliver guidance and training in key aspects of PV, with tools, templates and recommendations. The aim of the SCOPE Joint Action was to support the development of a consistent approach across the European Union (EU) network for all PV operations, in order to benefit medicines safety monitoring and communications to safeguard public health.

SCOPE was divided into eight separate work packages (WPs), with five WPs focusing on PV topics to deliver specific and measureable objectives, ranging from improvements in Adverse Drug Reaction (ADR) reporting to assessment of quality management systems.

Work Package 4 – ADR Collection was focused on national schemes for the spontaneous reporting of ADRs and was aimed to provide National Competent Authorities (NCAs) with a full understanding of good practices within national systems for collecting ADRs. Information was gathered from European MS institutions[4] to understand their national ADR system, PV Information Technology (IT) system capabilities, as well as implementation of patient reporting, types of reporting forms developed, and electronic reporting developments, including those from clinical healthcare systems. This information was used to create best practice guidelines, performance indicators and a media toolkit for raising awareness of ADR IT systems, which will be supported through delivery of a training course for institutions.

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[1] Directive 2010/84/EU of the European Parliament and of the Council

[2] Regulation (EU) No 1235/2010 of the European Parliament and of the Council

[3] Commission Implementing Regulation (EU) No 520/2012

[4] Term Member States' institution (MS) refers to institution responsible for Adverse Drug Reaction (ADR) reporting, collection, processing and analysis within the particular member state. Therefore, wherever the term 'Institution' is mentioned it does not necessarily refer to the National Competent Authority (NCA), although it will be synonymous in the majority of MSs.

Within WP4 there were five topics. Within the topic of Review of IT Systems and Special Forms of Reports, information about EU NCA IT systems was collected through a questionnaire completed by EU MSs. The questionnaire focused on national ADR IT systems and technologies that are being used across the EU, the current state of electronic ADR reporting, and integration between various systems containing patient data. The questionnaire was distributed in June 2014. Participants were asked to provide a description of their systems as they were at the end of 2013.

Please note: Guidance document on ADR IT systems, Version 1.0, published in September 2016, is subject to periodical updates. The new version of the document will be available on the SCOPE Joint Action website.

1.3 Definitions and abbreviations

Terminology	Description
ADR	Adverse Drug Reaction
AEMPS	Spanish Agency of Medicines and Medical Devices
DAP	Drug Analysis Print
DKMA	Danish Medicines Agency
DHMA	Danish Health Authority
DBMS	Database Management System
CHAFEA	Consumers, Health and Food Executive Agency
CMS	Content Management System
EEA	European Economic Area
EHR	Electronic Health Record
EMA	European Medicines Agency
ESTRI	Electronic Standards for the Transfer of Regulatory Information
EU	European Union
EV	EudraVigilance
EV POST	XML E2B files upload function
EVCTM	EudraVigilance Clinical Trial Module
EVDAS	EudraVigilance Data Analysis System
EVPM	EudraVigilance Post-Authorisation Module
FAQ	Frequently Asked Questions
FEDRA	Spanish National ADR Database
FTE	Full Time Equivalent

Terminology	Description
GP	General Practitioner
GPSoC	GP Systems of Choice
GVP	Guideline on Good Pharmacovigilance Practices
HALMED	Agency for Medicinal Products and Medical Devices of Croatia
HCP	Healthcare Professional
ICD	International Classification of Diseases
ICH IG	The International Conference on Harmonisation Implementation Guide
ICH	International Conference on Harmonisation
ICPC	International Classification of Primary Care
ICSR	Individual Case Safety Report
IT	Information Technology
MAH	Marketing Authorisation Holder
MedDRA	Medical Dictionary for Regulatory Activities
MHRA	Medicines and Healthcare products Regulatory Agency
MS	Member State(s)
NCA	National Competent Authority
NHS	National Health System
PV	Pharmacovigilance
PT	Preferred Term
Q&A	Question and Answer
RPhC	Regional Pharmacovigilance Centre
SCOPE	Strengthening Collaboration for Operating Pharmacovigilance in Europe
SNOMED CT	Systematised Nomenclature of Medicine Clinical Terms
SOAP	Simple Object Access Protocol
SOP	Standard Operating Procedure
SUSAR	Suspected Unexpected Serious Adverse Reactions
UMC	Uppsala Monitoring Centre
UK	United Kingdom
XCOMP	External compliance test environment
URL	Uniform Resource Locator

Terminology	Description
WHO	World Health Organisation
WHO DD	WHO Drug Dictionary
WHO PIDM	WHO Programme for International Drug Monitoring
WHO-ART	WHO Adverse Reaction Terminology
WHO-ICD	WHO International Classification of Diseases
WP	Work Package

2. Deliverables

The three-level approach applied in the named guidance document reflects the MSs' ADR IT system maturity levels based on the system functionalities in place

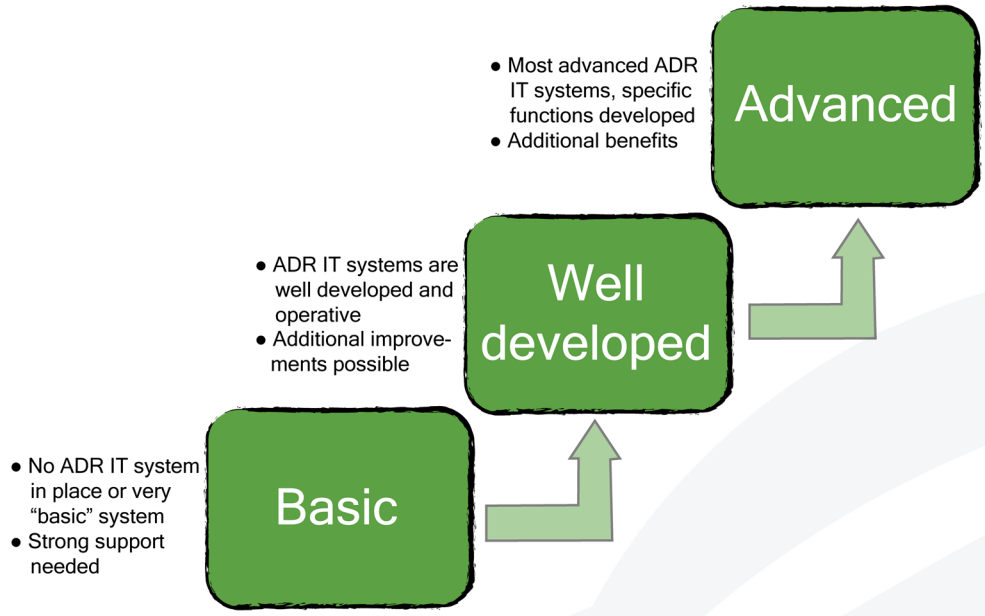

Figure 1. ADR IT system maturity levels

Basic systems

- Recommendations on what is available to use
- Systems (EudraVigilance (EV), VigiFlow – Uppsala Monitoring Centre (UMC)
- Uniform Resource Locator (URLs)
- (e.g. http://eudravigilance.ema.europa.eu/human/index.asp)
- Service desk contacts
- Collaboration with other MSs

Systems which are well-developed and operative

- Analysis of the current state
- Description of the ADR IT systems and specific functionalities

Advanced systems

- Best practices on specific functionalities
- Connection with registries and data exchange
- Connection with other systems containing patient records
- Applying business rules to ensure ADR message validity
- Mapping terms to Medical Dictionary for Regulatory Activities (MedDRA).

Sometimes strict borders between systems cannot be set and for that reason an overview of system functionalities is shown below. Certain functionalities were placed into categories according to ADR IT system maturity. System maturity levels can vary across different functionalities depending on IT development initiatives (e.g. an NCA can have a well-developed E2B system for transmission of ADRs, but no e-reporting in place).

Table 1. Categorisation of system functionalities

ADR IT system functionality					
ADR system maturity level		**Collect**	**Record**	**Report in E2B**	**Received ADR data analysis**
	Basic	• Phone • Paper reporting form • Email	• Spreadsheet (e.g. xls) • Basic Access database is used to record ADR data received	• EudraVigilance (EV) WEB • Vigibase	• NA
	Well developed	• Web reporting form • "Smart" (interactive) form	• Database MedDRA terminology incorporated • Different registries in use (e.g. medicinal product registry) • Data logging	• NCA system creates E2B file, but uses EudraVigilance (EV) POST to send the file	• Basic reporting, predefined parameters
	Advanced	• Mobile application • ADRs received from other systems (e.g. Electronic Health Record (EHR), registries) • Enhanced communication between reporter/sender and assessor and between Regional Centres and NCAs	• Business rules applied at data entry (validity check) • Duplicate detection in place at time of data entry • Signal detection (predefined criteria) • Additional monitoring in place • Medical term mapping (automatic, e.g. from the Systematised Nomenclature of Medicine – Clinical Terms (SNOMED CT) to MedDRA)	• Electronic Standards for the Transfer of Regulatory Information (ESTRI) gateway • Business rules applied during Individual Case Safety Report (ICSR) import and export process • Automated duplicate detection	• Causality assessment • Statistical disproportionality methods applied in NCA database

3. Basic systems

This section focuses on EU MSs with no ADR IT system in place and for those using simple spreadsheet tools. Through a questionnaire launched within the SCOPE project, we found that the most common reasons for not implementing ADR IT systems were high financial expenses and the lack of IT and PV staff support within the NCA.

3.1 SCOPE findings

In the Review of IT Systems and Special Forms of Reports questionnaire, MSs were asked about which IT system is used by NCAs, in order to get an overview of how many countries developed their own system and how many countries are using a commercially available system or have no system at all. The following chart presents the answers collected. It is important to mention that it was possible to provide more than one answer to this question.

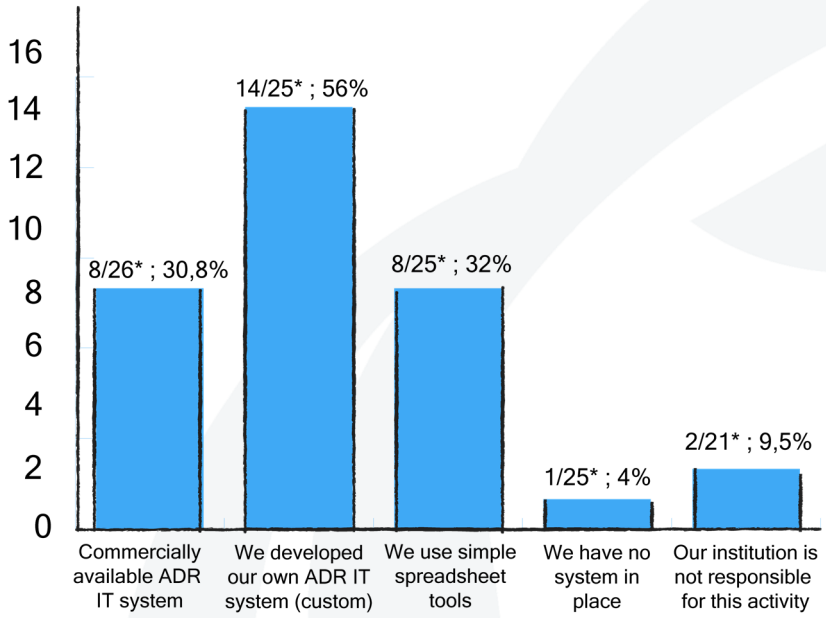

Figure 2. ADR IT system type

According to analysis of the data from this question, the current situation in the (European Economic Area) EEA is that 14 MSs have custom developed IT systems, 8 use commercially available ADR IT systems, 8 MSs use simple spreadsheet tools, 1 has no system in place and 2 stated that their institution is not responsible for the exchange of ICSRs. It's important to emphasise that some of the respondents (3 MSs) are using both commercially available and custom-developed systems in combination with simple spreadsheet tools.

Analysis of SCOPE survey responses showed that larger numbers of full-time equivalents (FTEs) are needed if there's no system in place or if simple spreadsheets are used; conversely, there is a lesser need for additional FTEs if a more advanced system is used.

Further to the answers collected, this section will contain recommendations for the implementation of publicly available ADR IT systems. The systems described are placed here as they are easily available and have a standard and known implementation procedure and not because they have a basic set of functionalities.

3.2 ADR IT systems

In this section, two ADR IT systems will be described. The systems are EudraVigilance, provided by the European Medicines Agency (EMA) and VigiFlow, provided by the World Health Organization (WHO). It is important to point out that neither VigiFlow nor EudraVigilance (EV) are just simple tools used for reporting. Both systems are complex and extensive ADR management systems which support collection, exchange, processing, data sharing and analysis of Individual Case Safety Reports (ICSRs). These systems are described here as they can be acquired easily and have strong user and technical support, which is important when a new system is being implemented.

3.2.1 EudraVigilance (EV)

EudraVigilance (EV) is the EU regulatory network system for managing information on suspected adverse reactions reported with medicines authorised in the European Economic Area (EEA)5. It is managed by the European Medicines Agency (EMA) on behalf of the EU medicines regulatory network.

EV is a system for ADR reporting, data processing and data management. The first operating version was launched in December 2001. The EV system supports:

- Electronic exchange of suspected adverse drug reactions reports (ICSRs) between EMA, National Competent Authorities (NCAs), Marketing Authorisation Holders (MAHs), and sponsors of clinical trials in the EEA
- Detection of safety signals associated with medicinal products for human use
- Monitoring and evaluating of safety issues in relation with ADRs reported
- A decision-making process based on broader knowledge of the adverse reaction profile of medicinal products.

[5] http://www.ema.europa.eu/ema/index.jsp?curl=pages/regulation/general/general_content_000679.jsp&mid=WC0b01ac05800250b5, accessed on 03 April 2016

EV provides two reporting modules:

- EV Clinical Trial Module (EVCTM): Electronic reporting of Suspected Unexpected Serious Adverse Reactions (SUSARs) as required by Directive 2001/20/EC
- EV Post-Authorisation Module (EVPM): Electronic reporting of ICSRs as required by Regulation (EC) 726/2004, Directive 2001/83/EC

EV contributes to the promotion and protection of public health in the EEA and provides a tool for monitoring the safety of medicinal products and minimising potential risks related to suspected adverse drug reactions.

Further information about EV can be gathered under the following links:

- New webpage containing information about access policy, enhancements of the EV system, stakeholder change management plan and Question and Answer (Q&A) section: http://www.ema.europa.eu/ema/index.jsp?curl=pages/regulation/general/general_content_000679.jsp&mid=WC0b01ac05800250b5
- Existing webpage containing information about EV organisation and user management, registration and access to the EVWEB reporting application. Registered EV users will continue to access the restricted area as usual: https://eudravigilance.ema.europa.eu/highres.htm

System components

The EV system consists of a few main system components. These components are:

- EV Organisation and User Management
  - Active directory service to manage all partners that have an obligation to report serious adverse drug reactions for medicinal products authorised in the EEA and clinical trials performed in the EEA
  - Key element for:
  - Uniquely identifying registered organisations
  - Implementing and monitoring security tracking functions within DBMS
  - Defining access rights to the DBMS
- EV Gateway
  - Electronic regulatory submission environment
  - Allows reporting to a common reporting point from where transactions are rerouted to the addressed NCAs and EMA; secure reporting mechanism

- EV Database Management System
  - Core element
  - Web-based information system that handles the safety report information according to International Conference on Harmonisation (ICH) specifications
  - Consists of two modules:
    - Eudravigilance Clinical Trial Module (EVCTM)
    - Eudravigilance Post-Authorisation Module (EVPM)
- EVWEB reporting application
  - Interactive tool for report generation and administration via the web interface called EVWEB
  - Allows sending and receiving of safety and acknowledgement messages in compliance with the latest ICH standards
- Extended Medicinal Product Dictionary
  - Purpose is to assist the PV activities
  - Supporting collection, reporting, coding and evaluation of authorised and investigational medicinal product information in a standardised and structured way
- EV Data Analysis System
  - Analysing safety data collected in EV
  - Range of analytical tools for measuring and reporting

Additional information and EV system overview on can be found at:
http://www.ema.europa.eu/ema/index.jsp?curl=pages/regulation/q_and_a/q_and_a_detail_000166.jsp&mid=WC0b01ac0580a68f78

Additional information on electronic reporting is available at:
http://www.ema.europa.eu/ema/index.jsp?curl=pages/regulation/general/general_content_000686.jsp&mid=WC0b01ac0580a69261

Registration process

Registration is the first step that needs to be made if an NCA wants to use EV as the ADR reporting tool. Registration is necessary to identify and manage organisations for electronic submission of ADR reports and information on medicines. It ensures privacy and security measures to comply with data integrity, accountability and data security principles.

Who needs to be registered?

Stakeholders that need to be registered with EV are Marketing Authorisation Holders (MAHs), National Competent Authorities (NCAs) and sponsors of clinical trials. The registration process differs depending on the different categories of stakeholder involved.

There are two solutions that can be used:

- Local Gateway and EV POST Function organisations. New organisations must be registered separately for both, test and production environment (external compliance – XCOMP and production environment)
- Web trader. EVWEB users need to be registered just in the production environment; test environment registration can be done if it is specifically requested.

A brief description of the registration process can be reached at: http://www.ema.europa.eu/ema/index.jsp?curl=pages/regulation/general/general_content_000687.jsp&mid=WC0b01ac0580a69262

A document describing the electronic registration process is available at: http://www.ema.europa.eu/docs/en_GB/document_library/Other/2016/04/WC500205473.pdf. Registered users gain access to a "locked" part of an EV web portal where additional services are available.

Training

At least one user from the NCA, MAH or sponsor should receive training, so that the quality of data entered into EV can be ensured.

Educated users will be able to start the electronic submission of ICSRs and ICSR acknowledgements in the context of clinical trials and post-authorisation of medicinal products.

Trainings programmes that are available are:

- EV training on electronic reporting of ICSRs in the EEA
- EudraVigilance Data Analysis System (EVDAS) Training for NCAs in EEA MSs.

More information about training programmes with current training courses and dates can be found at: http://www.ema.europa.eu/ema/index.jsp?curl=pages/regulation/q_and_a/q_and_a_detail_000162.jsp&mid=WC0b01ac0580a1a1fb

Once the registration, testing (if needed) and training process are finished, electronic exchange of ADRs can start. Once registered, users will continue to access the restricted area as before at: https://eudravigilance.ema.europa.eu/Decommissioned/Decommissioned.html

E2B R2 to E2B R3 Transition information and links

Since transition from ICH E2B (R2) to ICH E2B (R3) is planned, below you can find some additional information about the transition:

- ICH IG package and ICH E2B Q&As. Accessed: 29.03.2016, available from: http://estri.ich.org/e2br3/index.htm
- ICH guideline E2B (R3) – Q&As, January 2015. Accessed: 29.03.2016, available from: http://www.ema.europa.eu/docs/en_GB/document_library/Scientific_guideline/2009/09/WC500002779.pdf
- EU ICSR Implementation Guide, December 2014. This guidance specifies the technical requirements and the process of transmission of ICSRs and is applicable to all stakeholders that are exchanging ICSRs electronically within the EEA. Accessed: 28.10.2015, available from: http://www.ema.europa.eu/docs/en_GB/document_library/Regulatory_and_procedural_guideline/2014/04/WC500165979.pdf
- A section of the EMA webpage is dedicated to EV change management, and contains the latest updates and documentation for stakeholders. Accessed: 14.09.2016, available from: http://www.ema.europa.eu/ema/index.jsp?curl=pages/regulation/q_and_a/q_and_a_detail_000165.jsp&mid=WC0b01ac0580a69263
- A section of the EMA webpage dedicated to access to EV data, containing the latest updates and information for stakeholders interested in accessing EV data. Accessed: 14.09.2016, available from: http://www.ema.europa.eu/ema/index.jsp?curl=pages/regulation/general/general_content_000674.jsp&mid=WC0b01ac0580a69390
- EV stakeholder change management plan. This document details the changes taking place in the EV system and to the process of reporting ICSRs and Suspected Unexpected Serious Adverse Reactions (SUSARs). These changes are being brought about by changes to the post-authorisation and clinical trials legislation; organisations are advised to use this document as a starting point to develop their own internal plans to manage the changes that will take place once the new EV system is moved into production. Changes to this text are expected and organisations are advised to regularly check for the latest version. Accessed: 29.03.2016, available from: http://www.ema.europa.eu/docs/en_GB/document_library/Regulatory_and_procedural_guideline/2015/10/WC500196029.pdf

- GVP Module VI – Management and reporting of adverse reactions to medicinal products, Rev 1, September 2014, addresses the legal requirements detailed in Title IX of Directive 2001/83/EC [DIR] and chapter 3 of Regulation (EC) No 726/2004 [REG], which are applicable to competent authorities in MSs, MAHs and the EMA with regard to the collection, data management and reporting of suspected adverse reactions (serious and non-serious) associated with medicinal products for human use authorised in the EU. Recommendations regarding the reporting of emerging safety issues, or of suspected adverse reactions occurring in special situations, are also presented in this module. The requirements provided in chapters IV, V and IX of the Commission Implementing Regulation (EU) No 520/2012 [IR] shall be applied in this module. Accessed: 29.03.2016, available from: http://www.ema.europa.eu/docs/en_GB/document_library/Scientific_guideline/2014/09/WC500172402.pdf.

- EV communications plan: to inform stakeholders of the upcoming project milestones and corresponding communication activities: http://www.ema.europa.eu/docs/en_GB/document_library/Other/2015/10/WC500196040.pdf

Other pharmacovigilance links

Additional information regarding pharmacovigilance systems in the EU provided by the EMA, including manuals, legislation, good practices, risk management plans, medicines information, etc. can be found at: http://www.ema.europa.eu/ema/index.jsp?curl=pages/regulation/general/general_content_000258.jsp&mid=WC0b01ac05800241de

3.2.2 The WHO Programme for International Drug Monitoring (WHO PIDM)

The World Health Organisation (WHO) Programme for International Drug Monitoring (WHO PIDM) started in 1968 with its main goal being to identify PV signals to prevent possible drug disasters. It started with 10 countries pooling data from their national spontaneous adverse drug reaction reporting systems. Today, more than 120 countries have joined WHO PIDM, and an additional 29 associate members are awaiting full membership.

The WHO PIDM is a global initiative aimed to improve medicines safety and build a global safety culture. UMC provides scientific leadership and operational support to the WHO PIDM and its members. This includes a range of tools, services and technical support that facilitates the PV work at the national authorities. Some examples are:

- VigiFlow® – An ICSR management system that supports the collection, processing and data sharing of ICSRs, to enable analysis of the data in an effective manner. Seamless electronic reporting from patients and healthcare professionals (HCPs) can be connected to via the eReporting module.

- The Simplified E2B Guide – A useful guide for vendors, systems developers and similar target groups, which aims to describe a limited set of the ICH E2B standard and to provide understanding of the fundamentals of E2B. The Guide can be used by organisations that need to communicate safety data from their database system to recipients capable of managing ICH E2B messages.
- VigiLyzeTM – A search tool that enables all national authorities to access the data that member countries of the WHO PIDM collectively share in the WHO global ICSR database, VigiBase®.
- VigiMatchTM – A method for detecting suspected duplicates in VigiBase®.

More information regarding UMC and the WHO PIDM can be found at: http://www.who-umc.org/.

Joining the WHO Programme

The WHO Programme provides detection and identification of early signs of previously unknown medicine-related safety problems and ensures sharing of information captured throughout the world. Nonetheless, there are benefits and obligations each country must be aware of.

Benefits are:

- Access to VigiBase – worldwide medicine safety database
- Early information about potential safety issues
- Terminologies and software tools
- Support, training and guidelines
- International network access

Obligations / duties are:

- Compatibility with agreed reporting formats and quality of ICSRs
- Drug references – names and basic details of the medicinal drug must be included in WHO DDs
- Regulating information – sharing important information within a country via newsletters and bulletins
- Active participation

Additional information about being a member and joining the WHO PIDM can be found under the following links:

- Being a member: http://www.who-umc.org/graphics/28121.pdf
- Joining the Programme: http://www.who-umc.org/graphics/24730.pdf

Starting a pharmacovigilance programme

Countries starting PV programmes can receive support from the UMC and the WHO. The support is provided to countries by way of guides to good examples and best practices (e.g. designing an ADR report – http://www.who-umc.org/graphics/28521.pdf), determining minimum requirements for functional national PV systems (e.g. http://www.who-umc.org/graphics/24733.pdf), publishing different materials, such as information about the importance of PV, practical handbooks, scientific publications, etc. (http://www.who-umc.org/DynPage.aspx?id=105895&mn1=7347&mn2=7259&mn3=7298&mn4=7510).

VigiBase

VigiBase[6] is the name of the WHO global database containing ADRs received from the WHO Programme members. National Centres are sending ADRs to VigiBase on a continual basis and the frequency of sending cases into the database can differ from centre to centre, but the recommendation is to send reports at least quarterly.

The data in VigiBase is structured and indexed and allows analysis and retrieval of data collected. The VigiBase system is not a single database, it is linked with other databases containing medical and drug classifications. The linked databases are the WHO Adverse Reaction Terminology (WHO-ART)/MedDRA, the WHO-International Classification of Diseases (WHO-ICD) and the WHO Drug Dictionary.

Types of reports being held in the database are mainly serious and non-serious post marketing cases, cases from clinical trials and literature cases. ICSRs on medication errors, counterfeit/sub-standard medicines and therapeutic errors should also be submitted.

Other tools facilitating pharmacovigilance work

Members of the WHO PIDM have a number of tools and systems at their disposal for facilitating the PV work they do. The tools and systems they can use are:

VigiLyze

- Search and analysis tool
- Includes data on conventional medicines, traditional medicines (herbals) and biological medicines, including vaccines
- Can be used for:
  - Global, regional or national view of an ADR
  - Identification and monitoring of international patient data

[6] http://www.who-umc.org/DynPage.aspx?id=98082&mn1=7347&mn2=7252&mn3=7322&mn4=7326, accessed on 15 July 2016

  - Finding support when assessing case reports
  - Statistical view of global PV
- Access
  - Free of charge to all member countries of WHO Programme
  - Through custom searches for external customers
- Additional info: http://www.who-umc.org/DynPage.aspx?id=123391&mn1=7347&mn2=7252&mn3=7254&mn4=7695

VigiAccess

- VigiBase search interface
- Access - everyone, free of charge: http://www.vigiaccess.org/
- Additional info: http://www.who-umc.org/DynPage.aspx?id=132936&mn1=7347&mn2=7252&mn3=7254&mn4=7753

VigiFlow

- Web-based ICSR management tool
- Compliant with ICH E2B standard
- Additional module: eReporting allows receiving ICSRs from patients and healthcare professionals directly
- Additional info: http://www.who-umc.org/DynPage.aspx?id=97223&mn1=7347&mn2=7252&mn3=7254&mn4=7255

WHO Drug Dictionary

- Comprehensive source of medicinal product information
- Intended for:
  - Drug regulatory authorities
  - Pharmaceutical companies
  - Clinical research organisations
- Translates drug names into useful information used for coding of drug safety data
- Data entries refer to:
  - Prescription only products
  - Over the counter products
  - Pharmacist dispense preparations

  - Biotech and blood products
  - Diagnostic substances
  - Contrast media

- Additional info: http://www.who-umc.org/DynPage.aspx?id=98105&mn1=7347&mn2=7252&mn3=7254&mn4=7338
- Purchase: http://www.umc-products.com/

WHO-ART (WHO-Adverse Reaction Terminology)

- Terminology for coding clinical information in relation to drug therapy
- Covers most medical terms needed in ADR reporting
- Additional info:
- http://www.who-umc.org/DynPage.aspx?id=98107&mn1=7347&mn2=7252&mn3=7254&mn4=7339
- Purchase: www.umc-products.com/

Training

Uppsala Monitoring Centre (UMC) offers different training and education materials. Training courses can be face-to-face or web lectures. More information on dates, organisation list and web lectures is at: http://www.who-umc.org/DynPage.aspx?id=98079&mn1=7347&mn2=7252&mn3=7323

Useful links

- UMC: http://www.who-umc.org/
- UMC Frequently Asked Questions (FAQs): http://www.who-umc.org/DynPage.aspx?id=101247&mn1=7347&mn2=7252&mn3=7258
- UMC Contact: http://www.who-umc.org/DynPage.aspx?id=97230&mn1=7347&mn2=7251
- The World Health Organisation (WHO): http://www.who.int/en/

Example of the guidance document

Attached below is a guidance document published by Uppsala Monitoring Centre (UMC): Simplified E2B guide for transfer of pharmacovigilance data from primary reporters. The document is intended for the vendors, system developers and similar groups to easily understand fundamentals of E2B.

Simplified E2B guide_1.0.pdf

4. A well-developed and operative system

This section focuses on well-developed and operative systems that are being used to facilitate everyday PV work. These systems are often custom developed or purchased with minor adjustments applied later. From the chart shown in the previous section, it can be seen that most of the countries are using custom developed system (14/25 respondents) and commercially available ADR IT systems (8/26 respondents). Some of the respondents are using both commercially available and custom developed systems in combination with spreadsheet tools.

One of the questions asked in Review of IT Systems questionnaire was "Your ADR IT system is used for:

- Collecting of ADRs
- Processing of ADRs
- Communication between reporter and institution
- Data exchange with other IT system (e.g. national system with EV)
- Other, please specify
- Our institution is not responsible for this activity."

An overview of the answers collected through this question is shown below:

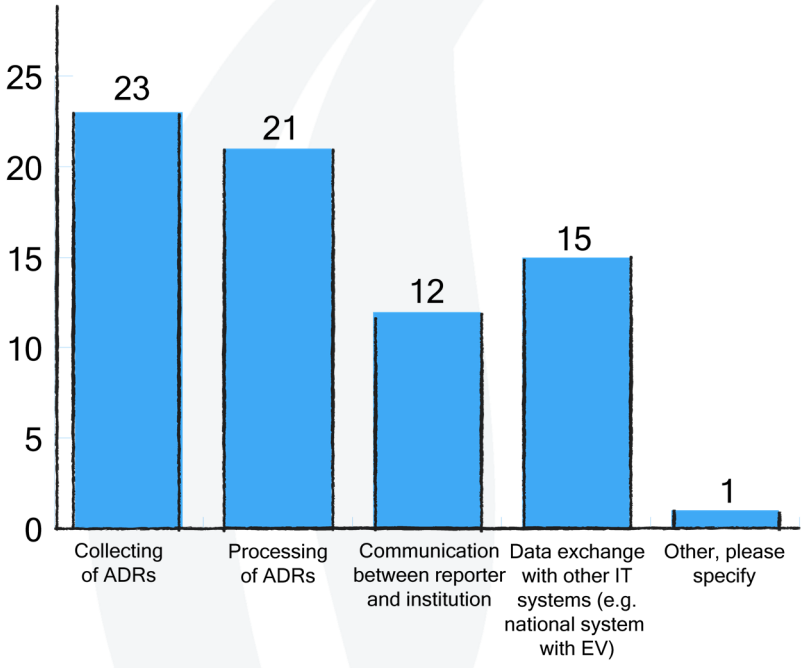

Figure 3. ADR IT system purpose

Twenty-six respondents answered this question and multiple answers could be selected. It can be seen that most of respondents are using their system for the collecting and processing of ADRs.

From the answers collected it is visible that most of the respondents are using their system for all four features (collecting, processing, communication and data exchange).

When we consider the results of the questionnaire alongside ADR IT system descriptions and pharmacovigilance business process descriptions, it can be concluded that well-developed systems are those that facilitate and improve pharmacovigilance staff work. A well-developed system also improves the quality of the information gathered, which contributes to the safety monitoring of medicines to safeguard public health.

4.1 System features

In this section, short descriptions of well-developed system features will be listed. Some of the features can be also considered as advanced features, though they are described in this section.

If we simplify the PV business process it would consist of three steps: receive/collect the ADR, process/assess the ADR and report (transmit) the ADR. There is also the possibility of additional communication between assessors and reporters (HCPs or patients), but it won't be taken into consideration for the purpose of this simplified process.

The following chart is a representation of the simplified PV business process.

Figure 4. Simplified PV business process

A data exchange feature can be added to above representation of PV business process, although it depends on the level of development of the ADR IT system.

4.1.1 Electronic data collection

ADR reporters should be able to make a report electronically. The best way to do it is by using electronic forms (web forms and/or "smart" forms like Adobe Interactive Forms or similar), which should be made available at least through the National Competent Authority (NCA) webpage. Links to web forms should also be made available through webpages of other organisations concerned with public healthcare, patient organisations, etc.

As mentioned earlier, the term 'electronic form' refers to web forms or "smart" forms. Differences between web forms and "smart" forms are:

- Web form[7]
  - Placed on a webpage
  - Allows user to enter data, which is sent to a server for processing
  - Can resemble paper or database form, because the forms are filled in using checkboxes, dropdown lists, text fields, etc.
- "Smart" form
  - Interactive forms, provide all features and functions needed for creating form based output
  - Two kinds of forms:
    - Online form – user enters required data into the form and submits it, following that, the data is automatically sent back to the system. The system extracts the data from the form and saves it into the database.
    - Offline form – internet connection is not required, i.e. requested information can be filled in while offline. Filled form is consequently sent (e.g. by email) back to its owner. Upon receiving a filled form, owner processes the form, after that the data is transferred into the DB or custom system.

Documents (Word, PDF, Excel or similar), which are required to be downloaded from a website, filled in, and sent via email in order to deliver the required data, and do not include any automatic sending or processing of data, are not regarded as electronic forms.

Benefits of receiving ADRs in electronic forms over the paper form or telephone service are:

- No need for manual entry of the ADR data into the IT system. If ADRs are received electronically, there's no need for retyping the ADR data into the system (manual data entry). The administrative staff need less time to prepare an ADR report and send it for the assessment
- Data entry is controlled. Where applicable, data registries (e.g. medicinal product registry) should be used to facilitate data entry for the reporter
- Data validation. Data validation rules should be implemented. The rules should meet at least the ICH E2B standard[8]. Minimum required data and additional validation rules should also be built in if needed to meet specific business or regulatory needs
- Term mappings. Terms should be mapped between dictionaries to help set up standardised terminology and to facilitate terms coding for assessors

[7] https://en.wikipedia.org/wiki/Form_%28HTML%29, accessed on 14 July 2016

[8] http://estri.ich.org/, accessed on 27 July 2016

- Time saving
  - This is achieved if there's no manual data entry or retyping of the data received into the system
  - Assessors have more time to perform assessment
  - A greater amount of ADRs can be assessed.

Through the SCOPE project, WP4, an ADR reporting web form has been developed. The web form consists of a frontend (form interface), backend (Content Management System (CMS)) and an Electronic Healthcare Record (EHR) management system. The CMS is used for customisation and administration of a web form, whilst the EHR allows management, including editing, of the reports received. The web form system can then be hosted by the NCA IT department or a third party supplier.

The web form will be made available to all of the MSs who would like to implement one into their systems or national PV infrastructure.

4.1.2 Sharing data between systems

Controlled data entry and data sharing between NCA systems should be used where possible. For example, the NCA system for medicinal product tracking could be used to populate the medicinal product section in the ADR report. Automatisation of data exchange between systems allows data to be shared as soon as it is created in one of the systems connected. If an automatic link between systems exists, there is no need for manual transcription of newly produced data and errors are less likely to appear. In general, when data sharing between systems is in use, there is single point of data entry. The data entered is just being shared and edited according to the rules implemented to manage such data.

4.1.3 Data dictionaries

Data dictionaries are important at the moment of data entry whether for the reporter when completing an ADR report or later in the process of ADR coding and mapping data (an assessor's work). When data dictionaries are in use, standardised data is used for populating data fields in electronic forms. Consequently, there is less chance of making an error at the data entry point, as there are no typing errors or incorrect wordings; instead, terms are chosen from lists and data entry is therefore quicker.

It is recommended to use data dictionaries wherever applicable to avoid errors in the process of data entry, which is crucial in the later stages for data processing and analysis. If shared dictionaries are used or if there is data synchronisation between dictionaries, strict rules have to be put in place to ensure data correctness.

Mapping terms between dictionaries is also possible (e.g. SNOMED CT to MedDRA), but it has to be noted that it requires intensive manual work in the beginning. When mapping is complete or almost complete, benefits become visible and have a long-term impact on data quality and assessment.

4.1.4 Connection with EudraVigilance

One of the questions asked in the WP4 Review of IT Systems questionnaire was related to automatic or manual case transmission into EudraVigilance (EV). From the answers received, it is clear that most of the respondents are still manually transmitting ADRs into EV. When manual transmission was chosen, most of respondents answered that they are using EVWEB for transmission. The second most common answer was that they are using a custom software/database solution. In the case of automatic transmission, 10 answers were received: five of the respondents are using a commercial software solution and the other five are using a custom software or database solution.

The following chart presents the answers collected.

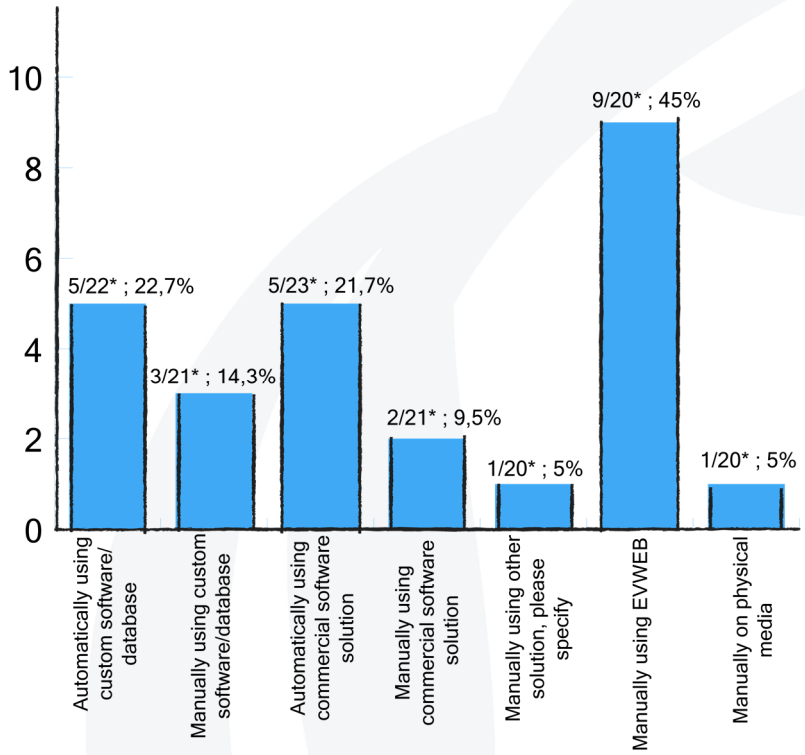

Figure 5. Case transmission between ADR IT system and EV

A connection between systems and automatic files exchange between them has some benefits. These benefits are related mostly to time saving, i.e. less time is spent for files preparation and sending of the files into EV. No additional staff is needed to take care of this part of the work and there is no possibility of human error in not sending ADRs into EV. The risk appears if there are no controls or Standard Operating Procedures (SOPs) in place for what to do in case of a system failure.

Files can be transferred in two ways. They can be exported automatically or manually, to a designated folder from which batch scripts[9] or a procedure can copy them to a server from which they are then sent into EV. A script file can be scheduled to run once a day or as frequently as required. Each time it will check specified folder contents, copy files to a server and will stop until the next scheduled run. The second way is via a web-service,[10] which checks if there are files prepared for sending and then picks (collects) them up and sends them to EV.

4.1.5 Data logging and analysis

Apart from data collected from ADR reports, the system should record additional metadata, which can later be used for providing information related to ADRs and activities carried out. This data can be administrative, for example, the date when an ADR report is received, the method of submission (paper form, electronically, telephone etc.), deadline, appointed employees, or related to ADR assessment.

Well-developed systems should reduce the amount of manually entered data; data should be entered automatically for those values that are known at the start. Even when manual entry of data is needed, the system can help (e.g. using the recorded information to show workload per employee, or the system can do duplicate detection depending on conditions set up).

Data logging allows us to monitor and analyse data received to optimise business processes, redistribute resources and improve efficiency. In addition to the above, data collected can be used to identify areas for improvement – for example, data quality or reporter experience.

[9] Batch script – script file which consists of a series of commands to be executed by command line interpreter and stored as plain text

[10] https://en.wikipedia.org/wiki/Web_service, accessed on 14 July 2016

5. Advanced systems

These are mature, well-developed systems with some additional functionality developed to facilitate PV work, HCP and patient efforts in e-reporting, to improve ICSR data quality and so on. Advanced systems are also able to receive ADR reports from any systems containing patient and medicinal data.

New technologies, such mobile applications for ADR reporting and social media applications, can also be considered as advanced systems. The model of reporting an ADR is the same, but the technology is innovative and it allows easier, faster and more user-friendly reporting of ADRs.

5.1 Advanced systems features

Features considered to be advanced are described in the following section.

5.1.1 Connection with Electronic Health Record (EHR) systems, registries and other systems containing patient or medical data

Through the questionnaire MSs were asked if they are receiving reports from any system containing patient records or medical data. The aim of this question was to see if there are MSs that are receiving ADRs from such systems and what influence this has on the number of reports received and the quality of reports.

Five respondents answered this question and from the chart below we can see that some of them have established connections with more than one system from which they can receive ADRs.

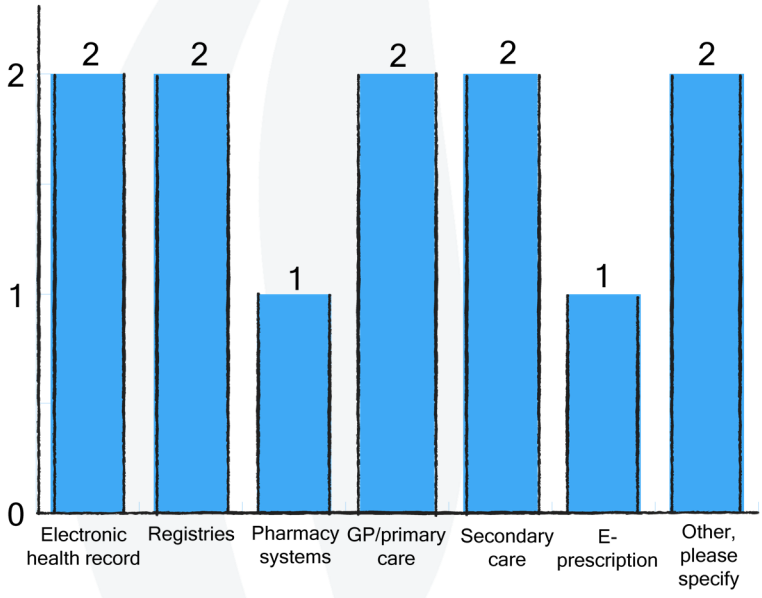

Figure 6. System containing patient records or medical data used for ADR reporting

From the answers received, it is visible that one MS has connections with four systems (EHR, pharmacy systems, general practitioner (GP)/primary care and secondary care). Another MS is receiving ADRs from more than one system (EHR, GP/primary care and e-prescription), and this can be also considered as an advanced system.

When an ADR report is received from any system containing patient or medical data, data quality depends on the data entered into the original external system. From the perspective of an NCA, data received can be considered as consistent, checked and valid.

5.1.2 Data exchange between connected systems

Data exchange is based on the ICH E2B standard[11], which defines data elements and message specification.

When ADRs are reported electronically, the information is transmitted from the electronic form into an NCA's database as an E2B XML data file and the file is processed through an automated workflow. The XML data file is validated against specific validations, e.g. minimum fields and format of message. Some of the errors can result in warnings and some of them will cause a rejection message. Errors must be additionally reviewed.

For the purposes of electronic data exchange, a web-service needs to be developed according to the E2B standard. All of the information related to the standard can be found at: http://estri.ich.org/. A download package contains ICH-ICSR schema files, reference instances, examples, code lists, technical information and guidelines.

5.1.3 Message validity checking

Business rules need to be applied to electronic ADR messages received to ensure the ADR message is valid. Validation is based on system rules automatically applied to the XML file (ICSR) being received. The rules should comply with EV rules, but they can be extended. Typically, the minimum criteria[12] for submitting a valid report should be the same:

- Name of suspect drug or substance
- Suspected ADR
- Information about the patient (e.g. initials, age and gender)
- Information about the reporter.

[11] http://estri.ich.org/, accessed on 25 July 2016

[12] http://www.ema.europa.eu/docs/en_GB/document_library/Scientific_guideline/2014/09/WC500172402.pdf, accessed on 25 July 2016

Additional XML fields mapped to an electronic form can be set as mandatory and without them it won't be possible to submit a report. The received XML file needs to be additionally checked when first validation is finished and when the file comes to an assessor. Usually additional data needs to be entered; coding must be done if it is not entered in acceptable terminology (e.g. MedDRA coding). If automatic mapping is implemented, it will be done automatically for known terms and manual mapping will be needed just for those terms that are not already mapped.

5.1.4 Medical term mapping

Medical term mapping is preferred to be automatic, based on a mapping created between terminologies and by using software, although the basis for each mapping is manual. Automatic mapping is an upgrade to manual mapping mentioned in section 4.1.3. Data dictionaries.

The SCOPE questionnaire asked how medical term mapping is performed if medical terms need to be mapped to a certain terminology. Answers were collected from three MSs. All of them answered that they are doing it manually on a case-by-case basis and two of them are also doing it automatically based on manual mapping done previously. Preparation and initial mapping is done manually and it is the prerequisite for this way of mapping. Only one out of these three MSs is additionally performing automatic, software-based mapping.

5.1.5 Communication between reporter and assessor

Communication between the reporter and assessor is preferred to be two-way (exchange of incoming and outgoing messages). If two-way electronic communication is in place, communication between assessor and reporter (HCP) is much easier and quicker. Additional data needed to assess suspected ADRs can be acquired faster.

One MS reported that communication between assessors and ADR reporters tends to be one-way, inbound communication, in the form of an electronic report. Only one MS has implemented two-way communication and it is implemented over the gateway where every registered user (MAH) owns an inbox through which they can receive documentation. There is no messaging service implemented; MAH's have to check their inbox daily.

If e-reporting of ADRs is in place, at least automatic replies should be implemented. Automatic replies can be based on an XML containing ADR data validity (e.g. in one country upon submission of a direct ADR report the reporter receives an automatically generated email from the system as an acknowledgement of the receipt of the report. Further communication with the reporter is carried out via email or phone, and for MAHs via electronic exchange of E2B XML files through the EV gateway).

5.1.6 Signal detection

A signal is information that arises from one or more multiple sources (including observations and experiments), which suggests a new potentially causal association, or a new aspect of a known association, between an intervention and an event or set of related events, either adverse or beneficial, that is judged to be of sufficient likelihood to justify verificatory action[13].

In an advanced system, IT functionality enabling signal detection activities can be built in. For example causality assessment, disproportionality methods can be used to identify drug-event combinations for review and so forth.

Additional information on signal management is provided within SCOPE WP5 – Signal management and in Guideline on good pharmacovigilance practices (GVP) Module IX – Signal management, EMA/827661/2011, 20 February 2012. The objective of SCOPE WP5 is Implementing shared understanding of best practice in signal management across the EU network.

5.1.7 Additional monitoring

The concept of additional monitoring originates primarily from the need to enhance the ADR reporting rates for newly authorised products for which the safety profile might not be fully characterised or for products with newly emerging safety concerns that also need to be better characterised. The main goals are to collect additional information as early as possible to further elucidate the risk profile of the products when used in clinical practice and thereby informing the safe and effective use of medicinal products[14].

Additional monitoring can be integrated with a medicinal product case tracking tool. A flag or a status can be assigned to a medicinal product in the granting of a marketing authorisation or sometimes later if a new safety concern has been identified.

ADRs containing flagged medicinal products (additional monitoring) can be handled with special care. Specific workflows can be set in place, e.g. automatic routing of ADRs to senior assessors according to assignments or notifications to PV staff.

Additional monitoring flagging can be automatic if the minimum criteria set is known and determined. If set conditions are fulfilled then a system can add an additional monitoring flag by itself. If the minimum criteria set is not known or can't be determined, flagging of medicinal products should be manual. In this case, a register of medicinal products should be connected with the ADR system in order to identify if a specific medicinal product is referenced in an ADR report.

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[13] Guideline on good pharmacovigilance practices (GVP) Module IX – Signal management, EMA/827661/2011, 20 February 2012, accessed on 27 July 2016

[14] Guideline on good pharmacovigilance practices (GVP). Module X – Additional monitoring, EMA/169546/2012, 19 April 2013, accessed on 27 July 2016

More information regarding additional monitoring can be found in the SCOPE WP4 Additional monitoring deliverable document, Identification, management and raising awareness of ADR reports for drugs subject to additional monitoring.

5.1.8 Duplicate detection

Duplication of cases is an important data quality issue and can pose significant problems for analysing signals arising from pharmacovigilance databases by misleading clinical assessment or distorting statistical screening, both artificially inflating and masking signals of disproportionate reporting[15]. Duplicates are separate and unlinked records that refer to one and the same case of a suspected ADR[16].

Duplicate detection can be automatic if the minimum criteria set is known and determined. If mentioned conditions are fulfilled then a system can mark suspected duplicates at a data entrance point, for example, when loading the ADR report into the database. Depending on conditions a computer algorithm can be used for duplicate detection. Usually, basic conditions are patient details (e.g. age and sex), suspected/interacting medicinal products and adverse reactions. Duplicate detection algorithms should be reviewed periodically.

If a potential duplicate is detected, notifications could be sent to an assessor who can then make a manual review of the reports and start the duplicate management workflow / process.

More information regarding duplicate detection can be found in Guideline on good pharmacovigilance practices (GVP) Module VI – Management and reporting of adverse reactions to medicinal products, and good practices can be found within the SCOPE WP4 document, Duplicate Detection: Best Practice Guide.

[15] Norén GN, Bate A, Orre R. A hit-miss model for duplicate detection in the WHO drug safety database. In - KDD '05: Proceedings of the 11th ACM SIGKDD conference on Knowledge Discovery and Datamining, 2005, 459-468, accessed on 27 July 2016

[16] Guideline on good pharmacovigilance practices (GVP) Module VI – Management and reporting of adverse reactions to medicinal products (Rev 1) EMA/873138/2011 Rev 1*8 September 2014, accessed on 27 July 2016

6. Case studies

6.1 Medicines and Healthcare products Regulatory Agency – ADR IT reporting system

The Medicines and Healthcare products Regulatory Agency (MHRA) regulates medicines, medical devices and blood components for transfusion in the United Kingdom (UK)[17]. This includes collecting reports of suspected Adverse Drug Reactions (ADRs) via the Yellow Card Scheme as part of its PV responsibilities.

Yellow Card Scheme[18]

The Yellow Card Scheme has been in operation since 1964 and is a vital component in helping the MHRA to monitor the safety of all healthcare products in the UK. Reports can be made for all medicines including vaccines, blood factors and immunoglobulins, herbal medicines and homeopathic remedies, and all medical devices available on the UK market. Since May 2016, the MHRA is also collecting reports associated with e-cigarette products.

Reports are received from all types of healthcare professional, MAHs and members of the public. Reporting from members of the public was first introduced as a pilot in 2005, before being rolled out nationwide in 2008 in conjunction with the launch of a new Yellow Card website to provide a simple and easy way for patients to report. Reports can also be received on paper, via the telephone, directly from healthcare clinical systems and, since July 2015, via a Yellow Card smartphone app.

IT systems and case processing

The MHRA has a custom-built national ADR database holding ADR reports for medicines and vaccines dating back to 1963. Currently, the database holds over 800,000 UK spontaneous suspected ADR reports.

The MHRA has a multidisciplinary team of life science graduates and pharmacists responsible for the processing of ADR reports, which must be entered into the database within strict deadlines. The level of case processing required for an ADR report will depend on the method of reporting.

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[17] https://www.gov.uk/government/organisations/medicines-and-healthcare-products-regulatory-agency/about, accessed on 6 June 2016

[18] https://yellowcard.mhra.gov.uk/the-yellow-card-scheme/, accessed on 6 June 2016

For paper and telephone reports, each report must go through four stages of processing:

- Input verification: Confirms the case is valid and assigns a priority (based upon the seriousness of the case)
- Data capture: The detail of the case is entered onto the database
- Quality assurance: Confirmation of the coding of the case (correct or not)
- Assessment step: Determines the completeness of the information and whether a request for further information from the reporter is required.

Electronic ADR reports (received from HCP clinical systems, the MHRA website, the Yellow Card App or from MAHs) are automatically entered into the database. There are inbuilt system validations to ensure the case meets E2B specifications, EV business rules and MHRA-specific rules. MAH cases will commit automatically into the database or progress as far through the case workflow as possible until a coding issue is identified (e.g. drug name not matching the MHRA drugs dictionary or the nullification flag is set), which then requires manual intervention to resolve. Electronic reports from HCPs and members of the public are also automatically populated; however, they are programmed to enter the workflow at the data capture step to allow the MHRA's PV team to review the coding and ensure all relevant information has been captured in the appropriate structured fields before the case is committed into the database and available for signal assessment and data retrieval. The option to amend this programming is possible to allow the cases to commit automatically to the database if required for MHRA business processes (e.g. if volumes of ADR reports substantially increased).

Signal detection activities are then performed on the ADR reports on a weekly basis using disproportionality methods to identify drug-event combinations for review. This is carried out using Empirica Signal software.

Integrated electronic reporting from clinical systems

As reporting to the Yellow Card Scheme is voluntary, the MHRA undertakes a number of activities to promote reporting and increase awareness of the scheme through its Yellow Card Strategy. One of the main focuses for these activities includes the facilitation of electronic reporting through integration into clinical IT systems used by HCPs.

Reporting directly from clinical systems has a number of benefits: it improves access to Yellow Card reporting and reduces the effort required to complete the form through automatic population of information from the patient record. Reporters can be prompted to complete a Yellow Card within the system when specific tasks are completed in the systems, such as a medication being withdrawn.

In 2012, an information standard for electronic Yellow Card reporting (ISB – 1582[19]) was developed for the UK National Health Service (NHS). The standard defines the electronic message, standard requirements and a number of triggers that result in a user receiving a prompt to submit a Yellow Card. During the pilot phase (in 2011), an electronic ADR reporting feature was implemented into one primary care system, called SystmOne, for GPs. Analysis of received Yellow Cards showed an increase for GP ADR reports of almost 50% compared to 2010.

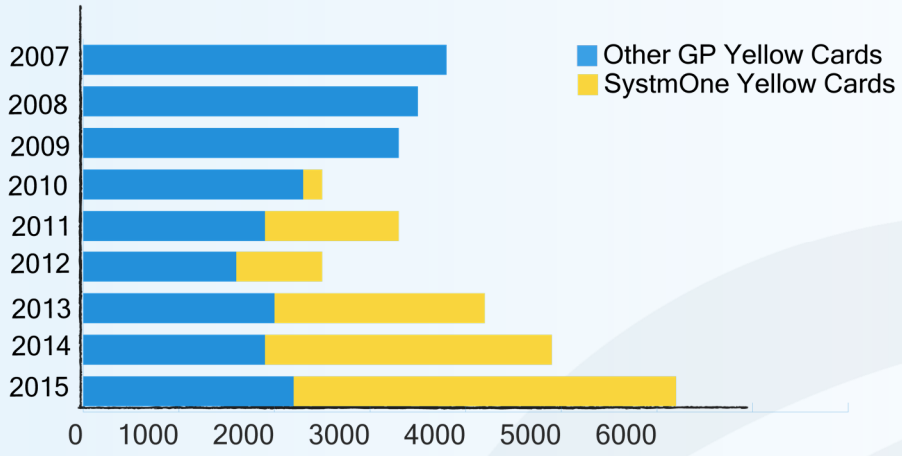

Figure 7. Yellow Card ratio and increase after direct reporting was implemented

This information standard was subsequently incorporated into the core requirements for the GP Systems of Choice (GPSoC) programme. This meant that all GP systems in England must include the capability of reporting an electronic Yellow Card to the MHRA directly from their respective systems. Testing of these remaining systems with software providers commenced in August 2014 with expected roll out in 2016. Although GPSoC only applies directly to England, the clinical systems that are also used in other parts of the UK will have the ability to use the same functionality.

The MHRA has developed a Simple Object Access Protocol (SOAP) web-service, which systems can connect to in order to submit XML files. Validation is based on system rules, automatically applied to XML ICSRs being received. These are similar to the EV business rules – they are available in the information standard, which includes a document detailing fields and validations. The web-service applies the validations specified – XML files can be either accepted, or rejected if they fail to meet the minimum requirements and to ensure the message is correctly formed. Where there are errors that would only result in an E2B 'warning', the message is accepted, and the errors are manually reviewed. The sender of the message can be identified as each IT system has a separate login to submit to the web-service, and also uses separate ICSR World Wide Reference numbers.

[19] http://webarchive.nationalarchives.gov.uk/+/http://www.isb.nhs.uk/documents/isb-1582, accessed on 9 June 2016

MedDRA or SNOMED CT is accepted for medical terms, and the MHRA have built up mappings between SNOMED CT concepts and MedDRA Preferred Terms (PTs). An internal process converts SNOMED CT concepts to MedDRA PTs before the Yellow Card is processed automatically onto the MHRA ADR database. Yellow Cards received where the SNOMED CT codes have not been mapped fall into a web-service staging area where a manual mapping is performed by the team. When a suitable term is selected for an unmapped term by an assessor, it is stored as a mapping for any future Yellow Cards. This enables future reports with the same term to not fall out of the workflow and be automatically loaded into the MHRA's PV database. Medications are coded in the UK NHS using a terminology called dm+d, and the process of creating a mapping between dm+d and the MHRA's internal drugs dictionary has commenced and is expected to be available from summer 2016.

Outside of GP software systems, the MHRA has implemented integrated reporting from two other hospital based settings: MiDatabank software used by medicines information pharmacists based within NHS hospitals in the UK and e-prescribing modules within another hospital software system; and Cerner, which will be rolled out throughout 2016.

6.2 Spanish Agency of Medicines and Medical Devices – Integration with other systems

The Spanish Agency of Medicines and Medical Devices (AEMPS) is a public body that belongs to the Spanish Ministry of Health. Its mission is to give guarantees to the general public on the quality, safety, efficacy and accurate information on medicines and medical devices from research to end use and to protect and promote health in both humans and animals.

The AEMPS develops a wide range of activities within the framework of medicine evaluation and authorisation for human and animal use: clinical trials authorisation, continuous monitoring of medicine safety once medicines go on the market, quality control, authorisation and inspection of pharmaceutical laboratories, supervision of medicine supplies, certification, control and supervision of medical devices, combating illegal and counterfeit medicines and medical devices, monitoring safety procedures for cosmetics and hygiene products, and providing all relevant information to the public and healthcare professionals.[20]

The Spanish Pharmacovigilance System for Medicinal Products for Human Use is a decentralised body, coordinated by the AEMPS, which integrates the spontaneous reporting programme. It is composed of 17 regional pharmacovigilance centres (RPhC) and the AEMPS. The responsibilities are described in the Royal Decree 577/2013 of July 26, regulating the Pharmacovigilance of Medicinal Products for Human Use.

The AEMPS has a database called FEDRA, which has been developed internally. FEDRA is fully compliant with ICH E2B (R2)/M2 and, therefore ready for the electronic exchange of ICSRs. It is a unique national database accessible to RPhC and the AEMPS staff.

Regarding PV, the AEMPS has also developed and currently maintains BIFAP, a longitudinal population-based database of anonymised computer-based medical records of general practitioners (GPs) throughout Spain, to perform pharmacoepidemiological studies. BIFAP currently contains clinical and prescription data from around 4.8 million patients.

Integration with other systems

Two different ways for reporting ICSR are available: a paper form (Yellow Card template) or an electronic form[21].

ICSRs sent using paper forms are received by the RPhCs, which are responsible for the individual evaluation and the data entry activities.

[20] http://www.safeguard-diabetes.org/?q=content/aemps, accessed on 20 July 2016

[21] https://www.notificaram.es/, accessed on 18 August 2016

The information received by electronic form is included in a pre-database (PREFEDRA-WEB). Information received has to be validated/evaluated by the Regional Centre in order to be included in FEDRA.

ISCRs sent through MAHs are received electronically directly to a pre-database (PREFEDRA-MAH) and are managed in the same way as those received by notificaRAM[22].

In some Autonomous Communities[23] the information of ICSRs is obtained directly from electronic health records, primary care and an e-prescription system. There's no unique electronic medical record system/e-prescription system at country level. Each Autonomous Community manages their system and decides how to work with system vendors to implement the ADR reporting system, taking into account that no national legislation regarding this issue is available. Therefore, HCPs do not use the same system; it depends on the available system in the Autonomous Community where they work.

Examples of receiving reports and integration with connected systems were provided by AEMPS and are shown in the document.

Example 1

The electronic Yellow Card was integrated in the electronic healthcare record, primary care and e-prescription in 2010 and no testing process was performed before implementation. The information required for a valid electronic Yellow Card is similar to a paper Yellow Card: patient, drug, ADR and reporter.

In the toolbars of these applications there is an icon available for HCPs to access a Yellow Card and to complete a report for a suspected ADR.

For primary care and e-prescription reports, the reporter, patient and drug fields are automatically populated; however, for the electronic healthcare record in public hospitals, only the reporter and patient fields are automatically populated. Drug fields need to be entered manually by the reporter. The reporter needs to manually populate the other fields before sending the report.

Both mentioned systems use Nomenclator to integrate information relating to drugs. Nomenclator is a dictionary created and maintained by AEMPs and it is being used in FEDRA also. Indications and ADRs are free texts fields but the International Classification of Diseases (ICD), ninth revision, is recommended. For medication error reports, a mandatory field is included where a HCP can indicate if a medication error has occurred. If 'yes' is selected, the personal data of the primary source is automatically deleted.

Additionally, the system allows attaching files in different formats.

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[22] https://www.notificaram.es/, accessed on 18 August 2016

[23] https://en.wikipedia.org/wiki/Autonomous_communities_of_Spain, accessed on 18 August 2016

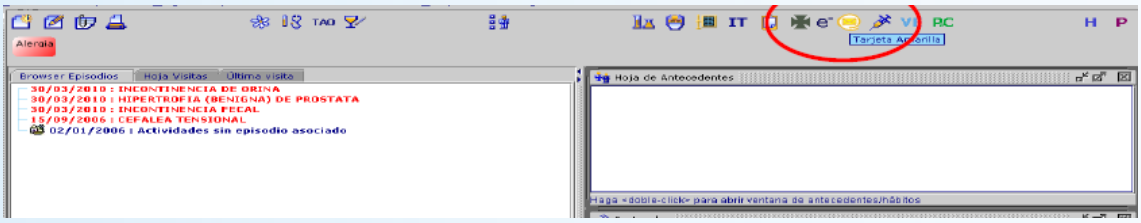

Figure 8. Spanish electronic healthcare record system with integrated Yellow Card access

Upon submission, a thank-you letter is sent automatically to the reporter.

These ICSR received are automatically loaded into the local database. The reports are recoded and manually loaded in FEDRA. In the next version of FEDRA it is planned for this information to be automatically integrated and loaded to facilitate the work of RPhCs.

Training activities are carried out by RPhCs to encourage and motivate HCPs to report ADRs and to do it using the integrated electronic Yellow Card. Training includes how to use the functionality coupled with a guide on how to use the system which has been developed by the RPhC and is available to HCPs.

The integration of ADR reporting in the EHR, primary care and e-prescription allows facilitating HCPs to reporting suspected ADRs and has shown an increase in the quantity of reports and the quality of information received, the latter unquantifiable as yet.

Example 2

At another RPhC, the electronic Yellow Card is available on the desktop of computers of medical specialists and is included as a link on the RPhC's website. In addition, the ADR reporting system is also integrated in the electronic medical record in primary care and in e-prescription. Information is manually entered by medical specialists and there are no dictionaries used for reporting medicines or ADRs. After completion of the electronic form, reports are sent electronically and are included automatically in a local database. Then, a technician includes the ICSR manually in the national database (FEDRA).

In primary care, when GPs add the International Classification of Primary Care (ICPC) classification of A85, which corresponds to 'Adverse Drug Effect; Correct Dose' within the patient's electronic medical record, the system prompts the GP to complete an ADR report. Should the GP select to do so, a new window appears where information relating to the ICPC and the patient are automatically populated, ready for the GP to complete details about the ADR. For the suspected medicine, the system allows the GP to specify the medication as free text, or to select between the patient´s prescriptions included into the clinical ADR record or through the Spanish drug database (Nomenclator).

Upon completion, the report is sent to the RPhC by email, where it is then included manually into the local database and also into the Spanish national database (FEDRA).

Finally, in Regional Centres, in which ICSRs are loaded into a local database directly from the EHR or other connected system, a daily review of the local database is carried out to check if a new ICSR is loaded in order to recode and, after that, load them manually into FEDRA. There are intentions to implement automatic transmission of information from local databases to the national database (FEDRA) to facilitate the work in the RPhC.

6.3 Danish Medicines Agency – Implementation of business rules

The Danish Medicines Agency (DKMA)[24] is the supreme pharmaceutical authority in Denmark. Together with the Danish Health Authority, it is responsible for monitoring the healthcare system, its actors and activities in Denmark. These boards are also responsible for advising the Minister of Health on health issues, controlling pharmaceuticals and pharmaceutical companies, and monitoring the economic use and consumption of pharmaceuticals[25].

DKMA responsibilities:

- Authorises and inspects pharmaceutical companies and licenses medicinal products in the Danish market
- Monitors adverse reactions from medicinal products and authorises clinical trials
- Monitors medical devices available in Denmark and supervises adverse incidents involving medical devices
- Appoints proprietary pharmacists, organises the pharmacy structure and supervises pharmacies and retailers.

DKMA has a custom-built database holding suspected ADR reports for medicines and vaccines dating back to 1968.

Reports are received from all types of HCP, MHAs and members of the public/consumers. Reporting from members of the public was first introduced in 2003. The number of ADR reports submitted to the DKMA has been increasing over the past years, reaching more than 7,500 initial reports in 2015.

The DKMA has a multidisciplinary team of life science graduates and pharmacists responsible for the processing of ADR reports, which must be committed to the database and transmitted to external stakeholders within strict deadlines. The level of case processing required for an ADR report will depend on the method of reporting (electronic vs. paper, etc.) and on the type of reporter (industry vs. non-industry).

[24] https://laegemiddelstyrelsen.dk/en/about, accessed on 21 July 2016

[25] https://www.ispor.org/HTARoadMaps/Denmark.asp, accessed on 21 July 2016

At DKMA, the procedure for handling ADR reports received from other reporters than industry involves internal coding and quality review in the workflow to ensure that data is correctly coded before being committed to the database and made available in outputs to industry, the public via Drug Analysis Prints (DAPs), and for signal detection, which is carried out (via Empirica Signal software) on a weekly basis using disproportionality methods to identify drug-event combinations for review. Usually, electronic reports received from industry are automatically committed to the database without manual intervention and, therefore, reports from industry are often available in the public domain (DAPs) as initially coded by the MAH. Sometimes reports from industry are not committed directly to the database due to various reasons, e.g. the drug name not matching the DKMA drugs dictionary, and so DKMA will handle these reports manually to ensure correction of data.

DKMA strives to maintain close dialogue with MAHs to avoid errors and low-quality reports from industry, as entering these into the DKMA database could have serious consequences, such as missing signals or creating false signals where ADRs are duplicated. Furthermore, such errors and quality issues generate a large volume of enquiries. This results in further work to update the case and/or contact the originator company to request an update to their case. Each enquiry that requires a case update will generate an updated version of the report, which is also a significant administrative burden for both industry and DKMA.[26]

Validation rules have been built into the systems to ensure that basic quality standards are met.

Business rules implementation

In Denmark the vast majority of ADRs are reported electronically either from MAHs or directly from HCPs and consumers. The information is transmitted from the electronic reporting form or the MAH into the DKMA database as E2BXML files and the file is processed through an automated workflow in the DKMA database. Additional manual processing is often necessary at some point in the workflow, e.g. MedDRA coding needs to be performed manually, and all reports, excluding reports from MAHs, are handled manually after the initial automatic transmission to the database. Upon submission of a direct ADR report, the reporter receives an automatically generated email from the system as an acknowledgement of receipt of the report. Further communication with reporters is carried out via emailing or by phone. For MAHs, electronic exchange of E2BXML files goes through Axway, which generates a positive 'ACK' as an acknowledgement of successful receipt of the file or a negative 'ACK' if transmission has failed.

Validation rules are integrated both in the electronic reporting forms and in the DKMA database. Validation rules differ to a small extent from the EV validation rules; however, the rules are basically the same as in EV, which prevent errors in MAH reports when those reports are forwarded to EV.

[26] https://laegemiddelstyrelsen.dk/en/sideeffects/side-effects-from-medicines/companies-reporting-of-side-effects/~/media/B95846036A24403695DD5C30DD105D91.ashx, accessed on 22 July 2016

Further validation of reports from HCP and consumers is carried out manually through different stages of processing: input verification to confirm the case is valid and to determine the seriousness of the case; data capture to ensure that details of the case are entered into the database and; quality assurance to ensure the coding of the case is correct.

The minimum requirements for submitting a valid report are equal to the commonly known four minimum criteria:

1. Name of suspect drug or substance
2. Suspected ADR
3. Information about the patient (preferably birth date or social security number, but initials, gender or age would render the report valid)
4. Information about the reporter (incl. contact details).

If ADR report data is received as an XML document via the Electronic reporting forms for consumers and HCPs (separate Eforms), the obligatory fields that need to be populated are:

1. Reporter details (for consumers: phone number, name, address; for HCPs: qualification, first and last name and workplace)
2. At least one patient identifier
3. At least one drug
4. Batch number (or to tick a box saying that batch number is not held by the reporter. For HCPs only)
5. At least one reaction and reaction outcome (for consumers the list only consists of 3 choices: 'Yes', 'No', 'Recovering')
6. Seriousness criteria (only for HCP)
7. Other medication (or selecting 'No other medication')
8. Other health problems (only for consumers).

In the electronic form, the above mentioned fields are mandatory, and it is not possible to submit without filling them.

The XML is further validated when it reaches the DKMA database (same validation as for MAHs), with the exception of a few DKMA customised XML fields. All other non-coded fields are added to free text fields.

All other obligatory fields are populated by the Eform/EHR system (dates, sender, receiver and ID numbers).

ADRs can also be received from connected systems (e.g. patient registry or electronic prescription) and for this purpose a web-service was developed. The web-service enables electronic transmissions directly from patient registries. There is a legal obligation to register patient data into various patient registries, however it is not primarily intended for PV purposes. The DKMA does not transmit any data to such registries. At the moment of preparing this case study, the DKMA was not receiving data through the web-service, but was receiving data from two registries on a regular basis, in non E2B format (manual data entry at the DKMA).

If ADR report data is received through the web-service (ADRs from EHRs) the obligatory fields are:

1. Primary source country (=DK)
2. Occur country (=DK)
3. Transmission date (and format)
4. Report type (=Spontaneous)
5. Receive date (and format)
6. Receipt date (and format)
7. Additional document (=2)
8. Fulfil expedited criteria (=1)
9. Medically confirm (=1)
10. Reporter country (=DK)
11. Qualification
12. Sender details (fixed values)
13. Seriousness
14. Age – must be <120 years.

Additional validations:

- At least one field relating to patient information – e.g. patient age, sex, initials or date of birth – must be completed
- Patient autopsy (yes/no) is mandatory if “Patient death” is populated
- Parent sex is mandatory if any data element in the “Parent” section is populated
- Primary source reaction or reaction MedDRA LLT should be populated
- Reaction outcome is mandatory for each reaction
- Either active substance name or medicinal product should be populated
- Characterisation of drug (1 = suspect, 2 = concomitant, 3 = interacting).

All other obligatory fields are populated by the Eform/EHR system (dates, sender, receiver, IDs).