EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

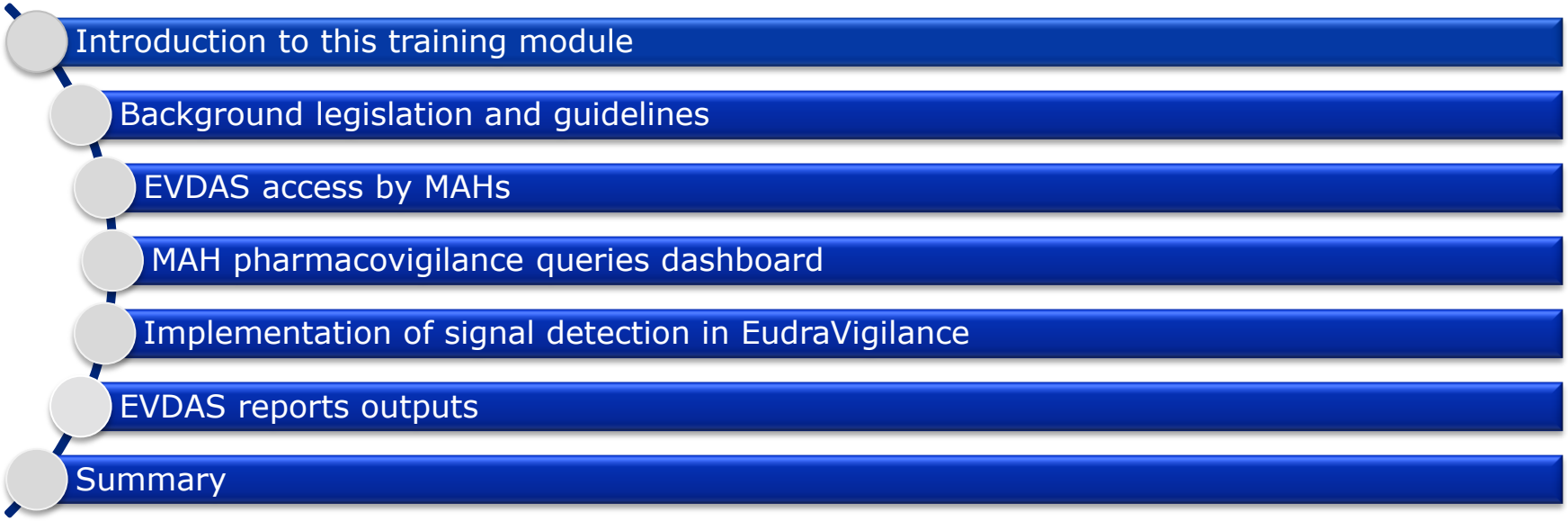
EV-M5b - EVDAS training for Marketing Authorisation Holders

Overview of the EVDAS functionalities and level 1 access to EudraVigilance by Marketing Authorisation Holders to comply with their pharmacovigilance obligations with regards to signal detection and management

Rodrigo Postigo, Signal and Incident Management, Pharmacovigilance and Epidemiology department

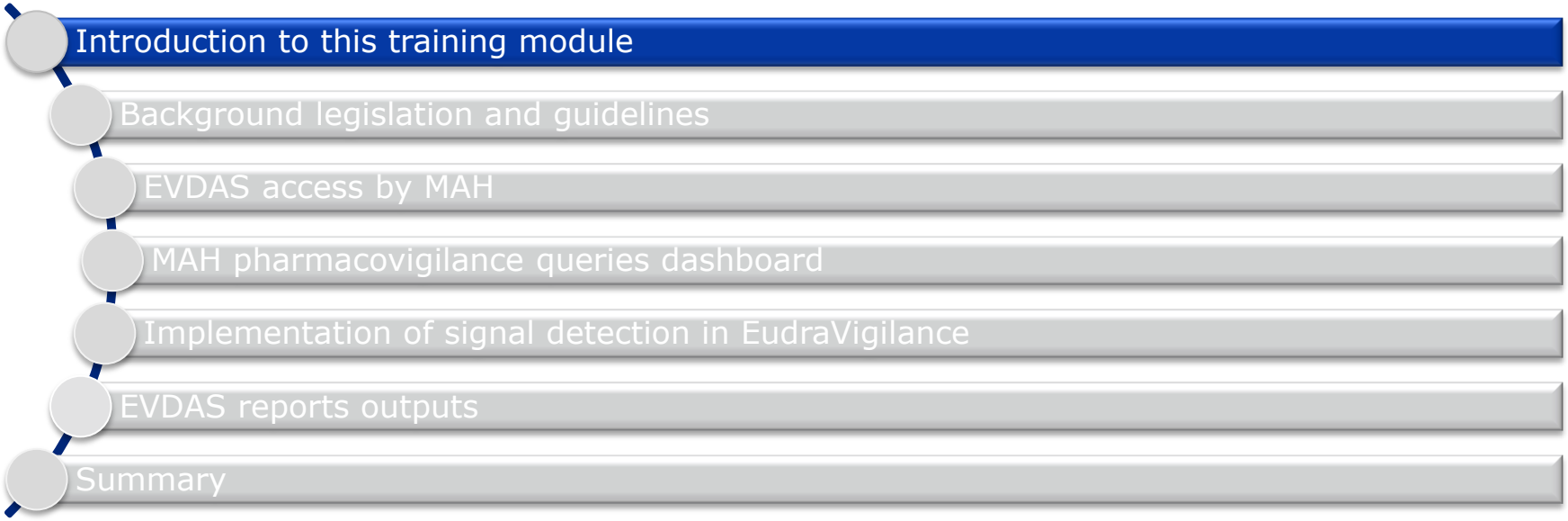
An agency of the European Union

Content Summary



Version 0.0

Content Summary



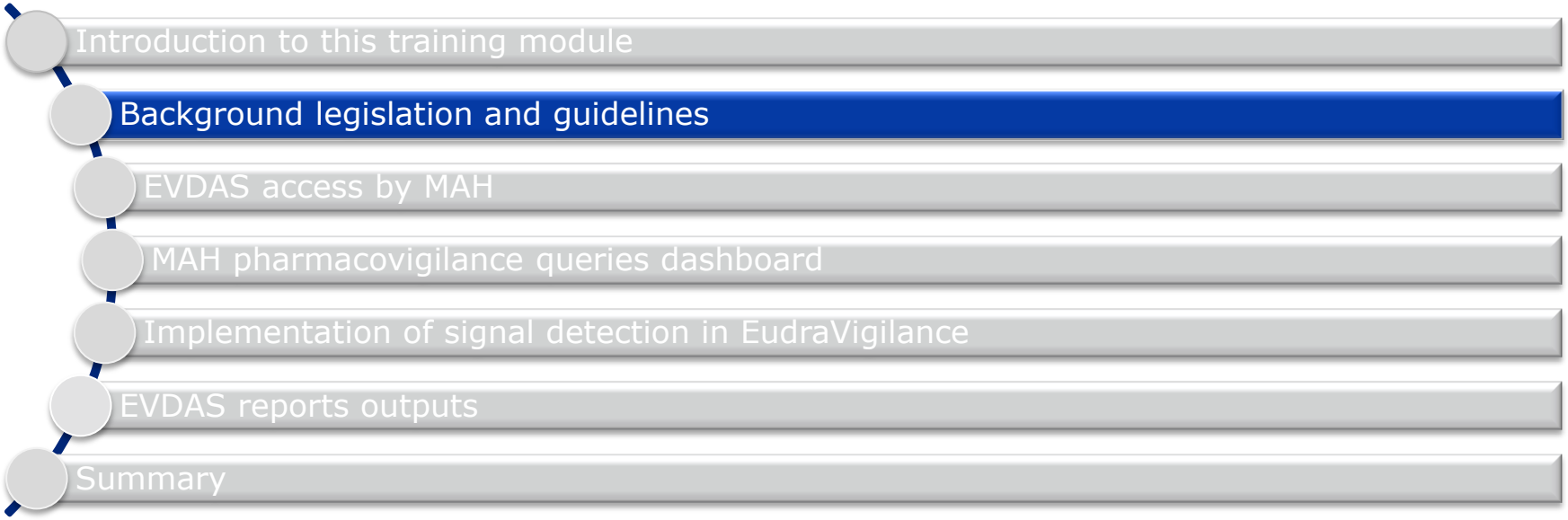
Introduction: Context EV-M5b

- Target audience for this training module:
  - Marketing Authorisation Holders (MAHs) in the European Economic Area (EEA)

Introduction: Learning Objectives

- At the end of this module participants will be able to:
  - Understand the access to EudraVigilance provided via the EudraVigilance Data Analysis System (EVDAS).
  - Be familiar with the EVDAS user interface.
  - Be able to retrieve electronic Reaction Monitoring Reports (eRMRs), Line Listings and ICSR forms from EVDAS.
  - Understand the system functionalities for manipulating reports' outputs.
  - Understand how signal detection is implemented in EudraVigilance.
  - Understand the outputs of the EVDAS reports.

Content Summary



Section Overview

- In this section you will obtain understanding of the:
  - Main legislative requirements for monitoring the EudraVigilance database.
  - Which are the guidelines for signal detection and management in the EU.

EU Legislative Requirements

Updated pharmacovigilance legislation published in 2010 established the principles for monitoring the data in EudraVigilance and for the revision of the access to the database.

EU Legislative Requirements

Commission Implementing Regulation (IR) 520/2012 provides with the specific roles and responsibilities for monitoring EudraVigilance and established the different steps in the signal management process.

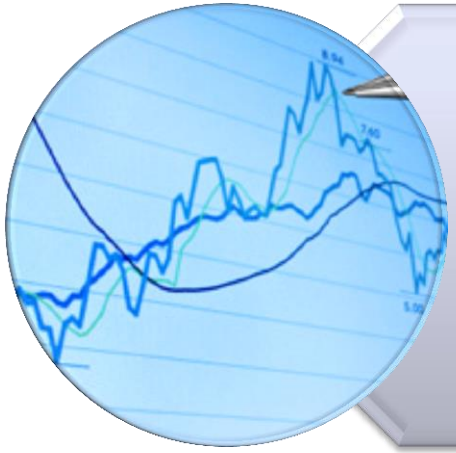
EU Legislative Requirements

Within the minimum requirements for monitoring EudraVigilance (Chapter III, IR), the IR states that MAHs, NCAs and the Agency shall ensure the continuous monitoring of EudraVigilance with a frequency proportionate to the risks and the need for additional information.

EU Legislative Requirements

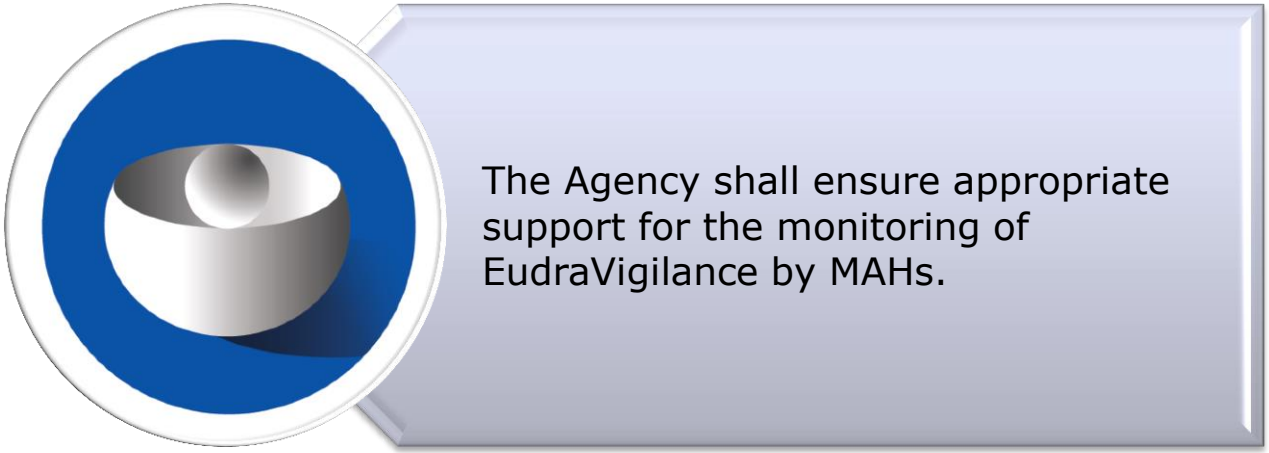
MAHs shall monitor EudraVigilance to the extent that they have access to the database.

EU Legislative Requirements



Signal detection within EudraVigilance shall be complemented by statistical analysis, where appropriate.

EU Legislative Requirements



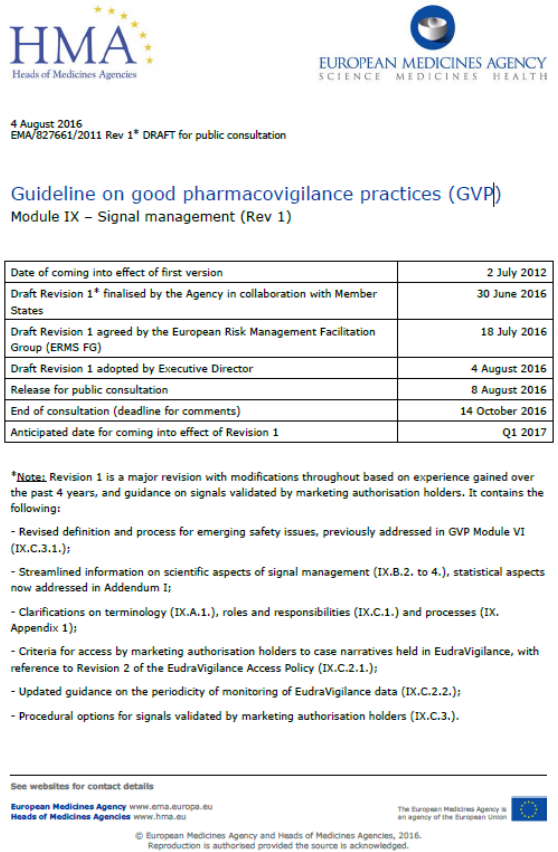
Details of the legal provisions that form the basis for the new EudraVigilance functionalities are provided in training module:

PhV-M1 New EudraVigilance Functionalities and the 2010 pharmacovigilance legislation – preparing for change

EU Guidelines

- GVP Module IX on Signal Management is currently undergoing a major revision.
- The Module was released for public consultation and will be finalised in 2017.

➢ Stakeholders should consult the final Module IX once adopted.



HMA Heads of Medicines Agencies

EUROPEAN MEDICINES AGENCY SCIENCE MEDICINES HEALTH

4 August 2016
EMA/827661/2011 Rev 1* DRAFT for public consultation

Guideline on good pharmacovigilance practices (GVP)
Module IX – Signal management (Rev 1)

Date of coming into effect of first version	2 July 2012
Draft Revision 1* finalised by the Agency in collaboration with Member States	30 June 2016
Draft Revision 1 agreed by the European Risk Management Facilitation Group (ERMS FG)	18 July 2016
Draft Revision 1 adopted by Executive Director	4 August 2016
Release for public consultation	8 August 2016
End of consultation (deadline for comments)	14 October 2016
Anticipated date for coming into effect of Revision 1	Q1 2017

*Note: Revision 1 is a major revision with modifications throughout based on experience gained over the past 4 years, and guidance on signals validated by marketing authorisation holders. It contains the following:

- Revised definition and process for emerging safety issues, previously addressed in GVP Module VI (IX.C.3.1.);
- Streamlined information on scientific aspects of signal management (IX.B.2. to 4.), statistical aspects now addressed in Addendum I;
- Clarifications on terminology (IX.A.1.), roles and responsibilities (IX.C.1.) and processes (IX. Appendix 1);
- Criteria for access by marketing authorisation holders to case narratives held in EudraVigilance, with reference to Revision 2 of the EudraVigilance Access Policy (IX.C.2.1.);
- Updated guidance on the periodicity of monitoring of EudraVigilance data (IX.C.2.2.);
- Procedural options for signals validated by marketing authorisation holders (IX.C.3.).

See websites for contact details

European Medicines Agency www.ema.europa.eu
Heads of Medicines Agencies www.hma.eu

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GVP Module IX - Signal Management Rev 1 – DRAFT

This revision incorporates the following updates:

- Revised definition and process for emerging safety issues, previously addressed in GVP Module VI.
- Streamlined information on scientific aspects of signal management.
- Clarifications on terminology, roles and responsibilities and processes.
- Criteria for access by MAHs to case narratives held in EudraVigilance.
- Updated guidance on the periodicity of monitoring of EudraVigilance data.
- Procedural options for signals validated by MAHs.

The appropriate frequency of monitoring EV may vary depending of the knowledge of the safety profile of the product

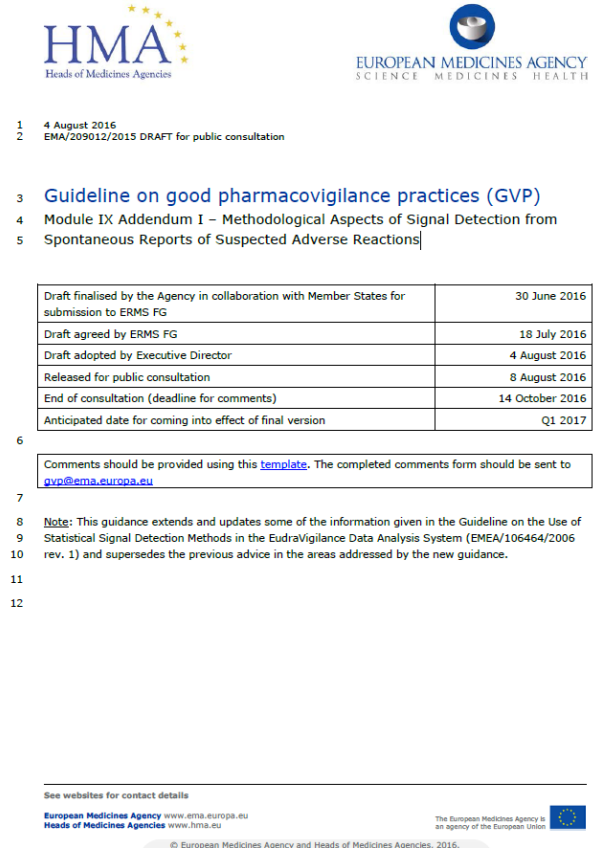
Periodicity of monitoring:

A two weeks' interval is recommended for active substances contained in medicinal products included in the additional monitoring list, unless the only reason for inclusion on the list is the request of a PASS

The interval between reviews of EV data should not exceed 6 months

EU Guidelines

- Addendum I to GVP Module IX provides with the principles and general methodological aspects of signal detection from spontaneous reports of suspected adverse reactions.
- This addendum is also subject to finalisation and adoption in 2017.



HMA Heads of Medicines Agencies

EUROPEAN MEDICINES AGENCY SCIENCE MEDICINES HEALTH

4 August 2016
EMA/209012/2015 DRAFT for public consultation

Guideline on good pharmacovigilance practices (GVP)
Module IX Addendum I – Methodological Aspects of Signal Detection from Spontaneous Reports of Suspected Adverse Reactions

Draft finalised by the Agency in collaboration with Member States for submission to ERMS FG	30 June 2016
Draft agreed by ERMS FG	18 July 2016
Draft adopted by Executive Director	4 August 2016
Released for public consultation	8 August 2016
End of consultation (deadline for comments)	14 October 2016
Anticipated date for coming into effect of final version	Q1 2017

Comments should be provided using this template. The completed comments form should be sent to gvp@ema.europa.eu

Note: This guidance extends and updates some of the information given in the Guideline on the Use of Statistical Signal Detection Methods in the EudraVigilance Data Analysis System (EMEA/106464/2006 rev. 1) and supersedes the previous advice in the areas addressed by the new guidance.

See websites for contact details
European Medicines Agency www.ema.europa.eu
Heads of Medicines Agencies www.hma.eu

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EU Guidelines

- The EMA in collaboration with the Member States has published a guideline on screening adverse drug reactions in EudraVigilance.
- The guideline updates and supersedes the previous guideline on the use of statistical signal detection in EudraVigilance (EMEA/106464/2006 rev. 1).
- Describes the methods and practicalities for statistical signal detection in EudraVigilance.
- Includes the changes incorporated from research activities including PROTECT (http://www.imi-protect.eu/)

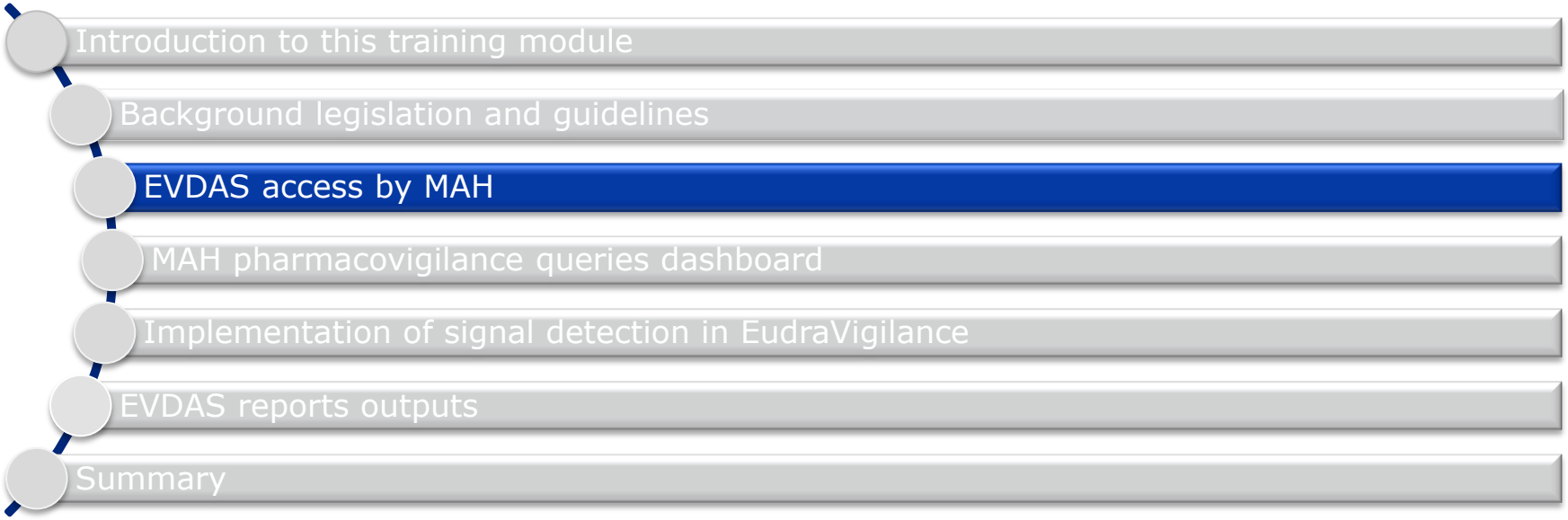
➢ Further details on the implementation of signal detection in EudraVigilance are provided in the relevant section within this training Module.

Section Summary

In this section you obtained an understanding of:

- Main legal requirements for monitoring the EudraVigilance database.
- EU guidelines on Signal Management.

Content Summary

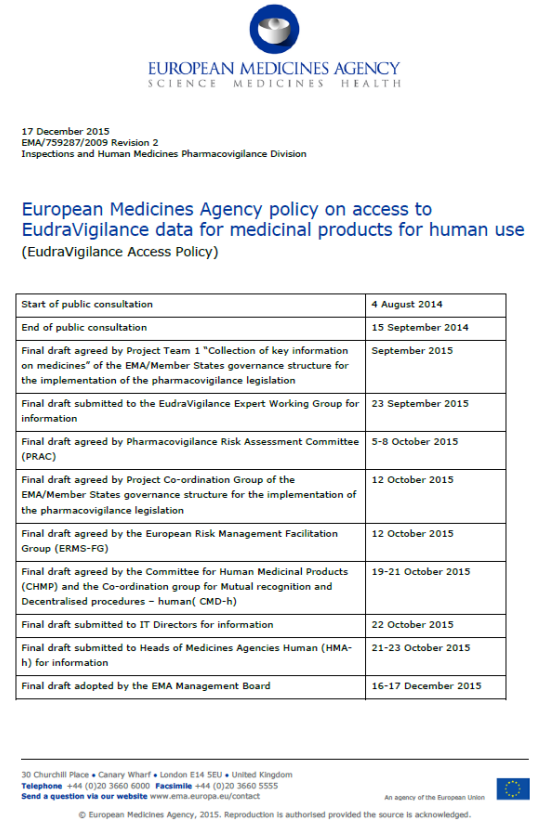


Section Overview

- In this section you will obtain understanding of the:
  - Main principles for the access to the EVDAS by MAHs to comply with their pharmacovigilance obligations.
  - How to access EVDAS.

The EudraVigilance Access Policy

- The access to EudraVigilance data is established in the EudraVigilance access policy.
- The EudraVigilance access policy was revised as a result of the 2010 pharmacovigilance legislation and was adopted by the EMA Management Board in December 2015.
- Revision of the access policy will enter into force six months following the announcement by the Management Board of the Agency that based on an independent audit report, the EudraVigilance database has achieved full functionality.



EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

17 December 2015
EMA/759287/2009 Revision 2
Inspections and Human Medicines Pharmacovigilance Division

European Medicines Agency policy on access to EudraVigilance data for medicinal products for human use
(EudraVigilance Access Policy)

Start of public consultation	4 August 2014
End of public consultation	15 September 2014
Final draft agreed by Project Team 1 "Collection of key information on medicines" of the EMA/Member States governance structure for the implementation of the pharmacovigilance legislation	September 2015
Final draft submitted to the EudraVigilance Expert Working Group for information	23 September 2015
Final draft agreed by Pharmacovigilance Risk Assessment Committee (PRAC)	5-8 October 2015
Final draft agreed by Project Co-ordination Group of the EMA/Member States governance structure for the implementation of the pharmacovigilance legislation	12 October 2015
Final draft agreed by the European Risk Management Facilitation Group (ERMS-FG)	12 October 2015
Final draft agreed by the Committee for Human Medicinal Products (CHMP) and the Co-ordination group for Mutual recognition and Decentralised procedures – human(CMD-h)	19-21 October 2015
Final draft submitted to IT Directors for information	22 October 2015
Final draft submitted to Heads of Medicines Agencies Human (HMA-h) for information	21-23 October 2015
Final draft adopted by the EMA Management Board	16-17 December 2015

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Send a question via our website www.ema.europa.eu/contact

Details of the revision of the EudraVigilance Access Policy and how stakeholders obtain access to the database are provided in the following training module:

PhV-M4 Revised EudraVigilance Access Policy: Impact on Stakeholders

EudraVigilance access policy

- MAHs will be provided with access to defined ICSR data element sets in support of their signal det
- EVDAS ac according to Level 1 access for Stakeholders Group III.

Stakeholder Group III

Marketing Authorisation Holders

• EVWEB including ICSR Export Manager	• ICSRs electronic (XML) format
• EVDAS	• e-RMRs and active substance groupings • ICSR line listings • ICSR forms

ce groupings

ased on predefined

- ICSR line listings (based on core ICSR data elements)
- ICSR forms (for individual case review)

This training Module will focus on the EudraVigilance access to MAHs via EVDAS

EVDAS Registration

Steps and process to be followed for the EudraVigilance and EVDAS registration including how to maintain the registered user information are provided in the following training module:

EV- M1 How to register with EudraVigilance and EVDAS

MAHs (Stakeholders III) access via EVDAS – Principles

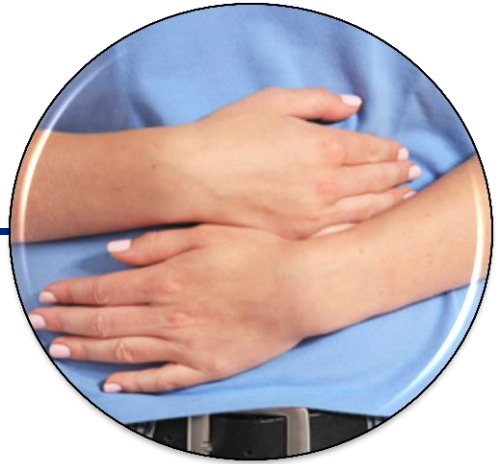
All MAHs with a medicinal product authorised in the EEA

MAHs (Stakeholders III) access via EVDAS – Principles

Substance level using the highest level of the active substance in the hierarchy of the XEVMPD

MAHs (Stakeholders III) access via EVDAS – Principles

All the substances contained in products authorised in the EEA that have been coded as suspect/interacting in at least one post-authorisation ICSR



MAHs (Stakeholders III) access via EVDAS – Principles

Access to individual cases where the specific substance is coded as suspect/interacting

MAHs (Stakeholders III) access via EVDAS – Principles

Access to cases in EVPM

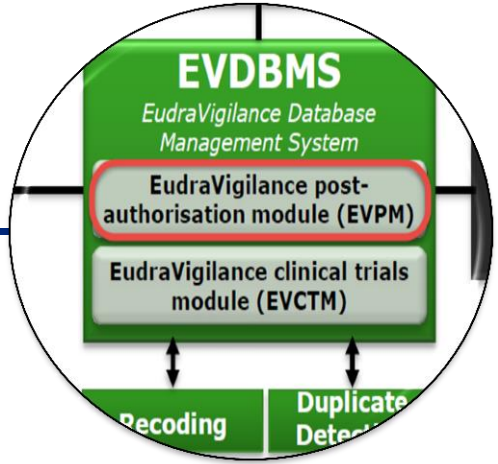
Report type:

1) *Spontaneous*

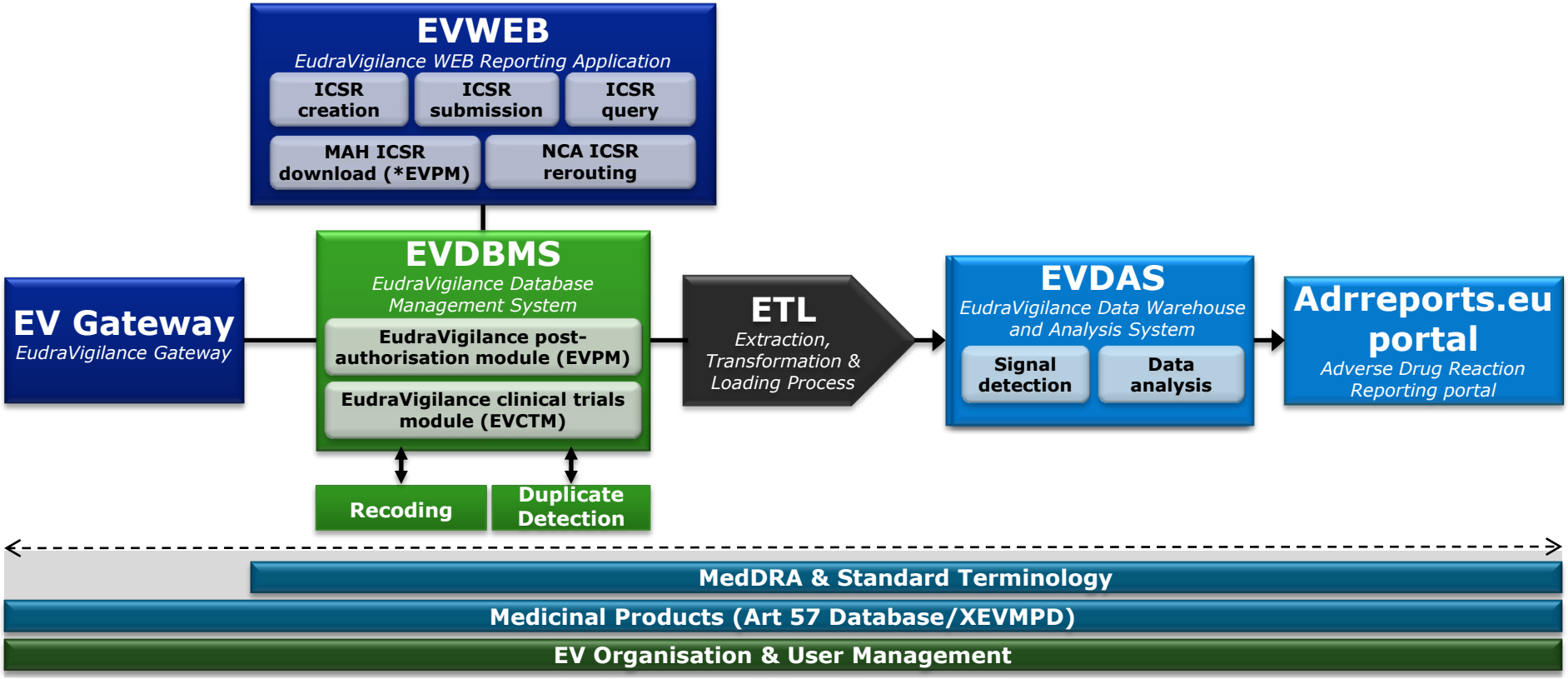
2) *Reports from studies* (including 'individual patient use and other studies')

3) *Other*

4) *Not available to sender*



EVDAS


EVWEB
EudraVigilance WEB Reporting Application
ICSR creation
ICSR submission
ICSR query
MAH ICSR download (*EVPM)
NCA ICSR rerouting
EV Gateway
EudraVigilance Gateway
EVDBMS
EudraVigilance Database Management System
EudraVigilance post-authorisation module (EVPM)
EudraVigilance clinical trials module (EVCTM)
Recoding
Duplicate Detection
ETL
Extraction, Transformation & Loading Process
EVDAS
EudraVigilance Data Warehouse and Analysis System
Signal detection
Data analysis
Adrreports.eu portal
Adverse Drug Reaction Reporting portal
MedDRA & Standard Terminology
Medicinal Products (Art 57 Database/XEVMPD)
EV Organisation & User Management

Full description of the EudraVigilance system components and system functionalities are provided in the training module:

EV- M2 Introduction to EV system components and system functionalities

Accessing EVDAS

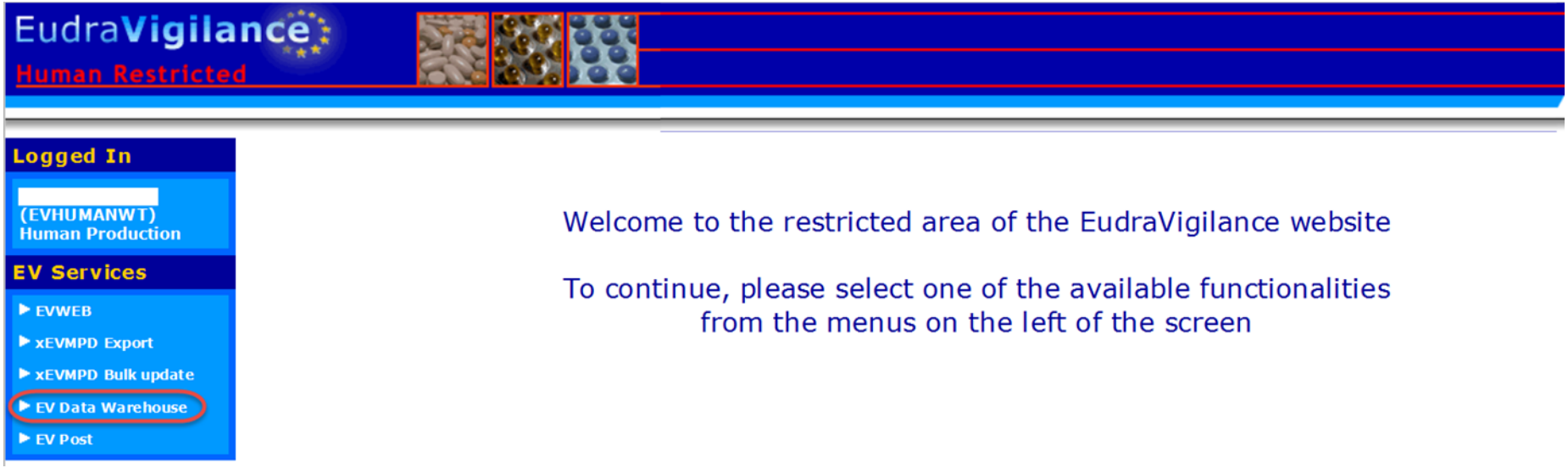
Users registered in EVDAS will be able to access the system through the following ways:

- Access via the EudraVigilance page on the EMA corporate website
- Access via EVDAS welcome page

Access via the EudraVigilance page

http://www.ema.europa.eu/ema/index.jsp?curl=pages/regulation/general/general_content_000679.jsp&mid=WC0b01ac05800250b5

Access via the EudraVigilance page



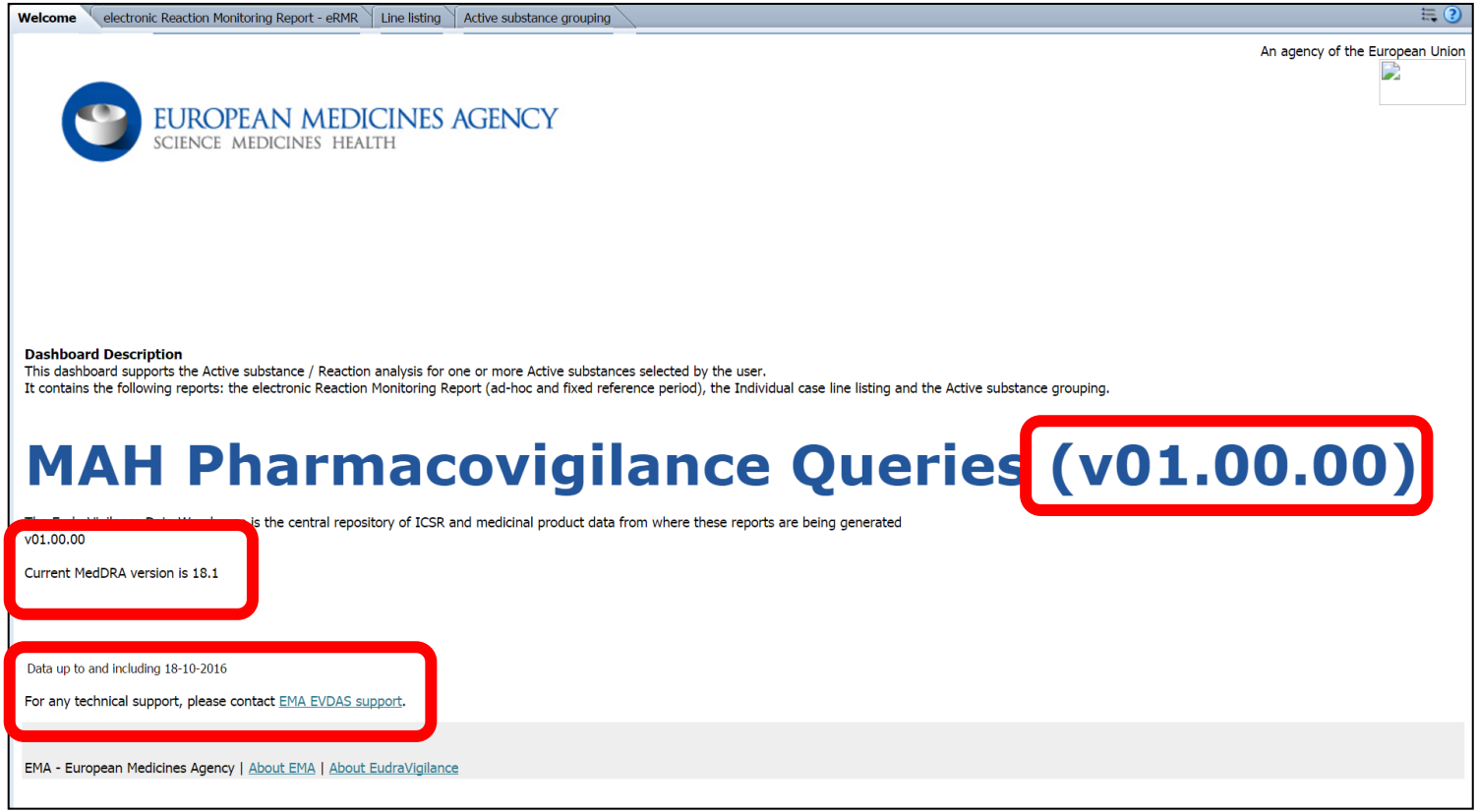
Accessing EVDAS

- Access via EVDAS welcome page:

  https://bi.ema.europa.eu/analytics/saw.dll?Dashboard&PortalPath=%2Fshared%2FMAH Pharmacovigilance Query Library%2F_portal%2FMAH Pharmacovigilance Queries

Accessing EVDAS

Welcome page



Section Summary

In this section you obtained an understanding of:

- Main principles of the access to EVDAS by MAHs.
- How to access EVDAS.

Content Summary

- Introduction to this training module
- Background legislation and guidelines
- EVDAS access by MAH
- **MAH pharmacovigilance queries dashboard**
- Implementation of signal detection in EudraVigilance
- EVDAS reports outputs
- Summary

Section Overview

- In this section you will obtain understanding of the:
  - The reports included in the MAH pharmacovigilance queries dashboard.
  - Active substance grouping report.
  - The eRMR report.
  - The line listing report.
  - General functionalities offered by the system.
  - How to work with returned reports.

MAH Pharmacovigilance Queries Dashboard

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electronic Reaction Monitoring Report - eRMR | Line listing | Active substance grouping

Dashboard Description
This dashboard supports the Active substance / Reaction analysis for one or more Active substances selected by the user.
It contains the following reports: the electronic Reaction Monitoring Report (ad-hoc and fixed reference period), the Individual case line listing and the Active substance grouping.

MAH Pharmacovigilance Queries (v01.00.00)

The EudraVigilance Data Warehouse is the central repository of ICSR and medicinal product data from where these reports are being generated
v01.00.00

Current MedDRA version is 18.1

Data up to and including 29-09-2016

For any technical support, please contact EMA EVDAS support.

EVDAS terminology – Prompts

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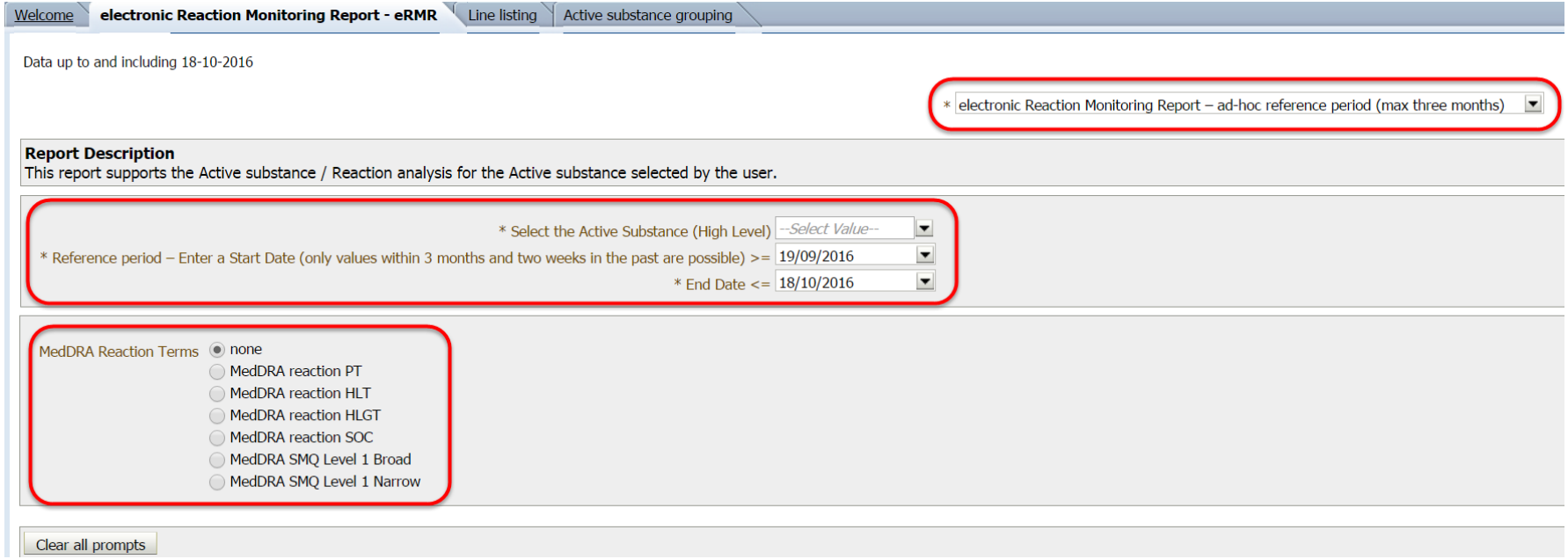
- ***Prompts*** are objects that enable users to select the conditions to be included in a report
- The following figure shows the prompts included in a report:



EVDAS terminology – Filters

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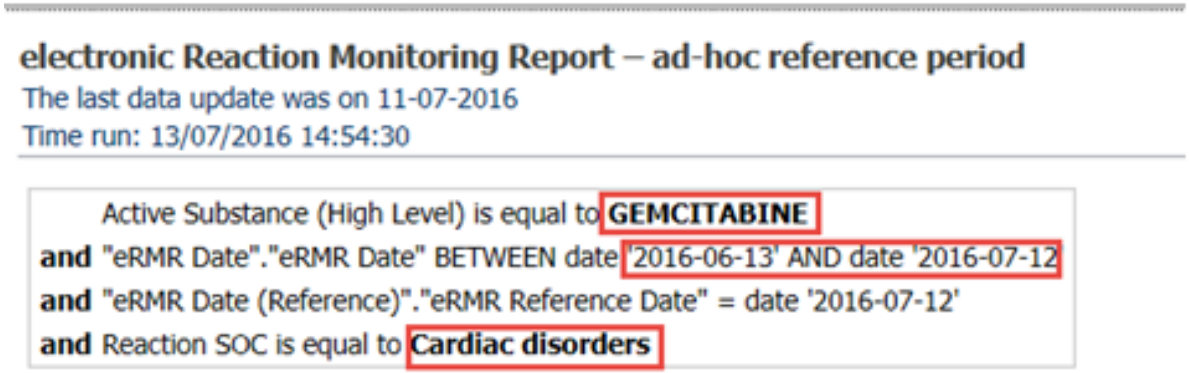
- ***Filters*** define the conditions that data must meet to be included in the report result set.

- Some filters can contain any number of conditions. For instance we can retrieve the data for different MedDRA SOCs or different MedDRA PTs.

- Only data that meets all of the filter conditions appears in the final result set of a report.

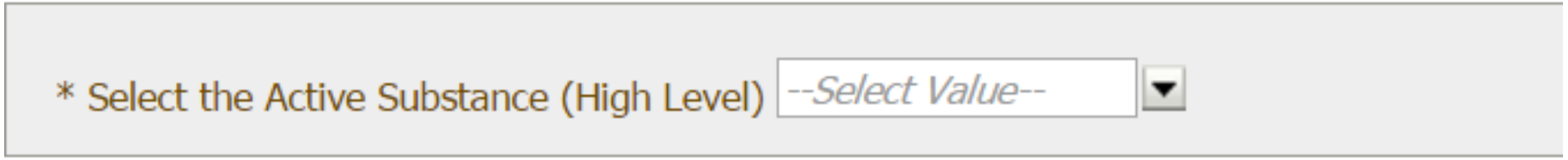
- The following illustration shows the report's filters



How to select an active substance using the high level grouping in the EVDAS prompts

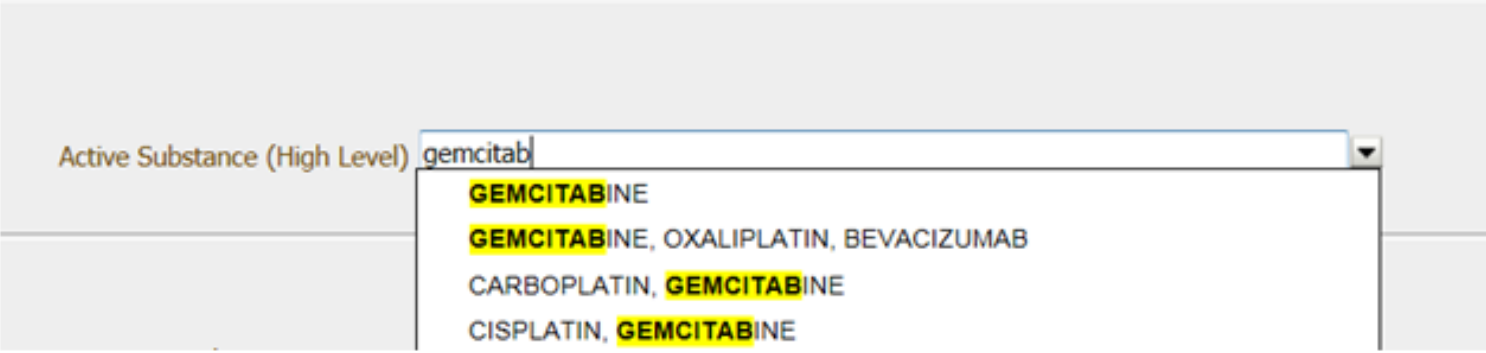
How to select a substance

The three reports in EVDAS will require the users to select an active substance high level from the prompt



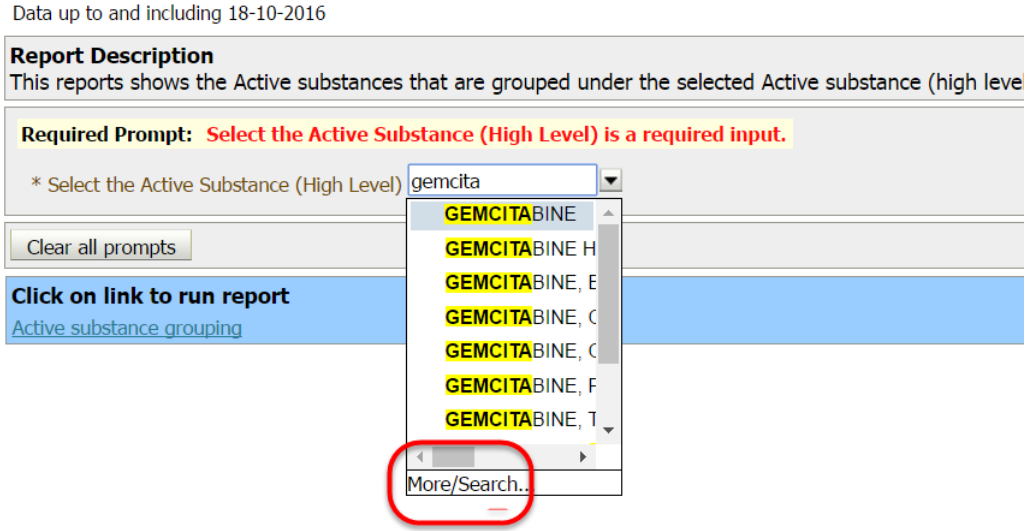
How to select a substance

- A substance can be selected by typing the name of the substance and then clicking on the substance name. EVDAS will offer you suggestions for the substance once you have typed the first letters.



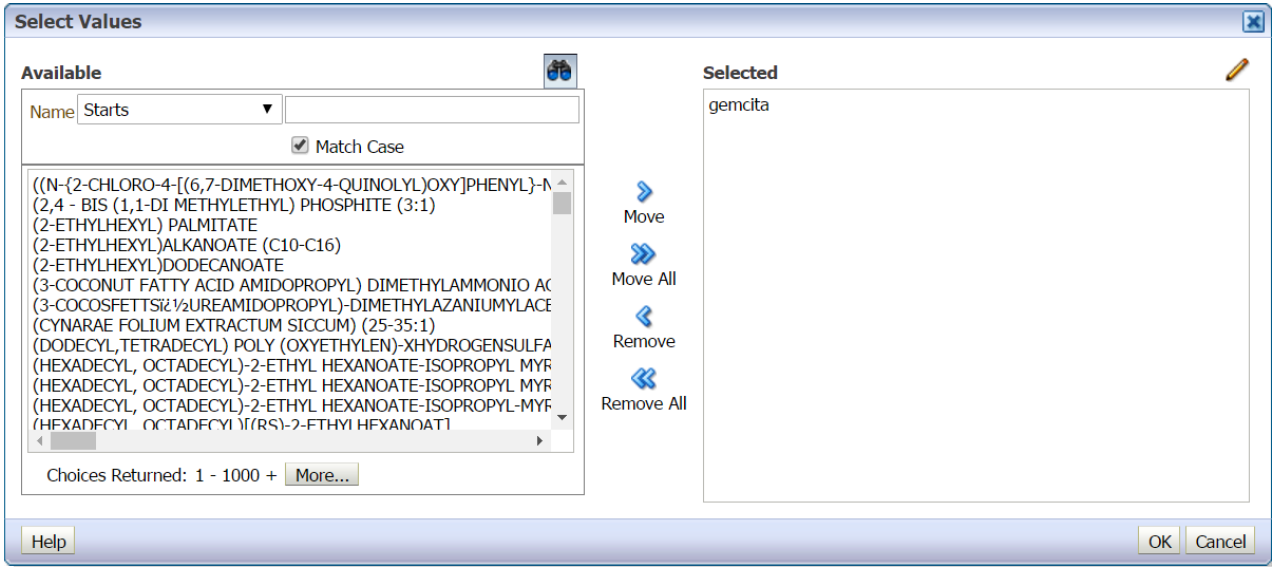
How to select a substance

- If you wish to search for more than one substance, then you can type the substance names separated by semicolons or you can select 'More/search' option



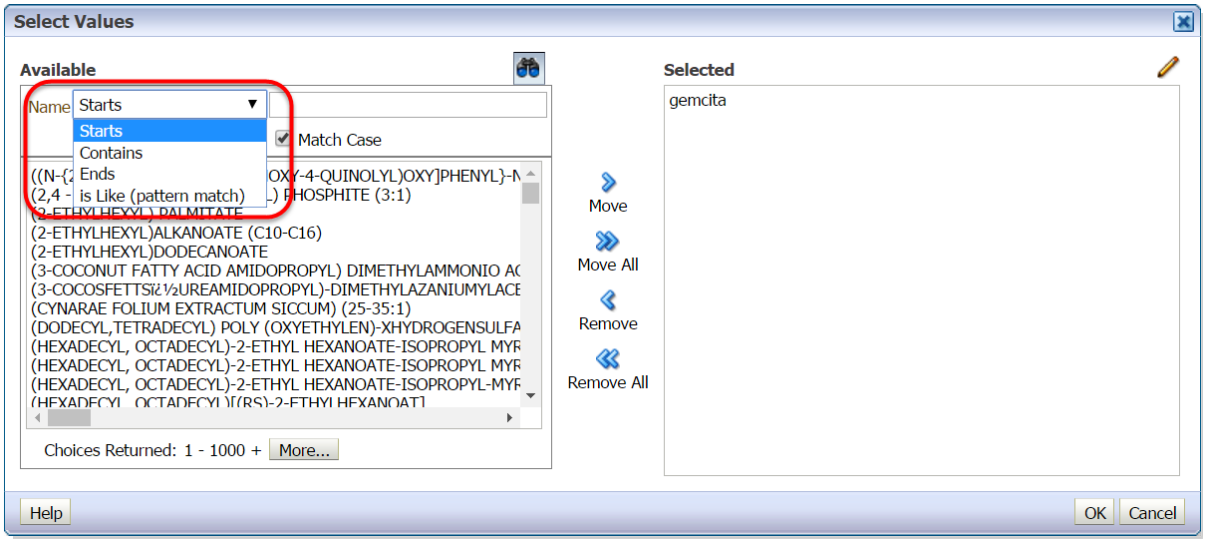
How to select a substance

The selection cart option will appear when you click in ‘More/search’



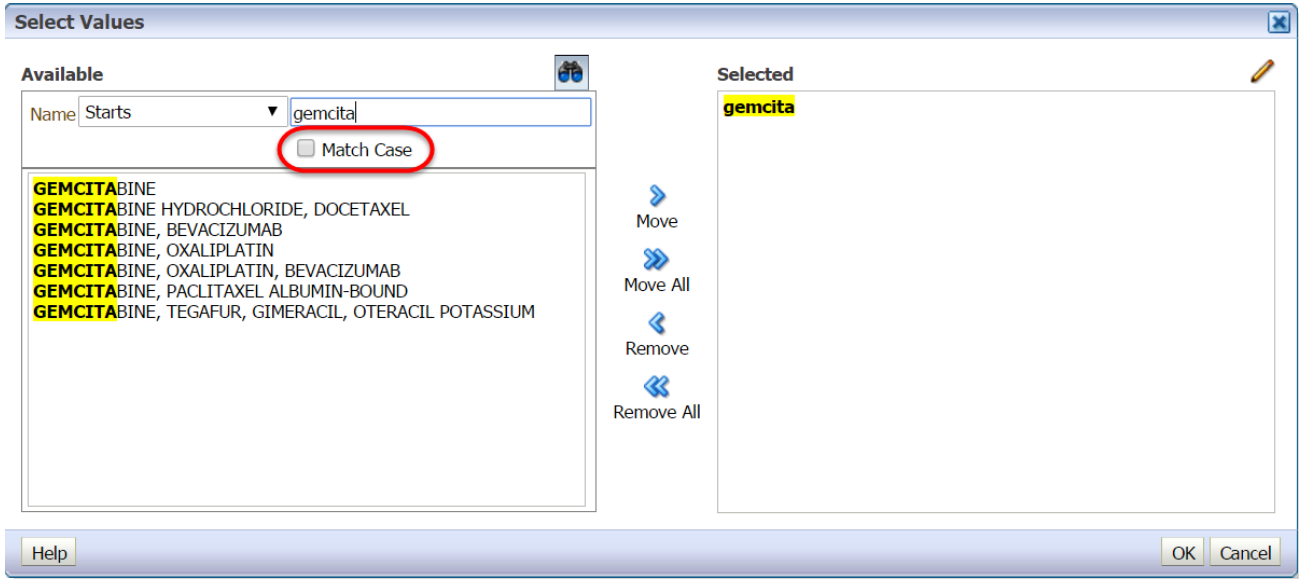
How to select a substance

- Once in the active substance selection cart, from the 'available' section select your operator using the drop down menu. The options are 'Starts', 'Contains' 'Ends' and 'Is like (pattern match)'.



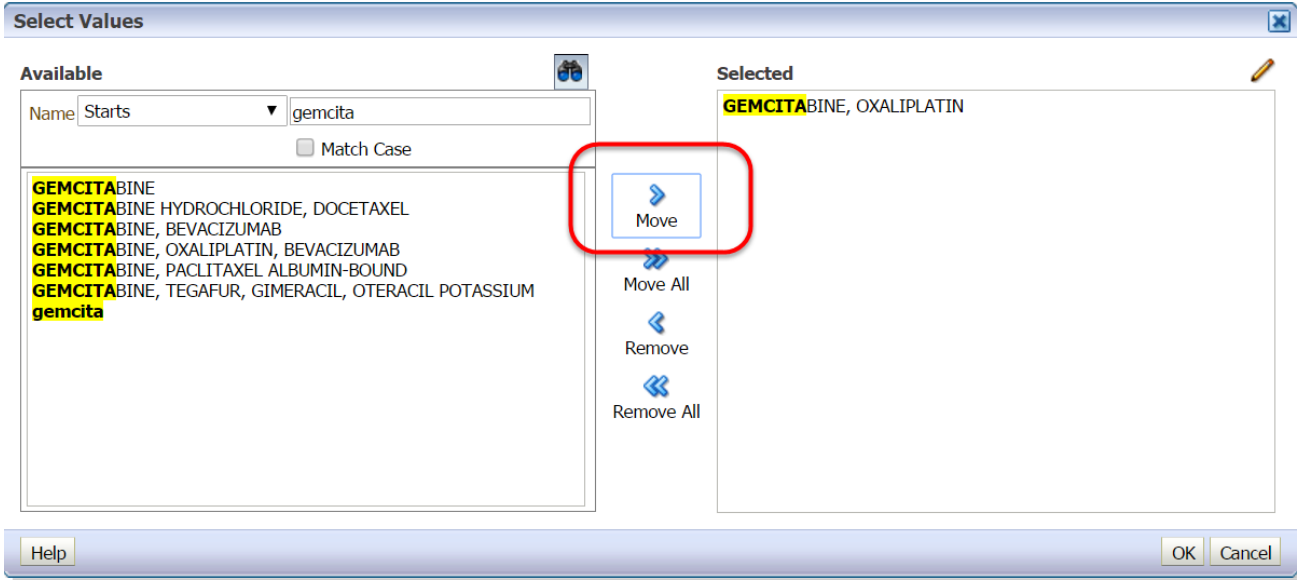
How to select a substance

- It is recommended that the 'Match case' is not selected so the system will start offering results. The more you type, the more refined the results will be.



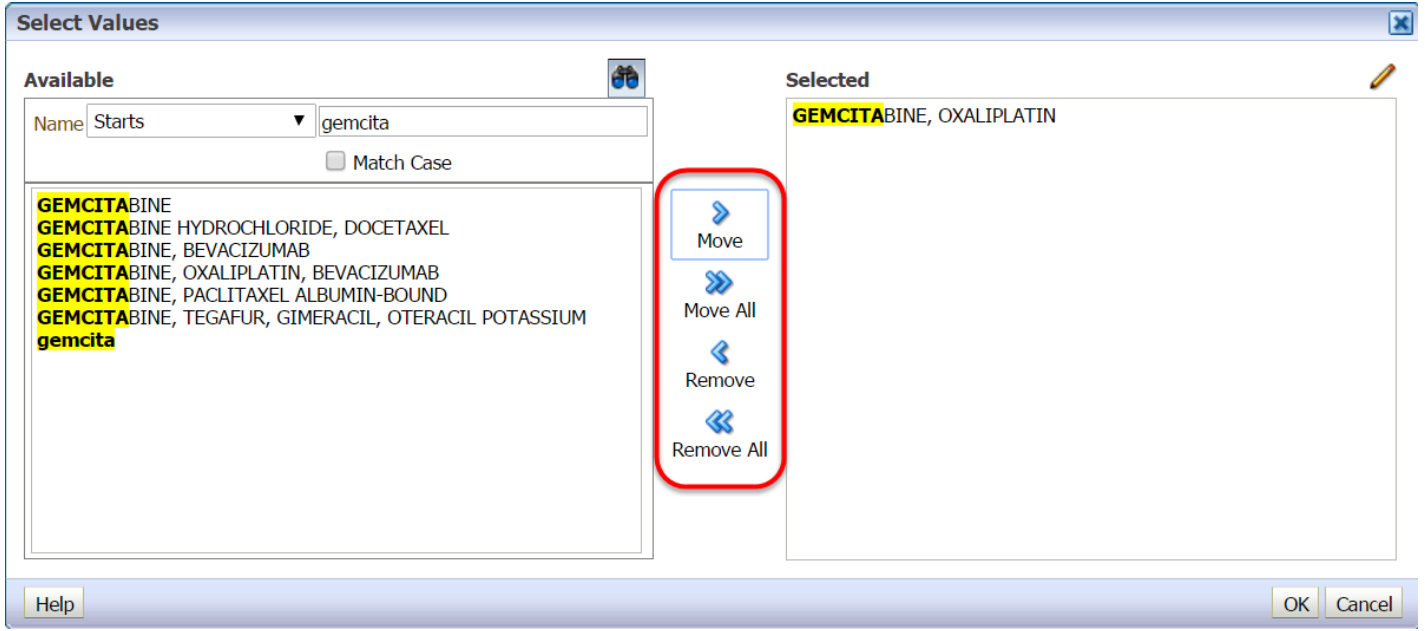
How to select a substance

- Once you typed the substance name, then select the desired substance by double clicking on the substance name or by selecting the substance and then clicking in the arrow 'move'



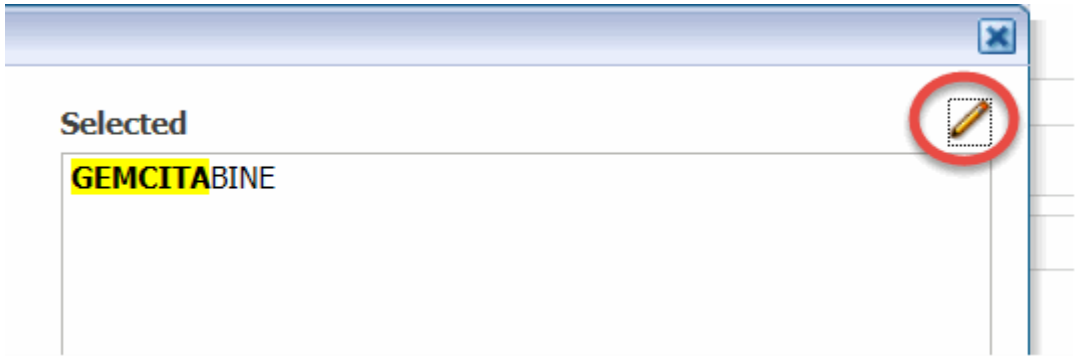
How to select a substance

- The arrows in the middle of the selection cart can be used to move the substances in between the two panels



How to select a substance

- Searched terms can also be edited or selected within the 'Selected' section by clicking the **Edit** (pencil) icon on the top-right of the selected section. This brings up the edit box, containing any selected terms.



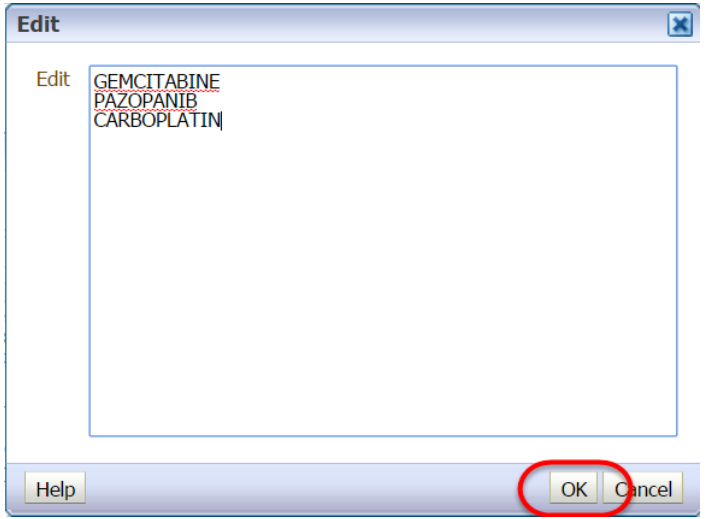
How to select a substance

- You can then edit or add any terms, including typing or pasting terms from other queries or sources.
- Please note that if you are pasting, typing in or editing terms, you will need to ensure:

(a) they are entered in capitals

(b) that they are spelled completely correctly and

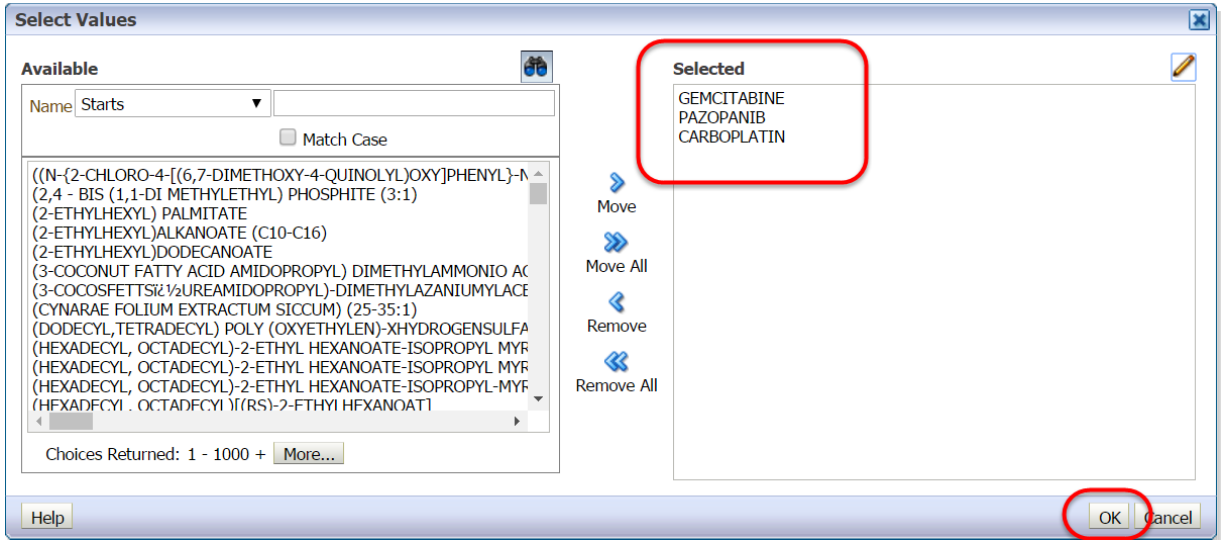
(c) that each term is on a separate line.



- click OK when all the desired terms are included

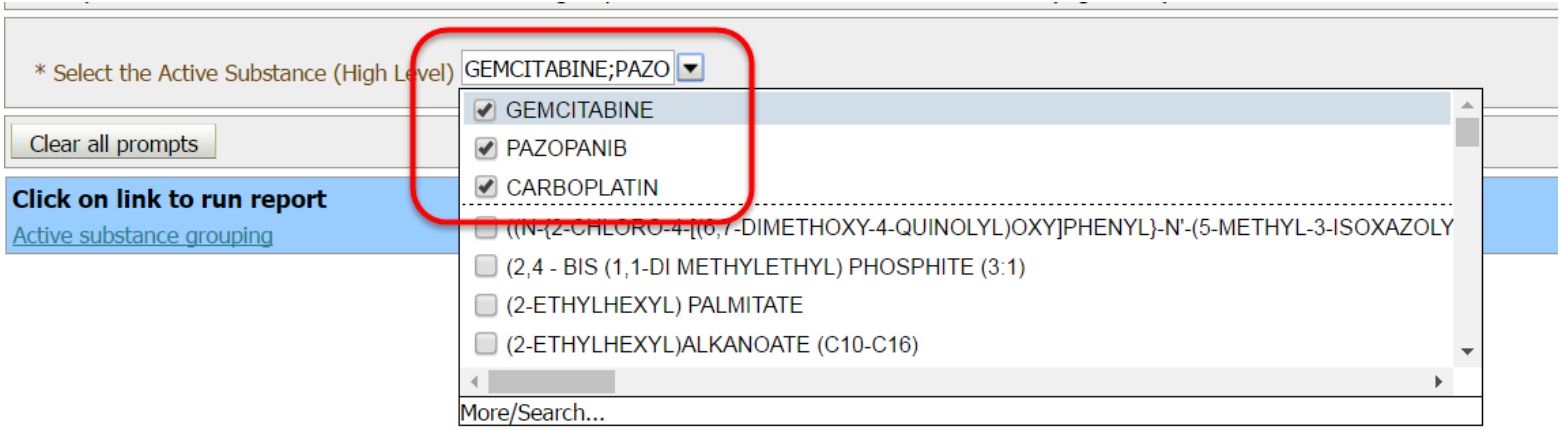
How to select a substance

- Once all the desired substances are shown in the selected panel, click ok to finish the substance selection.



How to select a substance

- The selected substances will be included in the prompt. You can double check by opening the drop down menu or opening the selection cart

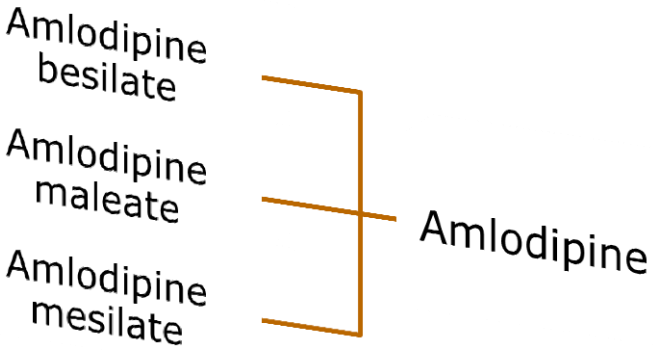


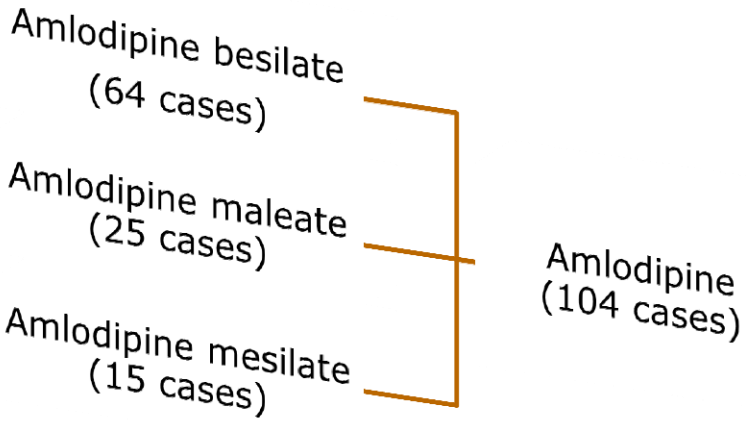
Active substance grouping report

Active substance grouping – The concept

- The active substance high level is formed by different names of an active substance (e.g. different salts).
- These groups of substances names that form one active substance high level are used to perform signal detection and to retrieve EudraVigilance data.
- This grouping needs to be performed when aggregated dataset is needed for a higher level analysis.
- Grouping is a manual activity performed by the Agency to facilitate such analysis.
- The active substance high level is generally used by default; the low level is used when there is an interest in e.g. a particular salt.

Active substance grouping





- The "Active substance grouping" report provides the user with an overview of the *Active Substances* in the XEVMPD that have been grouped to a specific *Active Substance High Level.*

As EVDAS access is provided at the level of active substance high level, users should determine which active substance high level should be used to query EVDAS

Active substance grouping report

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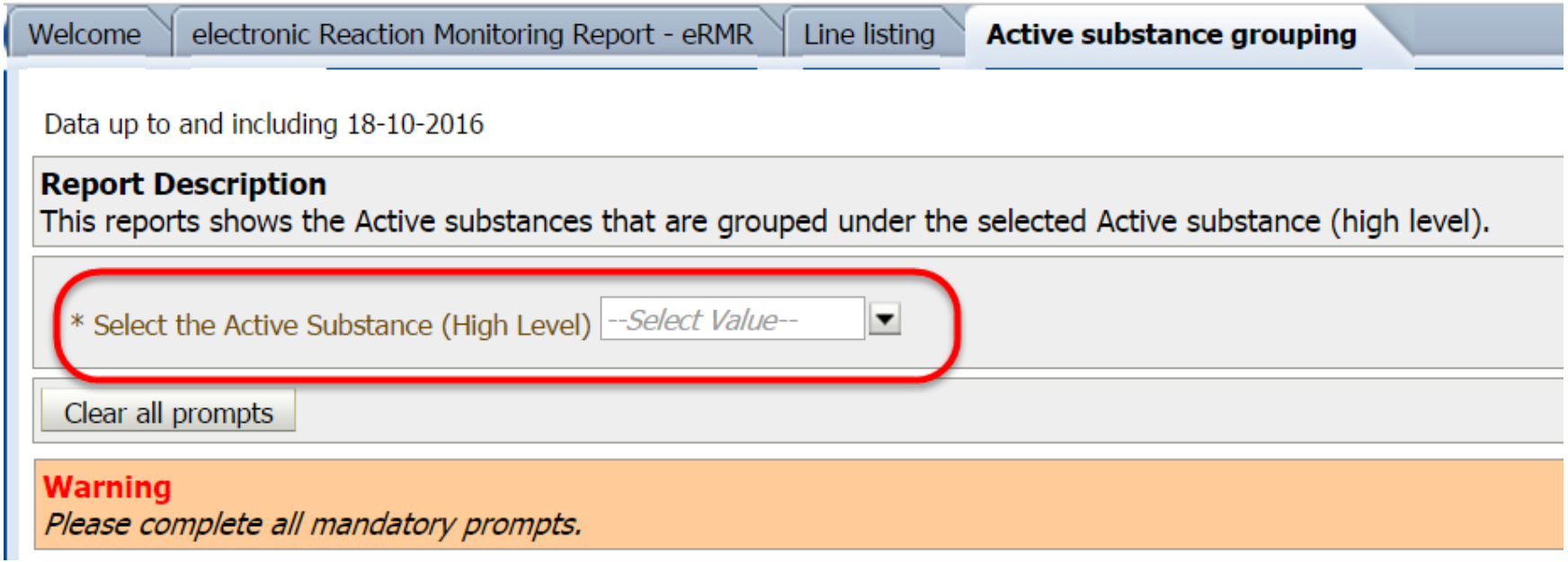
- The active substance grouping report contains one prompt



Active substance grouping

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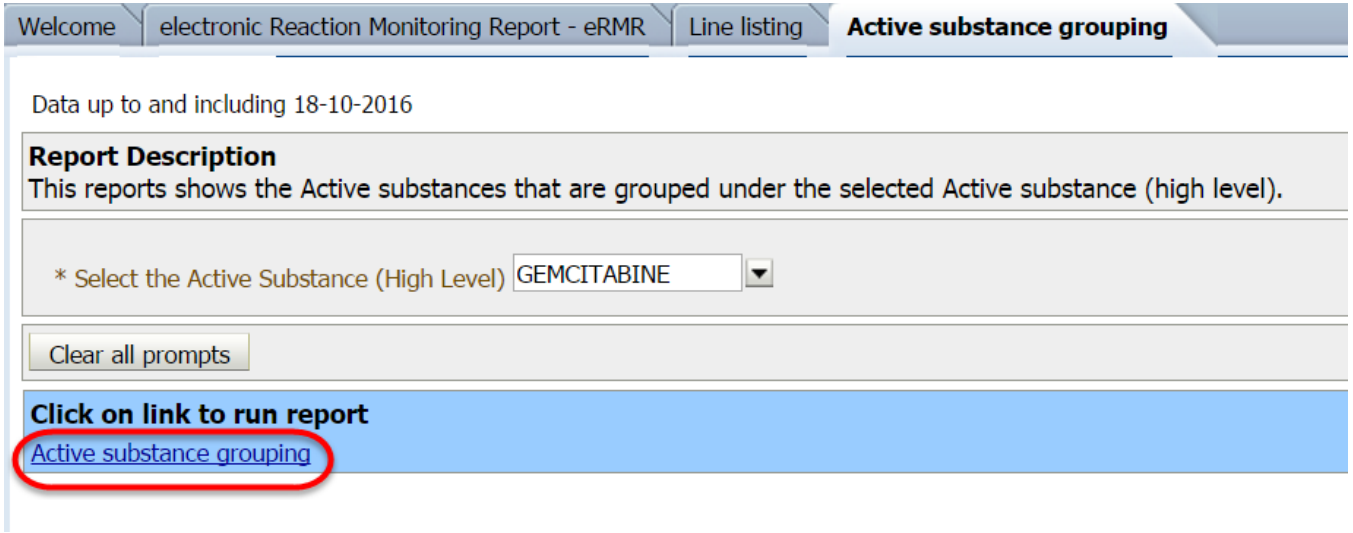
- To run the active substance grouping report, select an active substance and click on the active hyperlink ‘active substance grouping’ at the bottom of the report.



Active substance grouping outcome

- The outcome of the active substance grouping report is a table containing the substance names that have been grouped to a specific active substance high level

Active substance grouping

Data up to and including 18-10-2016

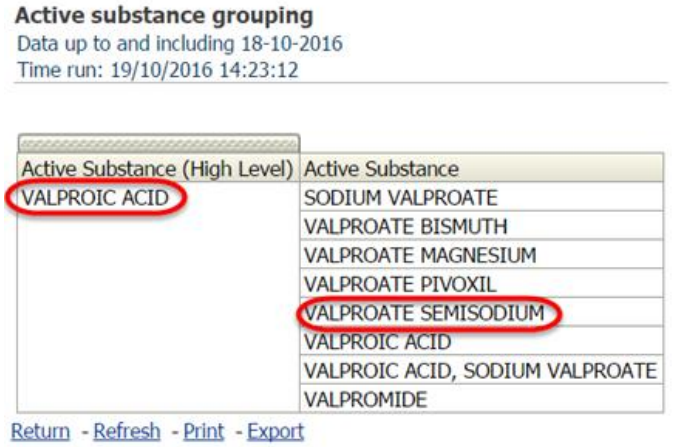
Time run: 19/10/2016 14:19:51

Active Substance (High Level)	Active Substance
GEMCITABINE	GEMCITABINE
	GEMCITABINE HYDROCHLORIDE

Return - Refresh - Print - Export

Other examples of the active substance grouping report

- By running the active substance grouping report, MAHs of valproate semisodium will know that 'valproic acid' is the active substance high level they should use to retrieve the data from EVDAS



Active substance grouping

Data up to and including 18-10-2016

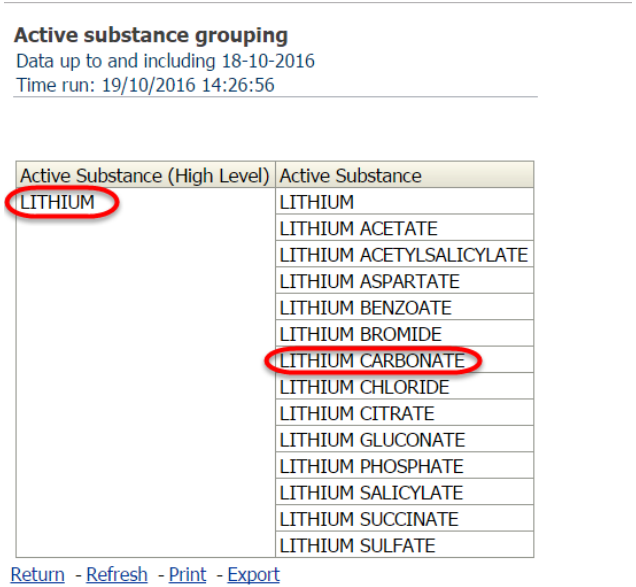
Time run: 19/10/2016 14:23:12

Active Substance (High Level)	Active Substance
VALPROIC ACID	SODIUM VALPROATE
	VALPROATE BISMUTH
	VALPROATE MAGNESIUM
	VALPROATE PIVOXIL
	VALPROATE SEMISODIUM
	VALPROIC ACID
	VALPROIC ACID, SODIUM VALPROATE
	VALPROMIDE

Return - Refresh - Print - Export

Other examples of the active substance grouping report

- By running the active substance grouping report, MAHs of lithium carbonate will know that lithium is the active substance high level they should use to retrieve the data from EVDAS



Active substance grouping
Data up to and including 18-10-2016
Time run: 19/10/2016 14:26:56

Active Substance (High Level)	Active Substance
LITHIUM	LITHIUM
	LITHIUM ACETATE
	LITHIUM ACETYLSALICYLATE
	LITHIUM ASPARTATE
	LITHIUM BENZOATE
	LITHIUM BROMIDE
	LITHIUM CARBONATE
	LITHIUM CHLORIDE
	LITHIUM CITRATE
	LITHIUM GLUCONATE
	LITHIUM PHOSPHATE
	LITHIUM SALICYLATE
	LITHIUM SUCCINATE
	LITHIUM SULFATE

Return - Refresh - Print - Export

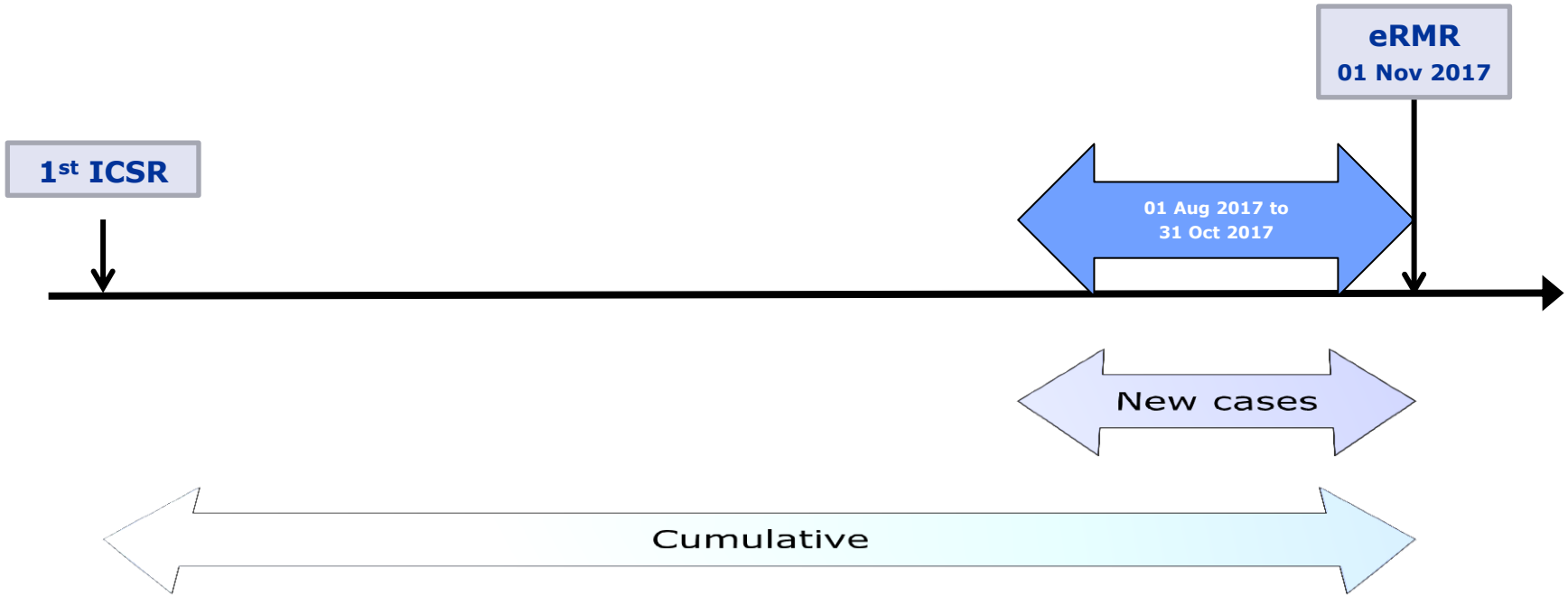

electronic Reaction Monitoring Report - eRMR
Line listing
Active substance grouping

- The electronic reaction monitoring report provides the user with aggregated data to be used for signal detection for a specific active substance high level according to a reference period. The report can be further filtered by MedDRA reaction terms.
- To access the eRMR report click on the electronic Reaction Monitoring Report tab in the MAH Pharmacovigilance queries dashboard.

The Reference Period

- Using a reference period in the eRMR allows to highlight and separate the new cases received during that period. Continuous monitoring.
- The reference period is based on EV Message Gateway Date and defines the start and end of the period for populating the columns in the eRMR with the new cases.

The Reference Period



Reference period - New cases

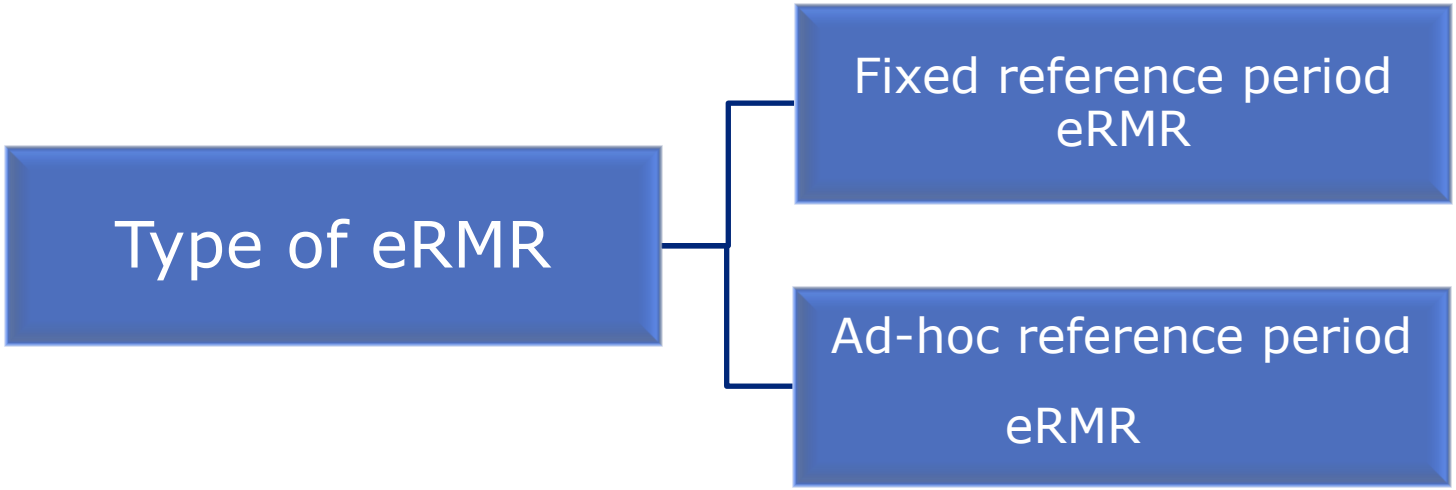
Cases received for the first time in EudraVigilance

Follow-ups

De-duplicated cases

- When two cases are identified as duplicates, these are merged in a new master case that is re-submitted to EudraVigilance. If the date of re-submission is within the reference period, only this case will appear as new (the 2 underlying duplicates will also not appear in the new/total column).

PTs	IME/DME	New EVPM	Total EVPM	New Fatal	Total Fatal
Ventricular fibrillation	IME/DME	2	4	1	1
Coronary artery thrombosis	IME	1	1	0	0
Atrioventricular block		2	3	1	2


Type of eRMR
Fixed reference period eRMR
Ad-hoc reference period eRMR

Fixed reference period eRMR

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Pre-generated by the EMA the first day of every month

The reference period for these eRMRs will be fixed to 6 months

e.g. for the eRMR pre-generated on 1st July 2017, the reference period is:

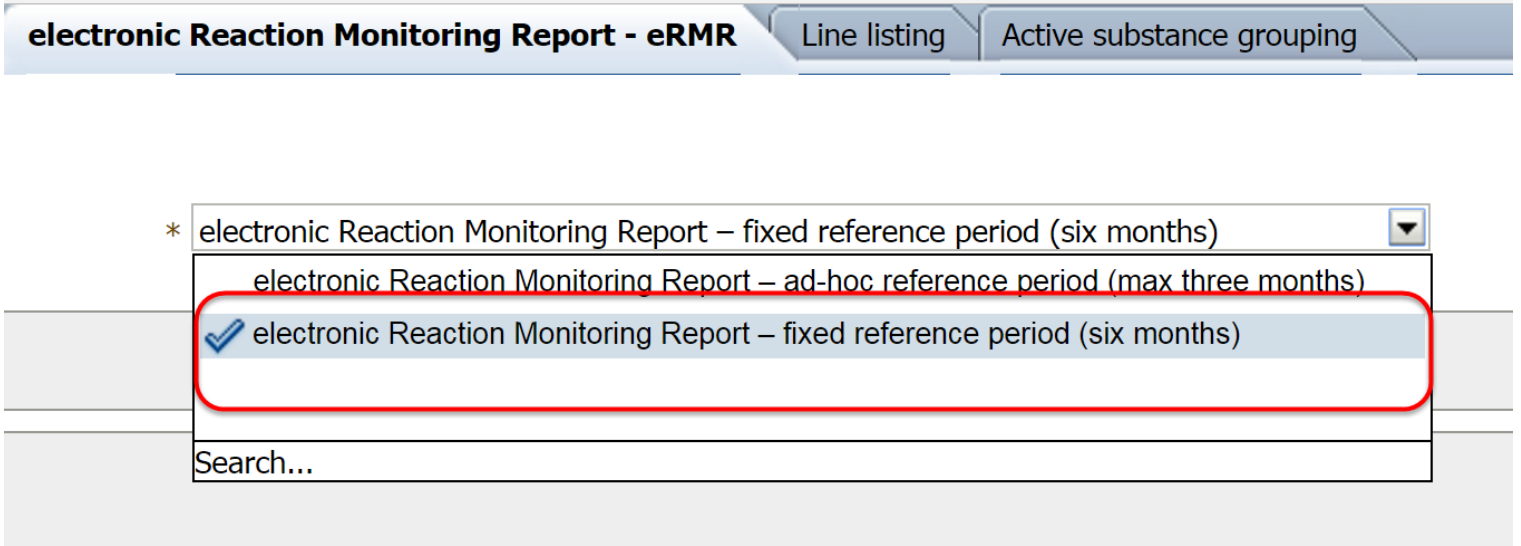
1st January 2017 –

30th June 2017.

The report will not change until a new eRMR is available, therefore running the report for the same substance the first day of the month or the last day of the month will provide the same results.

Fixed reference period eRMR

- To retrieve a fixed reference period eRMR, select the option from the 1st prompt in the eRMR report



Fixed reference period eRMR

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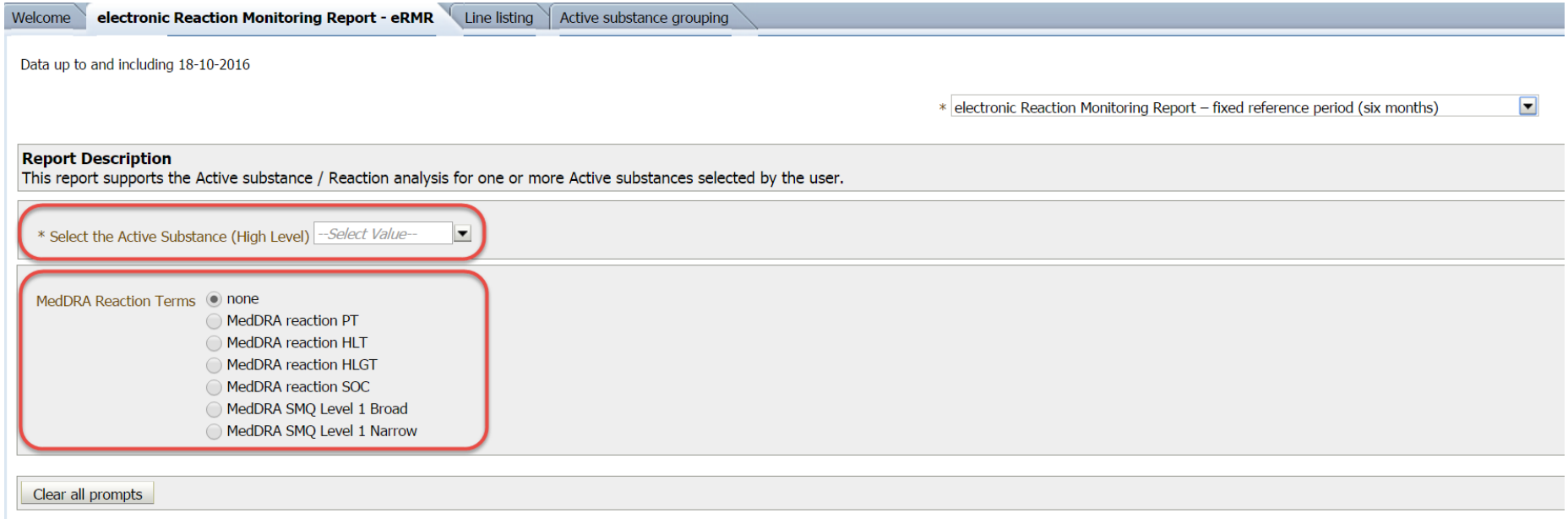
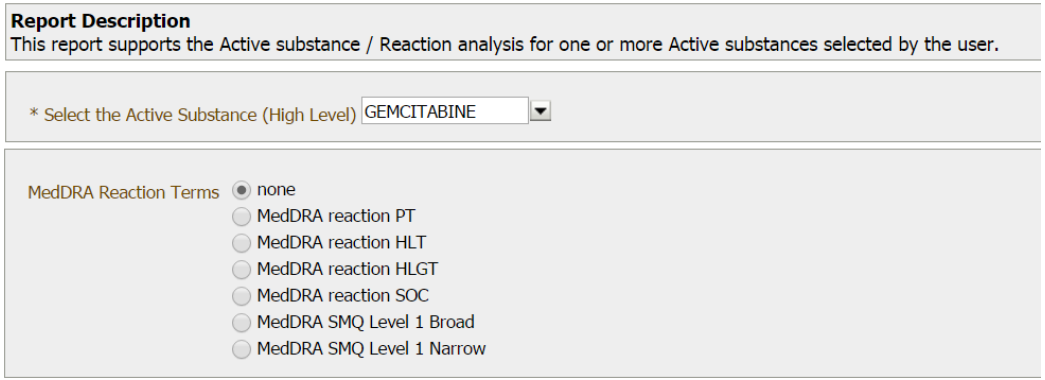
- The fixed reference period eRMR report contains 2 prompts



Fixed reference period eRMR

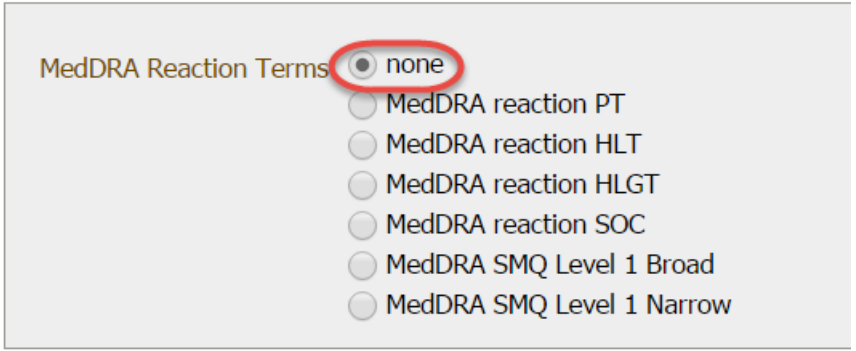
- Select an active substance/s high level



Filter on MedDRA term

- The system offers the possibility to restrict the data for a selected MedDRA term.
- The options for a MedDRA term selection are at the level of the SOC, HLGT, HLT and PT.
- Moreover, MedDRA SMQs level 1 Broad and Narrow can be also used.
- More than one term can be selected within the category (e.g 2 different PTs).
- When all the data is required, option 'none' (default option) should be left selected. With this option the report will retrieve all the ICSRs received for the selected active substances.

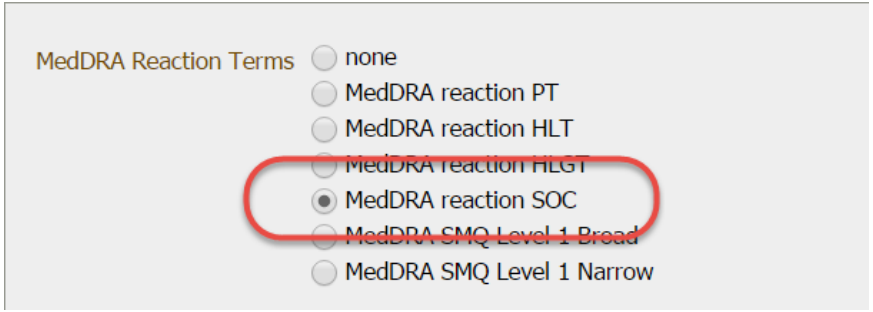
MedDRA Medical Dictionary for Regulatory Activities



Filter on MedDRA term

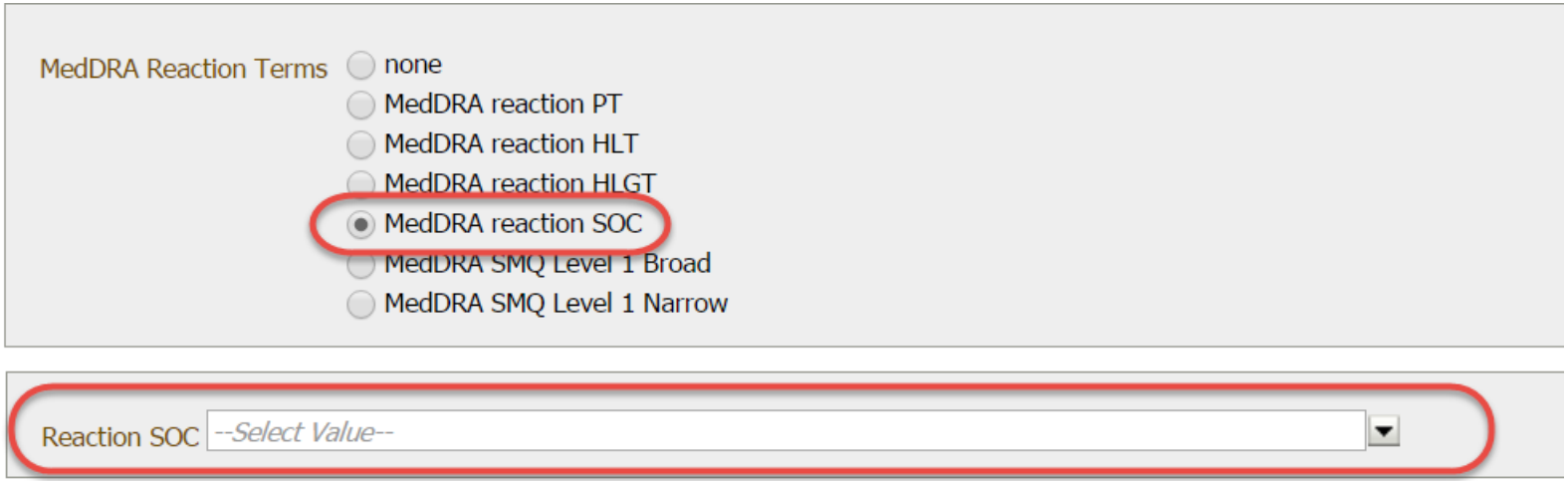
- In order to filter the data using MedDRA terms, select first the MedDRA hierarchy you want to use

➢ MedDRA reaction SOC in the example



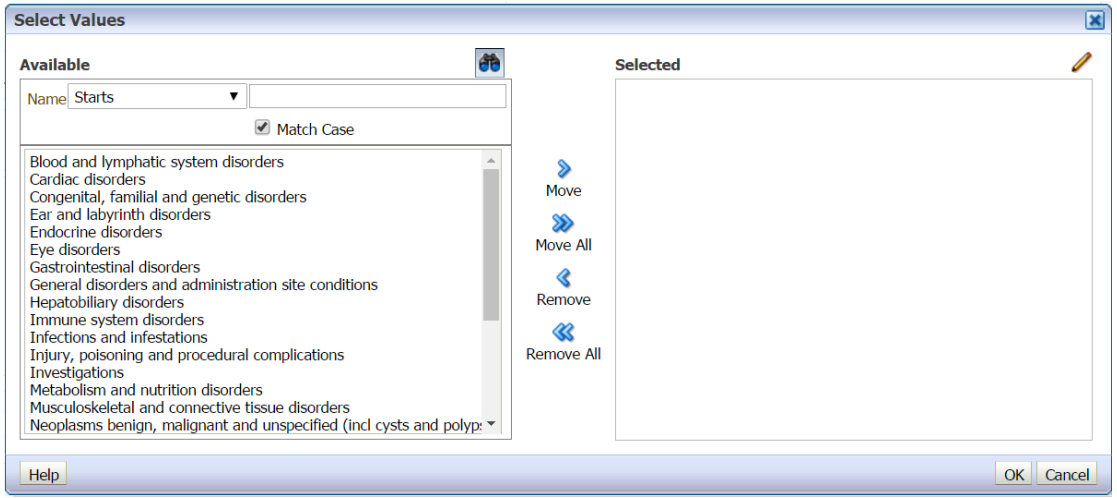
Filter on MedDRA term

- Once you have selected the MedDRA hierarchy, a new prompt will appear in the system for you to select the actual MedDRA term within the selected hierarchy



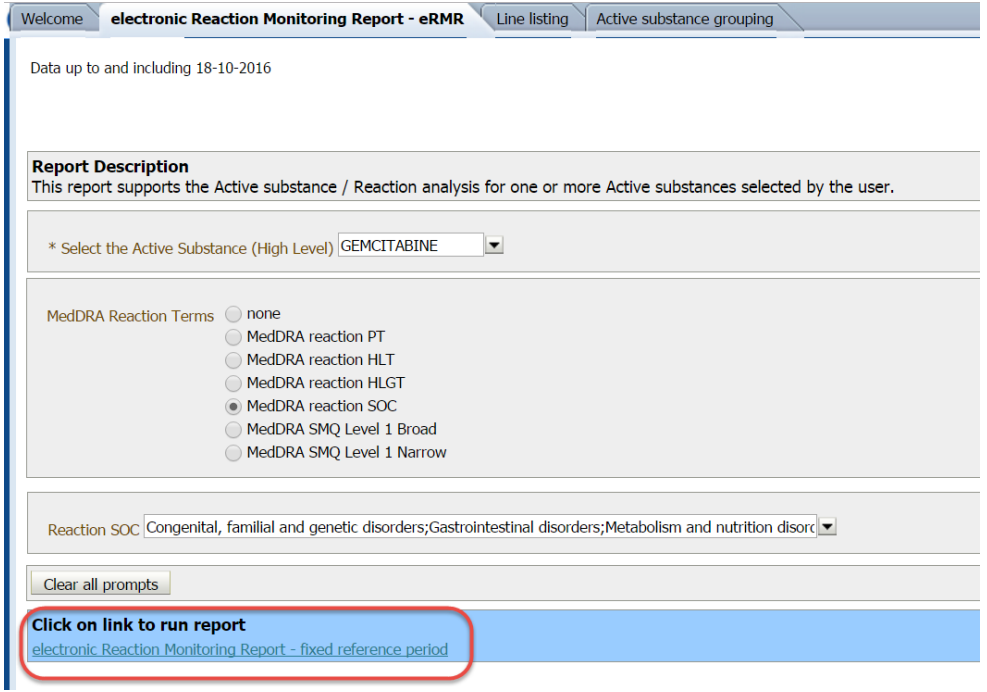
Filter on MedDRA term

- Please be aware that the selection of the MedDRA terms in the system follows the same logic as the selection of the substance:
  - You can type the term or you can open a selection cart by clicking the “search” function



Fixed reference period eRMR

- Once all the prompts are completed accordingly, click on the hyperlink at the bottom to run the report.
- Be aware that the hyperlink will not be activated if the mandatory prompts have not been completed.



Ad-hoc reference period eRMR

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The ad-hoc reference period eRMR report allows producing an eRMR with a reference period selected by the user.

There are two measures in place to protect the performance of the system:

The reference period is restricted to 3 months and 2 weeks in the past from the day the report is run. The users are therefore able to define the reference period as being as short as a single day or as long as 105 days.

Only one substance can be selected each time the report is run.

Ad-hoc reference period eRMR

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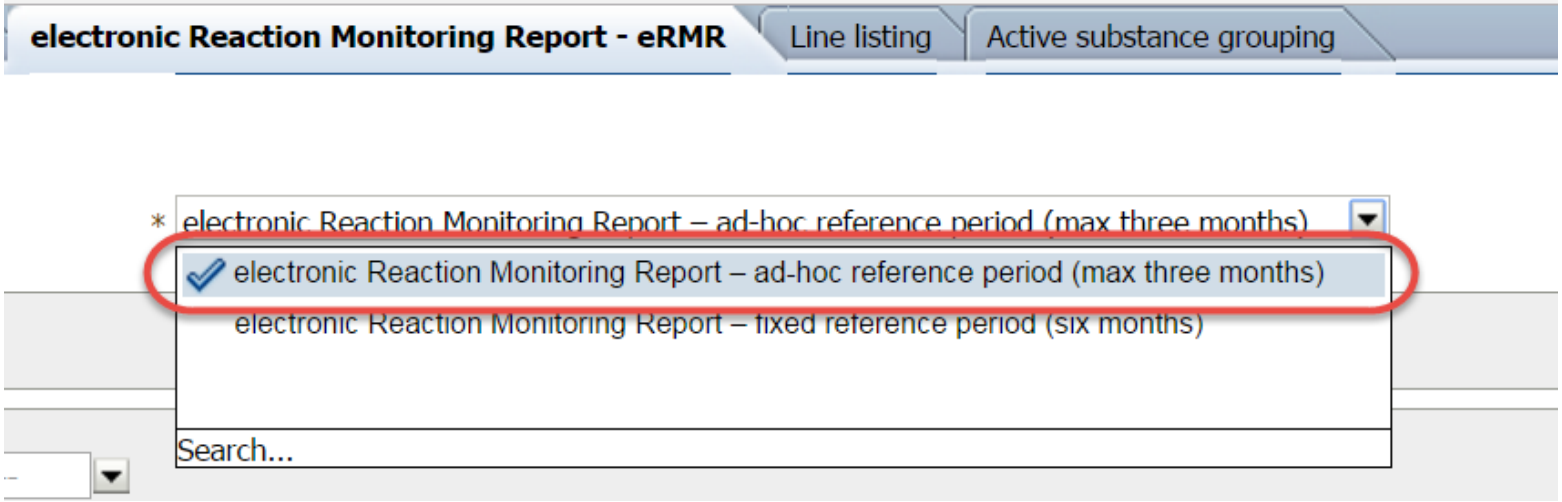
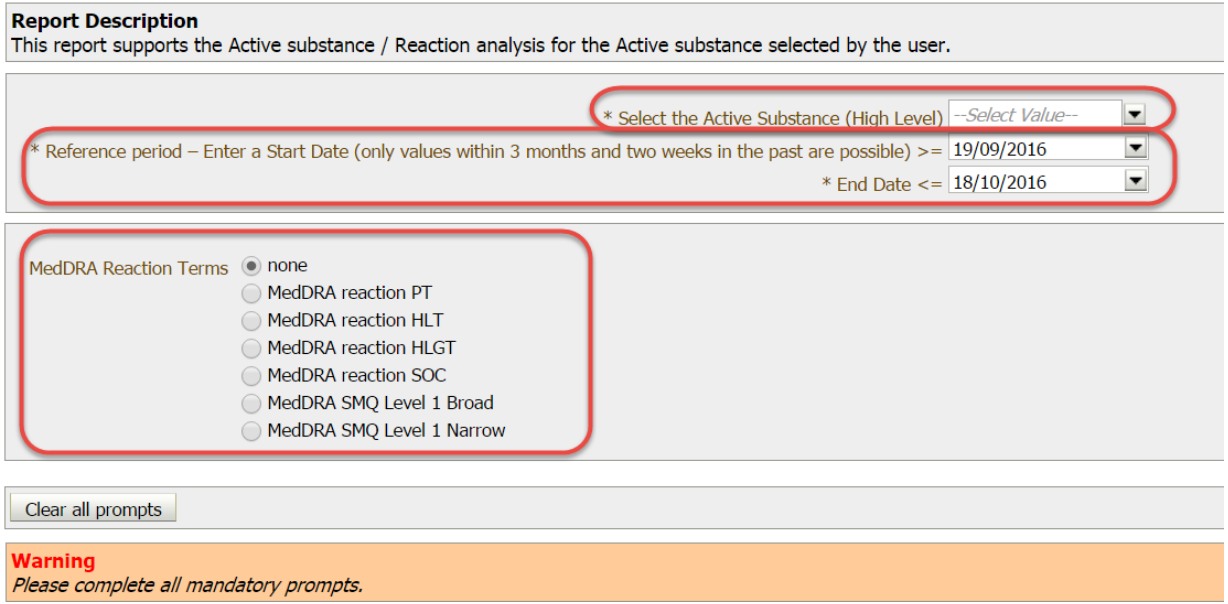
- To retrieve an ad hoc reference period eRMR, select the option from the 1st prompt in the eRMR report (this is the default option)



Ad-hoc reference period eRMR

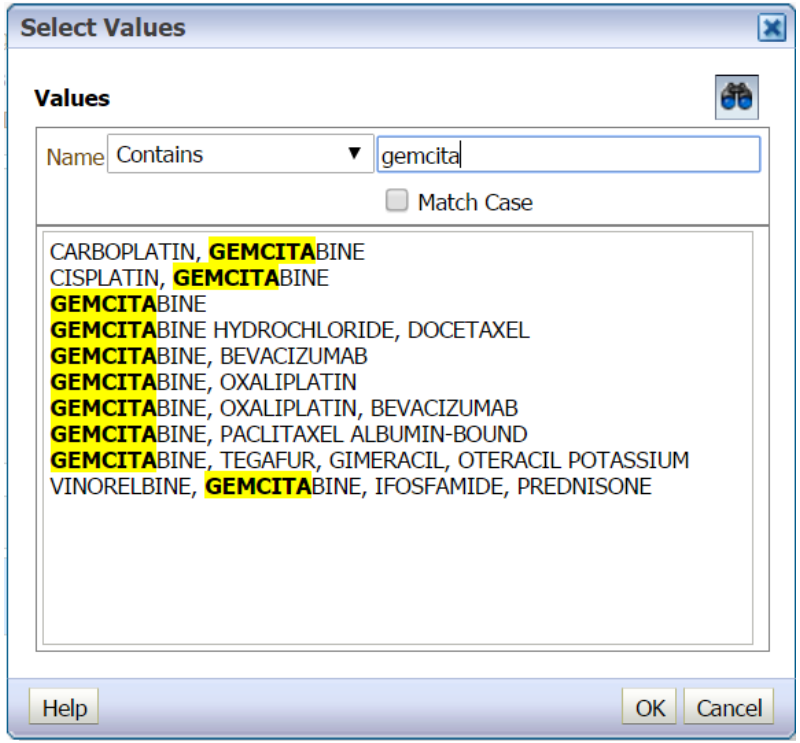
EUROPEAN MEDICINES AGENCY

- The ad hoc reference period eRMR report contains 3 prompts



Ad-hoc reference period eRMR

- Select an active substance high level
- Please remember that only one active substance can be selected in this report and therefore the selection cart option only contains one panel.



Ad-hoc reference period eRMR – start date

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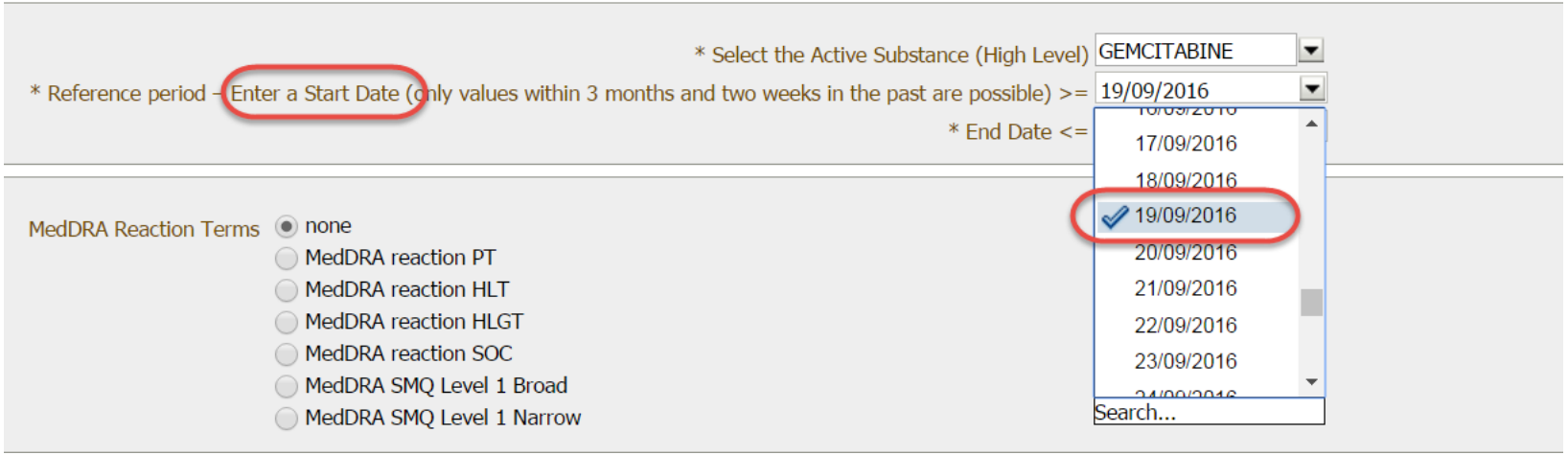
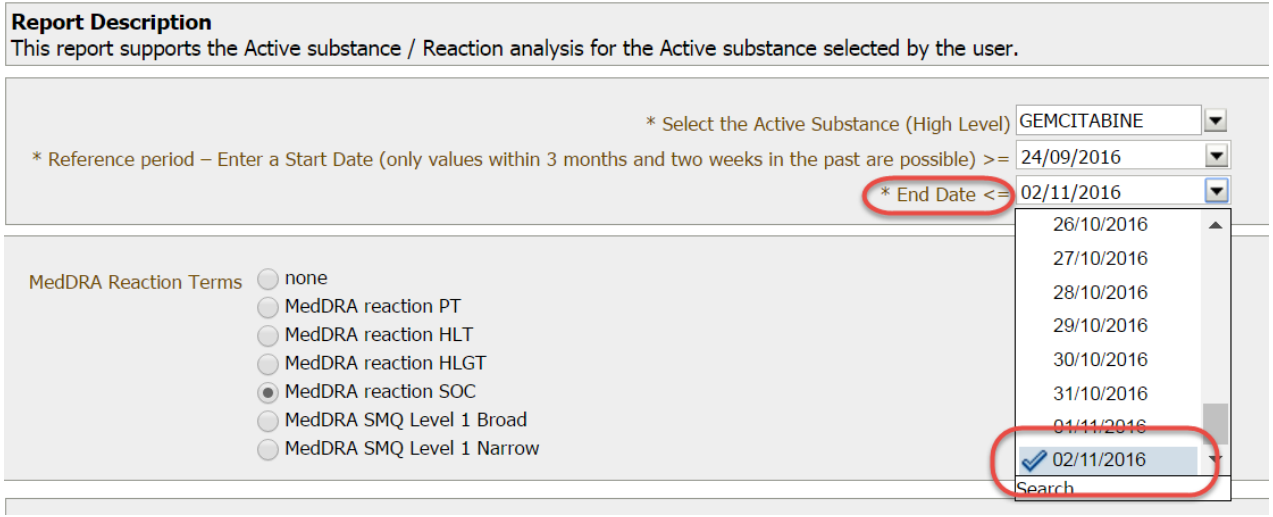
- To select the reference period, select a start date from the options provided in the prompt.
- Remember the start date can only cover a period of up to 105 days in the past from the day you are running the report.
- The default option is one month from today's date.



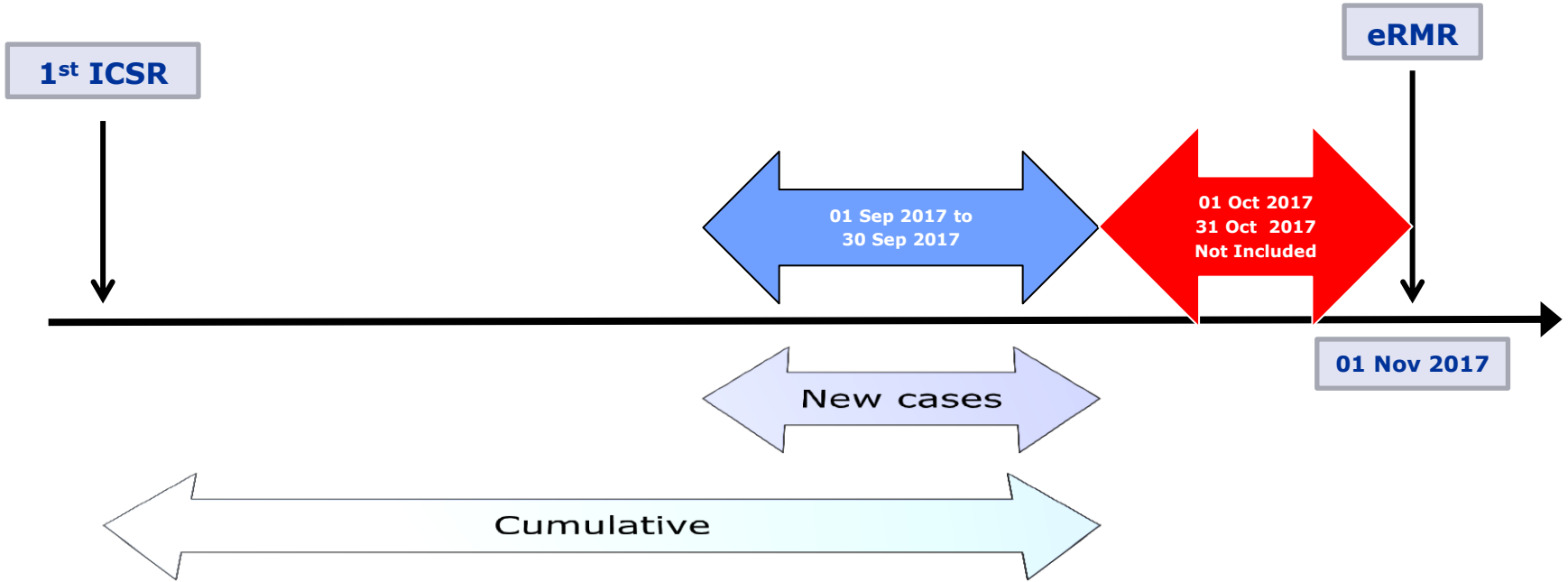
Ad-hoc reference period eRMR – end date

- The end date of the reference period defines the limit for the cases to be included.
- The default options is today's day -1 so in that way users will retrieve the cases from the most up to date database.



Ad-hoc reference period eRMR – end date

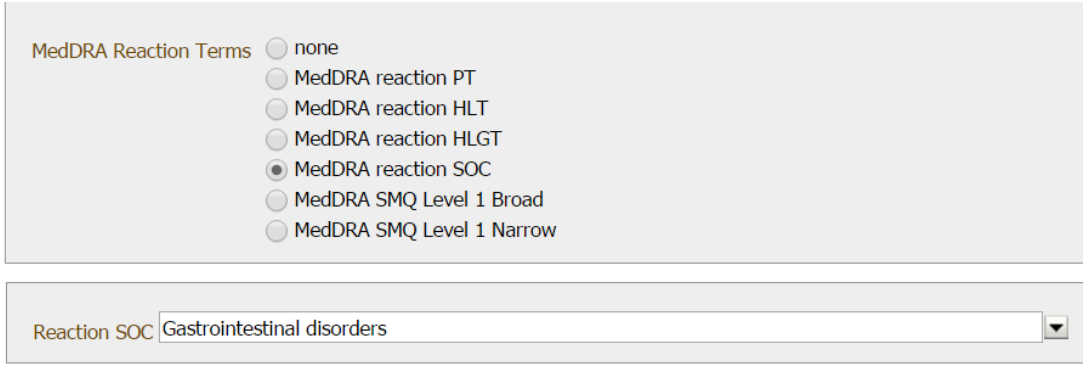
- Using an end date in the past is possible but the data retrieved will be according to the valid cases on the selected 'end date'



Filter on MedDRA Term

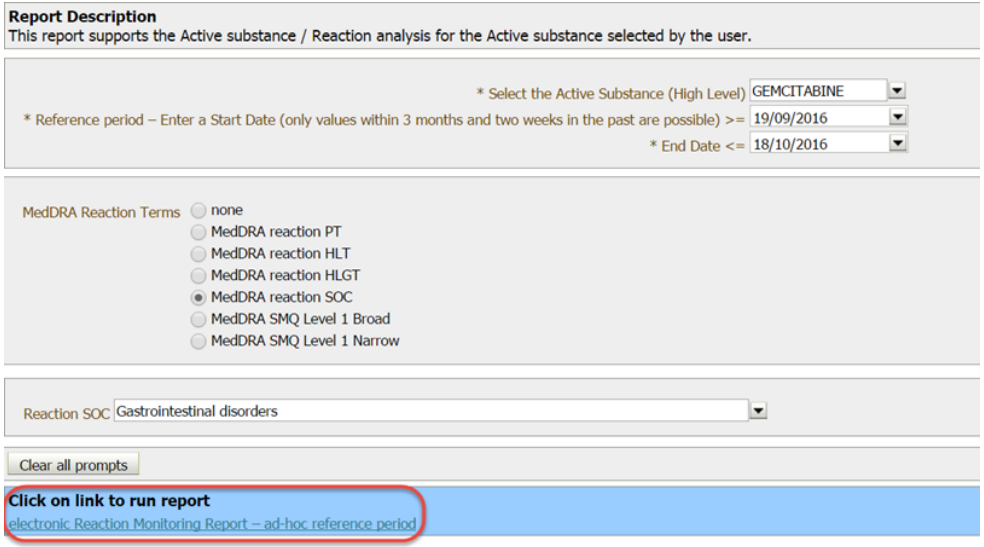
MedDRA Medical Dictionary for Regulatory Activities

- The ad hoc eRMR report also offers the possibility to filter the data by MedDRA terms in the same way as per the fixed reference period eRMR.

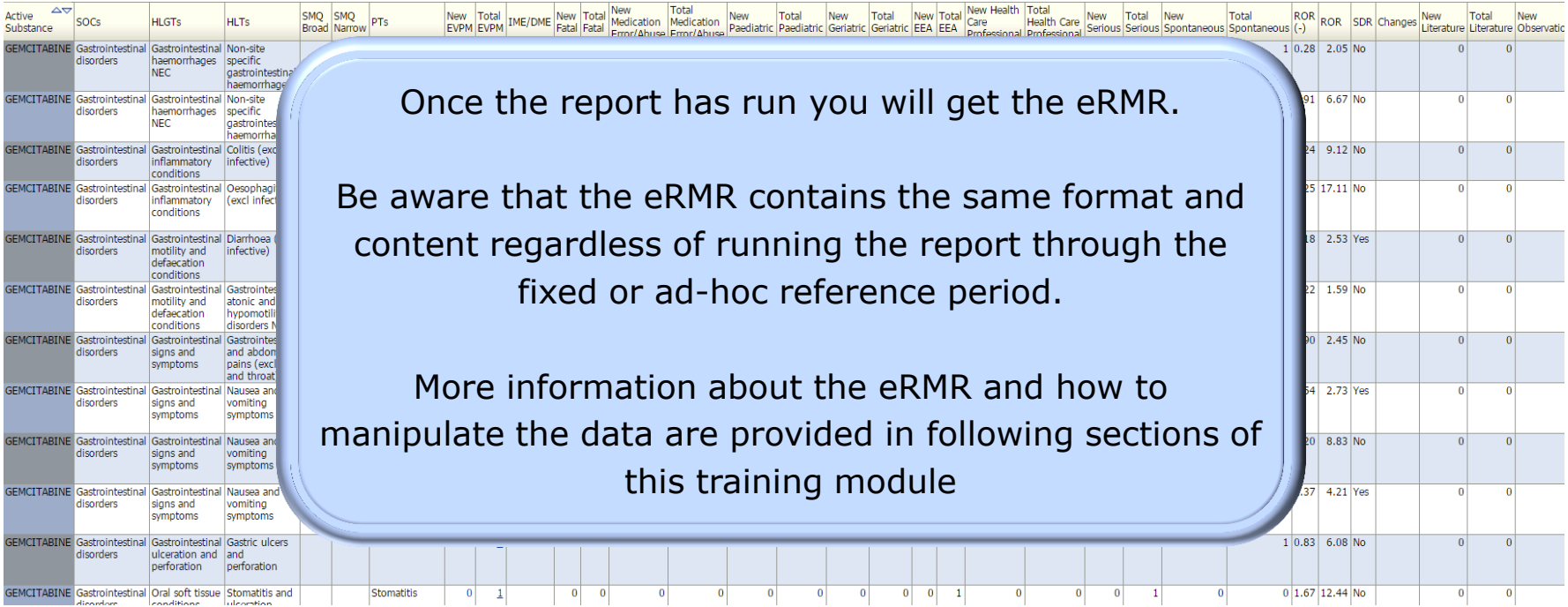


Ad-hoc reference period eRMR

- Once all the prompts are completed accordingly, click on the hyperlink at the bottom to run the report.
- Be aware that the hyperlink will not be activated if the mandatory prompts have not been completed.



eRMR report results



Active Substance	SOCs	HLGTs	HLTs	SMQ Broad	SMQ Narrow	PTs	New EVPM	Total EVPM	IME/DME	New Fatal	Total Fatal	New Medication Error/Abuse	Total Medication Error/Abuse	New Paediatric	Total Paediatric	New Geriatric	Total Geriatric	New EEA	Total EEA	New Health Care Professional	Total Health Care Professional	New Serious	Total Serious	New Spontaneous	Total Spontaneous	ROR (-)	ROR	SDR	Changes	New Literature	Total Literature	New Observatic
GEMCITABINE	Gastrointestinal disorders	Gastrointestinal haemorrhages NEC	Non-site specific gastrointestina haemorrhage																						1	0.28	2.05	No		0	0	
GEMCITABINE	Gastrointestinal disorders	Gastrointestinal haemorrhages NEC	Non-site specific gastrointes haemorrha																							91	6.67	No		0	0	
GEMCITABINE	Gastrointestinal disorders	Gastrointestinal inflammatory conditions	Colitis (exc infective)																							24	9.12	No		0	0	
GEMCITABINE	Gastrointestinal disorders	Gastrointestinal inflammatory conditions	Oesophagi (excl infec																							25	17.11	No		0	0	
GEMCITABINE	Gastrointestinal disorders	Gastrointestinal motility and defaecation conditions	Diarrhoea (infective)																							18	2.53	Yes		0	0	
GEMCITABINE	Gastrointestinal disorders	Gastrointestinal motility and defaecation conditions	Gastrointes atonic and hypomotili disorders N																							22	1.59	No		0	0	
GEMCITABINE	Gastrointestinal disorders	Gastrointestinal signs and symptoms	Gastrointes and abdon pains (exc and throat																							90	2.45	No		0	0	
GEMCITABINE	Gastrointestinal disorders	Gastrointestinal signs and symptoms	Nausea an vomiting symptoms																							64	2.73	Yes		0	0	
GEMCITABINE	Gastrointestinal disorders	Gastrointestinal signs and symptoms	Nausea an vomiting symptoms																							20	8.83	No		0	0	
GEMCITABINE	Gastrointestinal disorders	Gastrointestinal signs and symptoms	Nausea and vomiting symptoms																							37	4.21	Yes		0	0	
GEMCITABINE	Gastrointestinal disorders	Gastrointestinal ulceration and perforation	Gastric ulcers and perforation																						1	0.83	6.08	No		0	0	
GEMCITABINE	Gastrointestinal disorders	Oral soft tissue conditions	Stomatitis and ulceration			Stomatitis	0	1		0	0	0	0	0	0	0	0	0	1	0	0	0	1	0	0	1.67	12.44	No		0	0	

Once the report has run you will get the eRMR.

Be aware that the eRMR contains the same format and content regardless of running the report through the fixed or ad-hoc reference period.

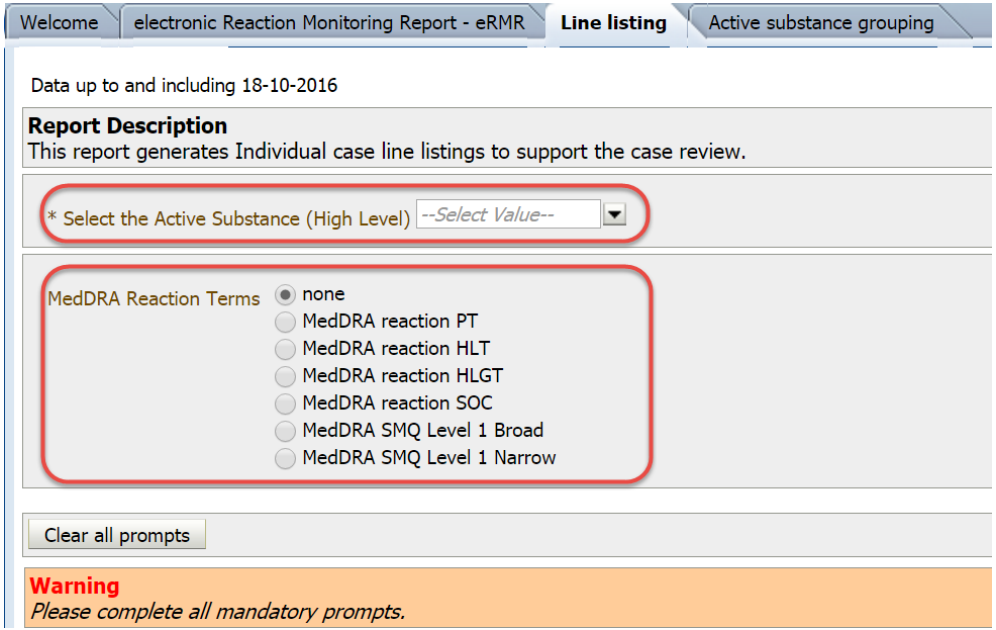
More information about the eRMR and how to manipulate the data are provided in following sections of this training module


electronic Reaction Monitoring Report - eRMR
Line listing
Active substance grouping

- The line listing report provides the user with the listing of individual cases for a specific substance/s and specific MedDRA terms.
- To access the line listing report, click on the line listing tab in the MAH Pharmacovigilance Queries Dashboard.

Line listing

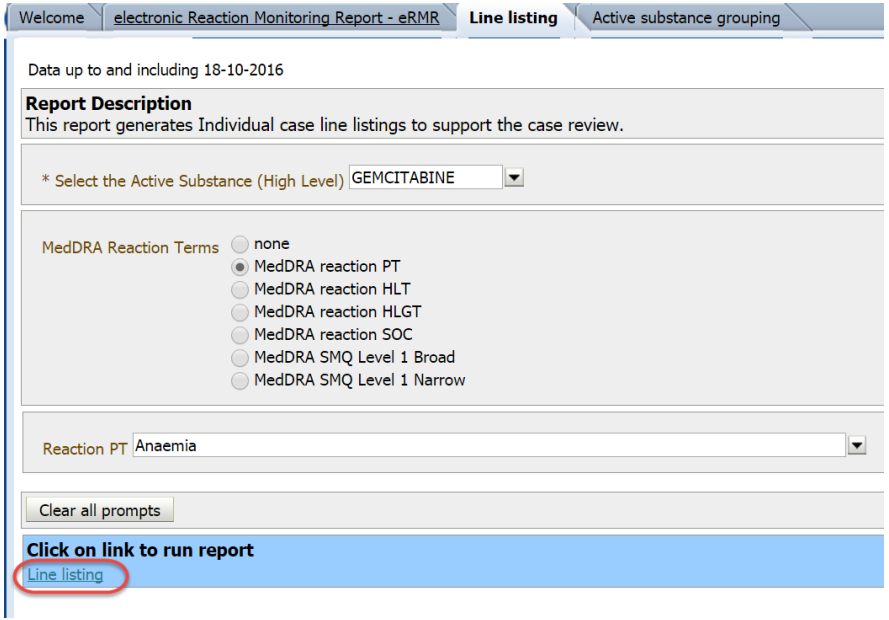
- The line listing report contains two prompts



Line listing

- To retrieve a line listing:

1. Select an active substance high level (more than one active substance can be selected)
2. Select a MedDRA reaction term, if applicable
3. Click on the hyperlink at the bottom of the report



Link eRMR – line listing

- Be aware that a line listing can be also accessible from a hyperlink in the eRMR that is placed in the number of cases ‘New EVPM’ and ‘total EVPM’
- This line listing will retrieve the cases for the specific active substance and for the specific MedDRA PT.
- The hyperlinks will work even when the eRMR has been exported.

Link eRMR – Line Listing

PTs	IME/DME	New EVPM	Total EVPM	New Fatal	Total Fatal	New Medication	Total Medication

EU Local Number	Worldwide Unique Case Identification	EV Gateway Receipt Date	Report Type	Primary Source Qualification	Primary Source Country for Regulatory Purposes	Literature Reference	Patient Age Group	Patient Age Group (as per reporter)	Patient Sex	Parent Child Report	Reaction List PT Outcome - Ser Criteria)
EU-EC-2333424	IT-PFMTEST-IT-2013-1292	06/06/2014	Other	Healthcare professional (Other health professional)	EEA	Not available	18-64 Years	Not Specified	Female	No	Nausea (2d - Recovered/Res Pyrexia (2d - Recovered/Res Retching (2d - Recovered/Res
EU-EC-2321881	US-ROCHE-1177559	28/08/2013	Spontaneous	Healthcare professional (Physician)	Non-EEA	Not available	18-64 Years	Not Specified	Male	No	Nausea (n/a - Recovered/Not Caused/Prolong Hospitalisation) Vomiting (n/a - Recovered/Not Caused/Prolong Hospitalisation)
EU-EC-2298993	NL-LRB-36647	04/07/2012	Report from studies		EEA	Not available	65-85 Years	Not Specified	Female	No	Hyponatraemia Unknown - Cau Hospitalisation) Nausea (n/a - Caused/Prolong Hospitalisation)

Bear always in mind that EV is updated every night, so if you run the eRMR and the line listing on different days, the number of cases may be different if new cases, nullifications, follow-ups or de-duplicated cases were received.

Line Listing report results

EUROPEAN MEDICINES AGENCY

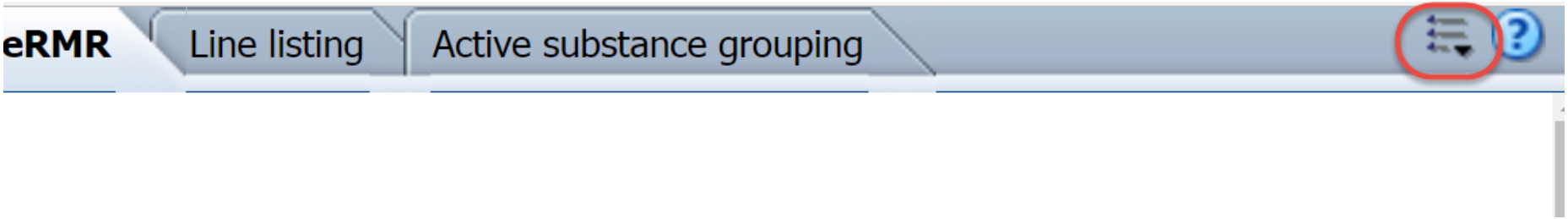
EU Local Number	Worldwide Unique Case Identification	EV Gateway Receipt Date	Report Type	Primary Source Qualification	Primary Source Country for Regulatory Purposes	Literature Reference	Patient Age Group	Patient Age Group (as per reporter)	Patient Sex	Parent Child Report	Reaction List PT (Duration – Outcome - Seriousness Criteria)	Suspect/Interacting Drug List (Drug Char - Indication PT - Action taken - [Duration - Dose - Route])	Concomitant/Not Administered Drug List (Drug Char - Indication PT - Action taken - [Duration - Dose - Route])
EU-EC-2330315	JP-SZ09-PHHY2014JP023764	10/03/2014	Spontaneous	Healthcare professional (Other health professional)	Non-EEA	Kawaguchi A, Hattori M, Kahno N, Kaise H, Iwata H.. Gemcitabine-induced tumor lysis syndrome caused by recurrent breast cancer in a patient without hemodialysis. Gan-To-Kagaku-Ryoho. 2013;40 (11):1529-1532	18-64 Years	Not Specified	Female	No	Anaemia (n/a - Unknown - Caused/Prolonged Hospitalisation), Depressed level of consciousness (n/a - Unknown - Caused/Prolonged Hospitalisation), Hepatic function abnormal (n/a - Unknown - Caused/Prolonged Hospitalisation), Hypercalcaemia (n/a - Recovering/Resolving - Caused/Prolonged Hospitalisation), Hyperuricaemia (n/a - Unknown - Caused/Prolonged Hospitalisation), Renal impairment (n/a - Unknown - Caused/Prolonged Hospitalisation),	GEMCITABINE [GEMCITABINE] (S - Metastases to bone - Unknown - [n/a - 1250mg/m2 - Not available])	Not reported
EU-EC-2324761	JP-OHUGAI-A201204580JROCHE121AAT	06/11/2013	Report from studies	Healthcare professional (Physician)									
EU-EC-2323715	JP-OHUGAI-A201204580JROCHE121121DEV	09/10/2013	Report from studies	Healthcare professional (Physician)									
EU-EC-2321901	NL-ROCHE-1143439	28/08/2013	Spontaneous	Healthcare professional (Other health professional)									Not reported
EU-EC-2321916	US-ROCHE-1149048	28/08/2013	Spontaneous	Healthcare professional (Other health professional)	Non-EEA	Borson R, Harker, G. Reeves, J. Beck, T. Hager, S. Horvath, W. Jones, M. Tillinghast, G. Arrowsmith, E. Harrer, G. Kudrik, F. Malamud, S. Bromund, J. Zeigler, H. Tai, D. Kornberg, L. Obasaju, C. Orlando, M. Yardley, D. Phase II study of Gemcitabine and Bevacizumab as first-line treatment in Taxane pretreated, HER2-negative, locally recurrent or metastatic breast cancer. Clinical Breast Cancer 2012 Oct 01;12 (5):322-330.	Not Specified	Not Specified	Female	No	Anaemia (n/a - Recovered/Resolved - Other Medically Important Condition), Febrile neutropenia (n/a - Recovered/Resolved - Other Medically Important Condition), Thrombocytopenia (n/a - Recovered/Resolved - Other Medically Important Condition)	AVASTIN [BEVACIZUMAB] (S - Breast cancer metastatic - Unknown - [n/a - 10mg/kg - Unknown]), NOT AVAILABLE [GEMCITABINE HYDROCHLORIDE] (S - Breast cancer metastatic - Unknown - [n/a - 2500mg/m2 - Intravenous (not otherwise specified)])	Not reported
EU-EC-2301563	NL-LRB-30511	19/07/2012	Spontaneous		EEA	Not available	65-85 Years	Not Specified	Male	No	Anaemia (n/a - Unknown - Caused/Prolonged Hospitalisation), Dermatitis (n/a - Unknown - Caused/Prolonged Hospitalisation), Leukopenia (n/a - Unknown - Caused/Prolonged Hospitalisation), Vomiting (n/a - Unknown - Caused/Prolonged Hospitalisation)	Not reported	Not reported

Once the report has run you will get a line listing with details of the individual cases.

More information about the line listing and how to manipulate the data are provided in following sections of this training module.

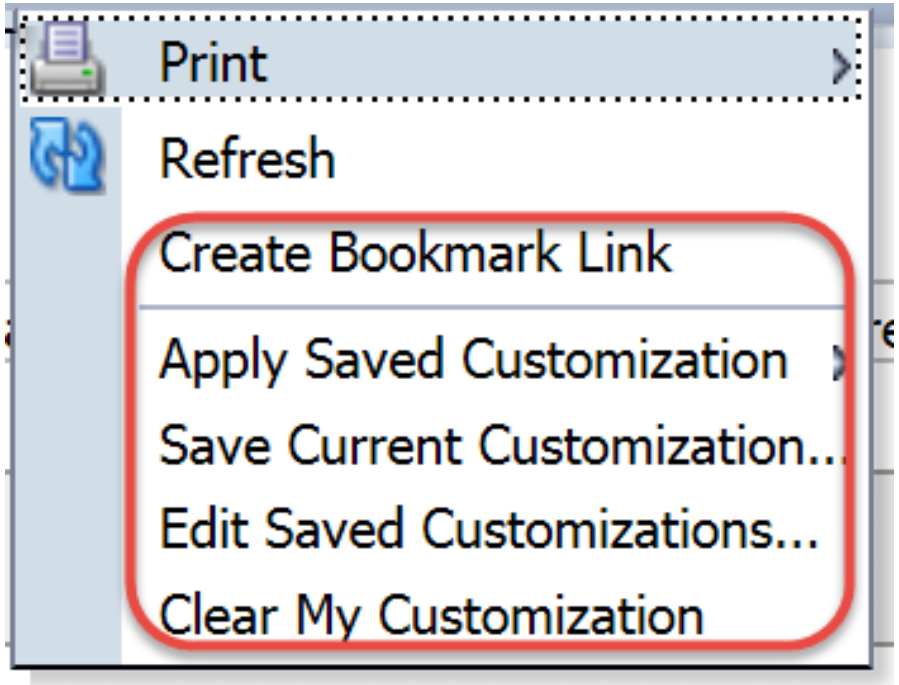
EVDAS - General functionalities – Prompt Page options

- When you are on the prompts page, as well as answering the prompts and running the report, the system offers options to customise your selections.
- To access these, click the **page options button** in the top right-hand corner of the prompts page.



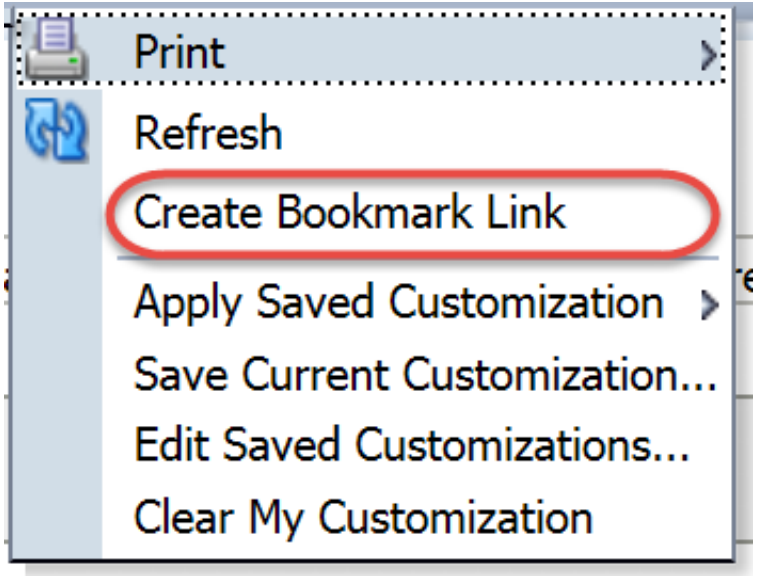
General functionalities – Prompt Page options

- Be aware that the Print and Refresh options are not active.

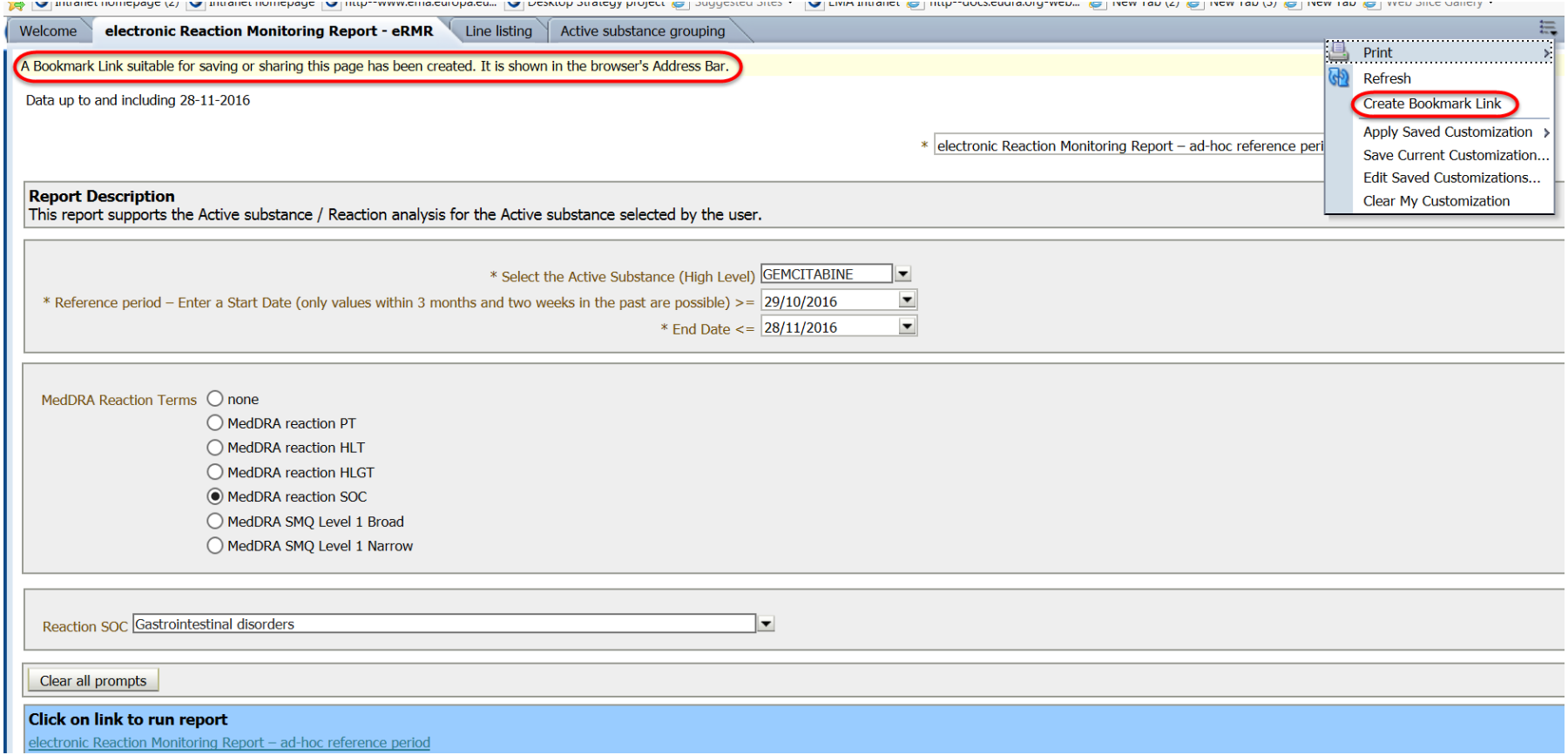


General functionalities – Prompt Page options
Bookmark link

- This option creates a dedicated URL suitable for saving or sharing the prompt page. It is shown in the browser's Address Bar

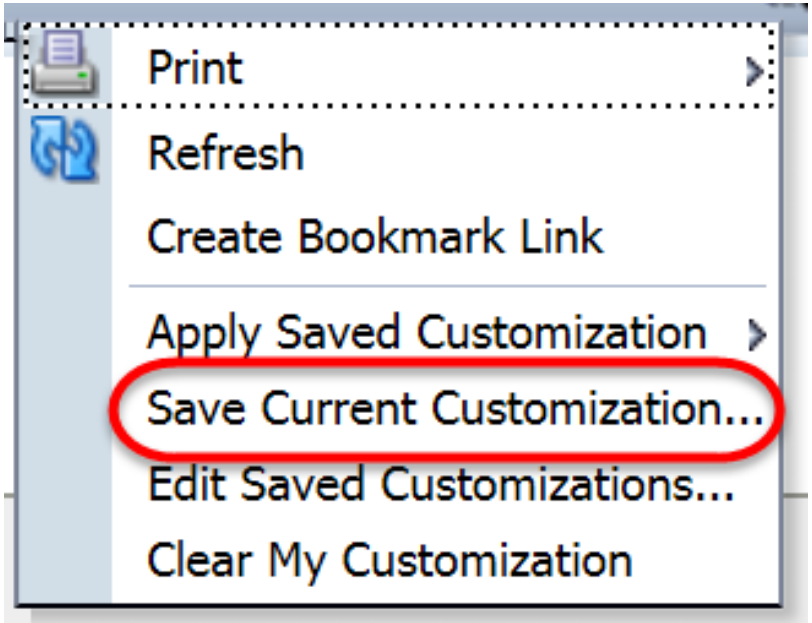


Bookmark link



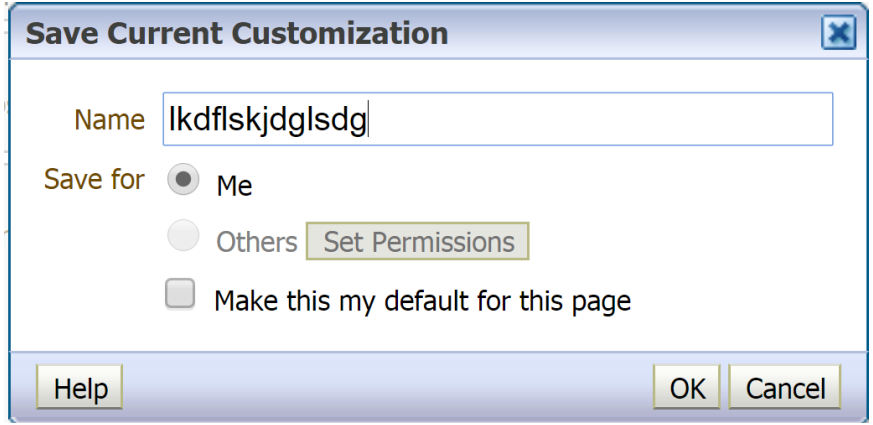
Prompt customisations – Save current customisation

- Once you have entered your prompt selections, you can choose to save these for future searches.
- To do so, once all the prompts are completed, click on 'Save Current Customization' in the prompt page options.



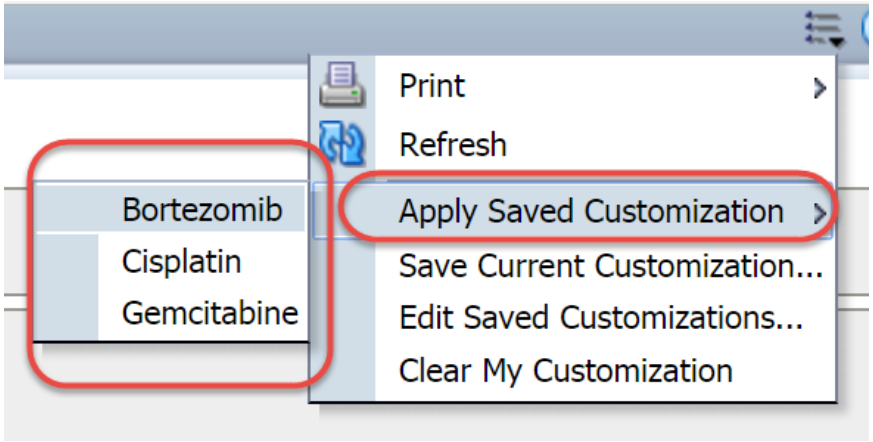
Prompt customisations - Save current customisation

- The system will offer you the possibility to name that customisation and to make this customisation the default option, so next time you open this report, the prompts will be populated with this default customisation.
- Be aware that saving customisations for other users is not an active option.



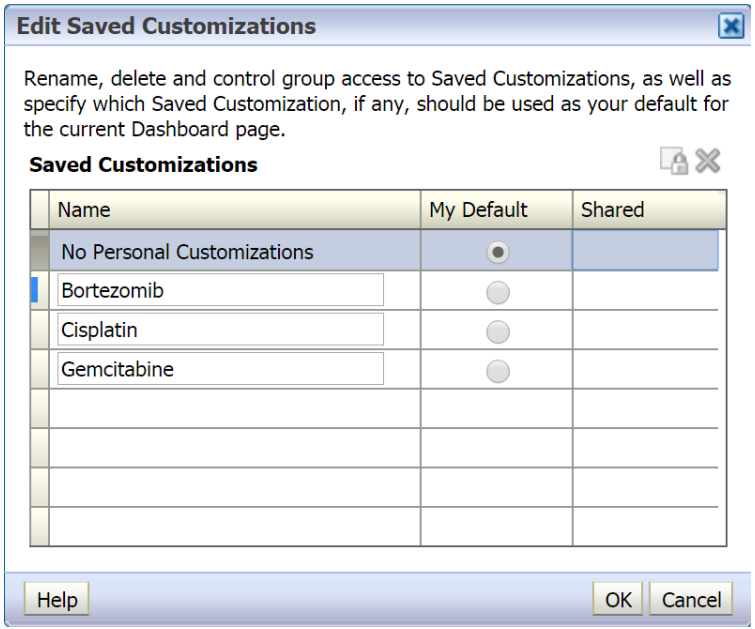
Prompt customisations – Apply saved customisation

- To apply a saved customisation to the report, click on 'Apply Saved Customisations' and the system will show the list of customisations you have previously saved.
- To apply one of the saved customisations simply click on the desired option.
- Please be aware that customisations can only be applied within the same report. You cannot run an eRMR report with a customisation saved for the line listing report.



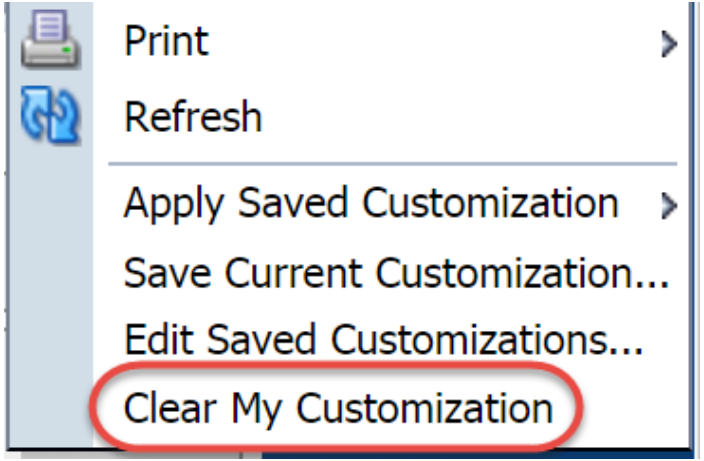
Prompt customisations – Edit saved customisations

- The option edit customisations gives you the possibility to modify your list of saved customisations.
- From here you can delete, rename or change the default option.
- If no default options is desired, then no personal customisations should be selected.



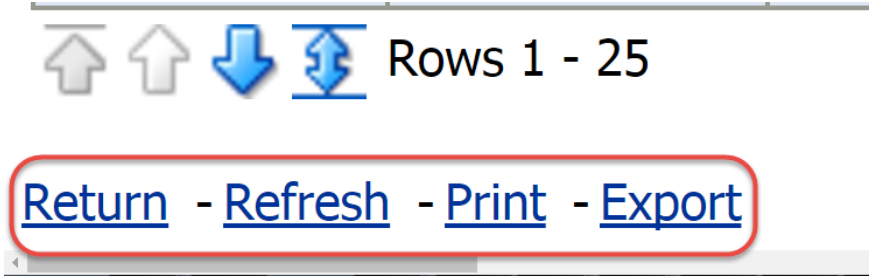
Prompt customisations – Clear customizations

- The option ‘clear my customisation’ removes all the answers to the prompts selected and restores the prompt page to the default answers.
- It is advised to clear your customisations when new reports are run so you do not carry over by mistake previous prompt selections.



General functionalities - Working with return reports

- Once the reports have run, you have 4 different standard options at the bottom left corner of the results page



General functionalities - Working with return reports

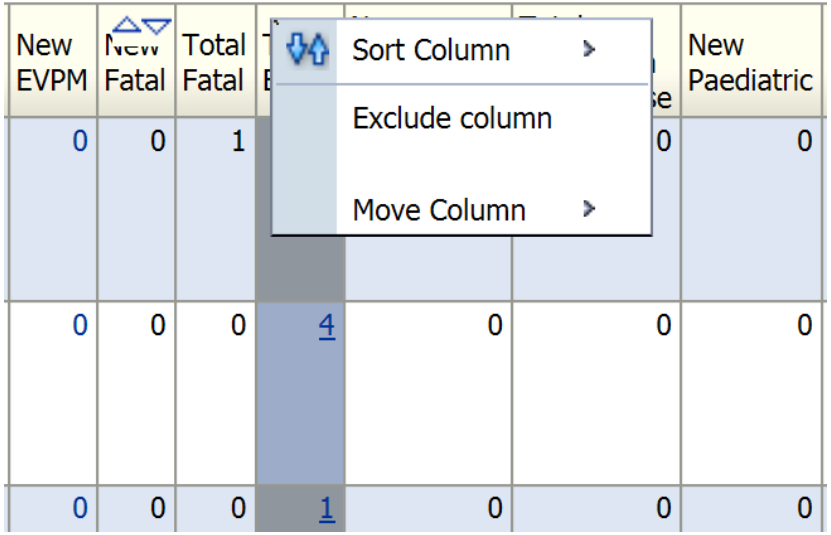
- **'Return'** takes you back to the prompt page with the options you selected for that report.
- **'Refresh'** re-runs the report with the options previously selected.
- **'Print'** exports the returned results in a printable format.
  - To print, click the **Print** link at the bottom of the page and the print menu will appear
- **'Export'** presents the returned results in a variety of formats for local storage, distribution and analysis.
  - To export, click the **Export** link at the bottom of the page and the export menu will appear.
- *Please note that to export it is recommended to use Excel 2007.*

Be aware that the report results cannot be saved directly from the EVDAS interface. You will need to export the results first in order to save them in your local systems.

General functionalities - Working with return reports

- Once you have retrieved an eRMR or a line listing, before you export them you can manipulate the layout by activating the right click menu; you can:

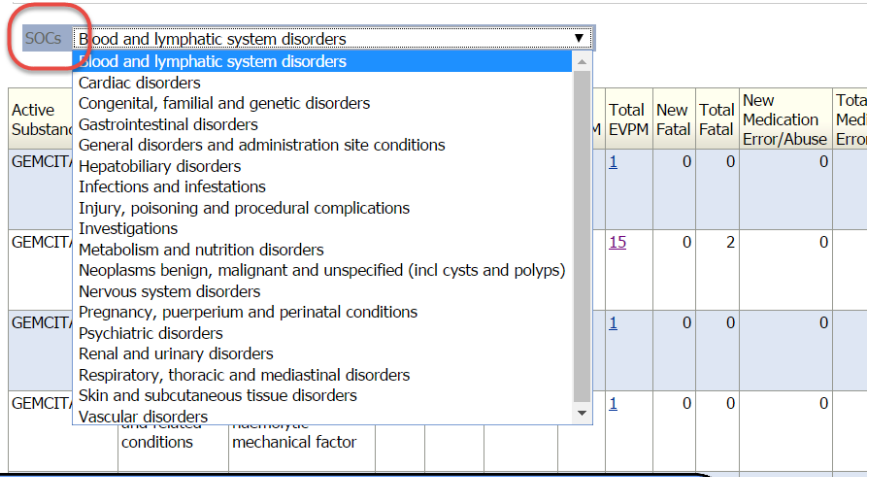
1. Sort the column
2. Exclude columns
3. Move columns



General functionalities - Working with return reports

- **Moving columns to prompts** allows you to convert the column into a prompt and from there select the data according to the options provided within that prompt.

➢ In the example provided, the SOC column in the eRMR has been moved to a prompt so you can see the eRMR for the selected SOC.



Please be aware that this functionality will not work if the column contains different values, for instance columns with number of cases in the eRMR or Line Listing columns (e.g drug list)

General functionalities - Working with return reports

- **Moving columns to sections** allows you to separate the data by a specific field.

➢ In the example, the female cases have been separated from the male cases in the same page.

Female

EU Local Number	Worldwide Unique Case Identification	EV Gateway Receipt Date	Report Type	Primary Source Qualification	Primary Source Country for Regulatory Purposes	Literature Reference	Patient Age Group	Patient Age Group (as per reporter)	Parent Child Report	Reaction List PT (Duration – Outcome - Seriousness Criteria)
EU-EC-2299083	NL-LRB-35483	04/07/2012	Report from studies		EEA	Not available	18-64 Years	Not Specified	No	Cerebrovascular accident (n/a - Unknown -

Male

EU Local Number	Worldwide Unique Case Identification	EV Gateway Receipt Date	Report Type	Primary Source Qualification	Primary Source Country for Regulatory Purposes	Literature Reference	Patient Age Group	Patient Age Group (as per reporter)	Parent Child Report	Reaction List PT (Duration – Outcome - Seriousness Criteria)
										Nausea (n/a - Not Recovered/Not Resolved - Caused/Prolonged

Please be aware that this functionality will not work if the column contains different values, for instance columns with number of cases in the eRMR or Line Listing columns (e.g drug list)

Full description of the MAH Pharmacovigilance queries dashboard is provided in the user manual:

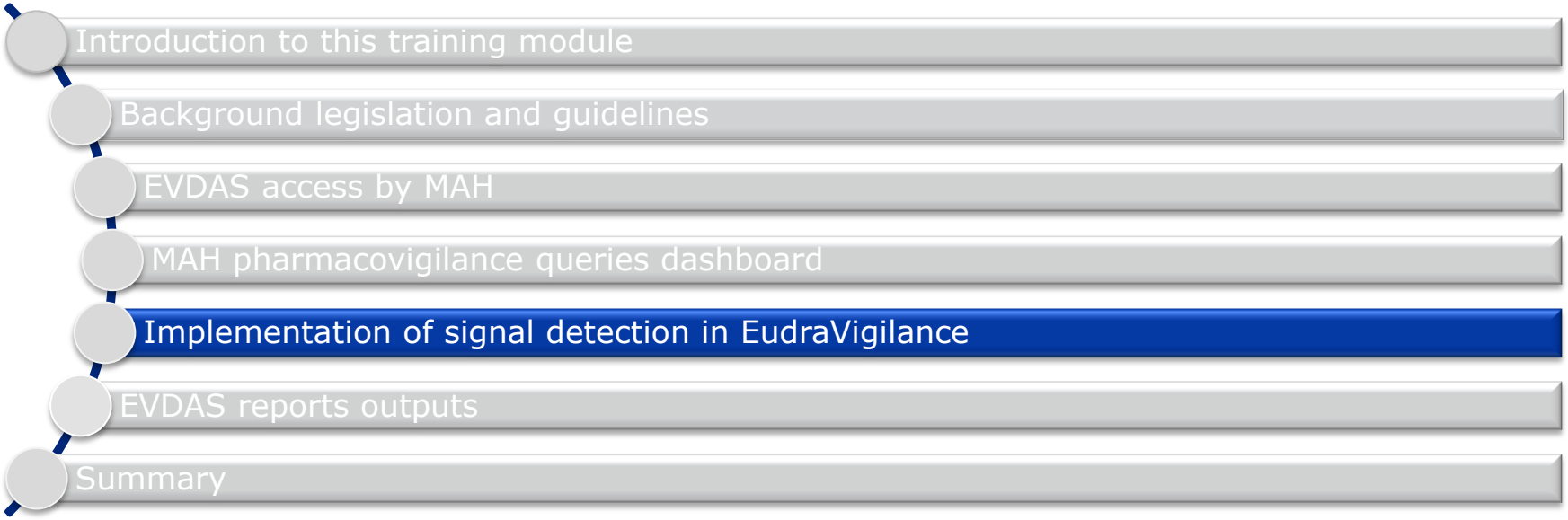
EV-G1a - MAH's level 1 access via EVDAS

Section Summary

In this section you obtained an understanding of:

- The different reports available in the MAH Pharmacovigilance queries dashboard
- How to select the “active substance high level” to be used in EVDAS
- How to retrieve different eRMRs
- How to retrieve a Line Listing
- How to manipulate and work with returned results

Content Summary

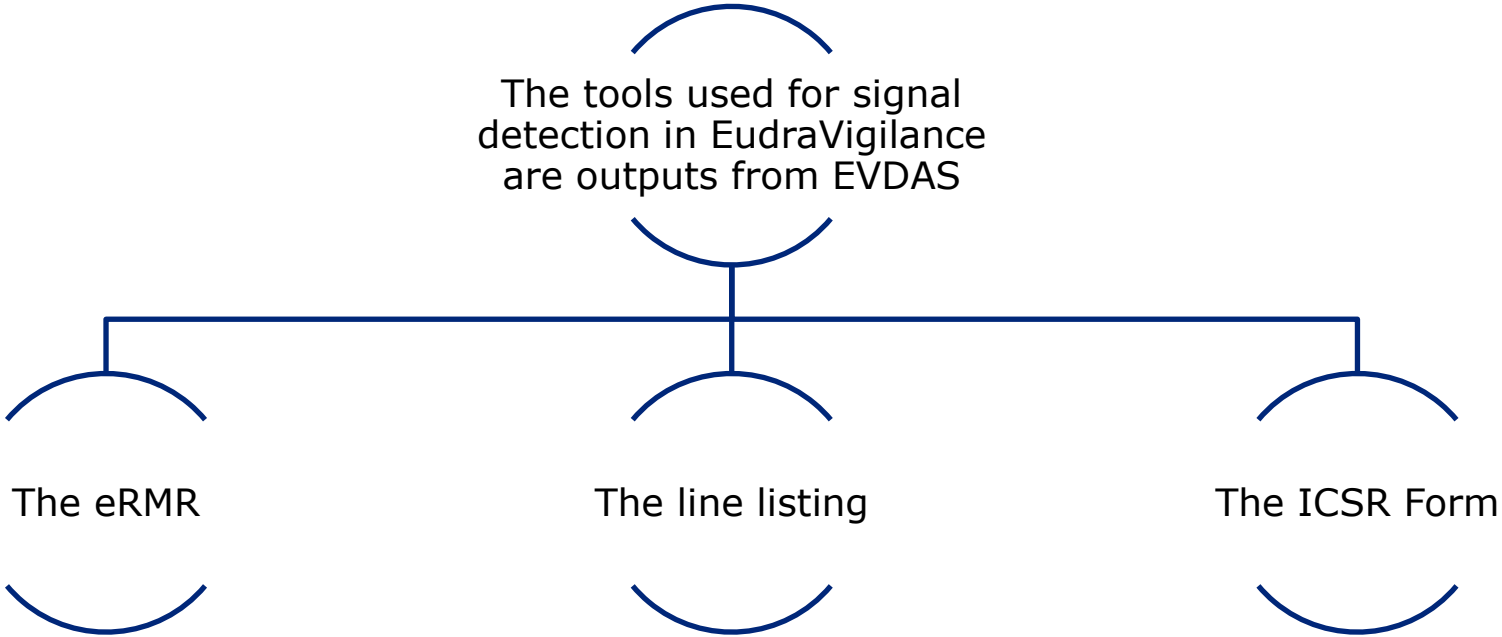


Section Overview

- In this section you will obtain an understanding:
  - How signal detection has been implemented in EudraVigilance

Principles and methods for statistical signal detection in EudraVigilance are developed in the EMA guideline 'Screening for adverse reactions in EudraVigilance'

Screening for adverse reactions in EudraVigilance



Screening for adverse reactions in EudraVigilance

- Measures of disproportionality are based on a ratio of the observed proportion of spontaneous cases for a drug-reaction/event combination (DEC) in relation to the proportion of cases that would be expected if no association existed between the drug and the reaction/event.
- The utility of this statistic for signal detection is based on the consideration that when a product causes the event, the number of observed reports for the DEC will tend to exceed the number based on chance alone.
- The disproportionality method used in EudraVigilance is the Reporting Odds Ratio (ROR) which is included in the eRMR.

Calculation of the ROR

- The calculation of the ROR is based on a two-by-two contingency table

	Event	Not Event
Medicinal product	a	b
Not product	c	d

$$ROR = \frac{a/b}{c/d}$$

- The 95% confidence interval of the ROR is also computed in the eRMR

a	Number of individual cases with the suspected medicinal product and the adverse event
b	Number of individual cases with the suspected medicinal product but not event of interest
c	Number of individual cases with the event of interest but not the medicinal product of interest
d	Number of individual cases with no event of interest or medicinal product of interest

ROR example

$$ROR = \frac{15/100}{5{,}000/100{,}000} = 3$$

	Event	Not Event
Medicinal product X	15	100
Not product X	5,000	100,000

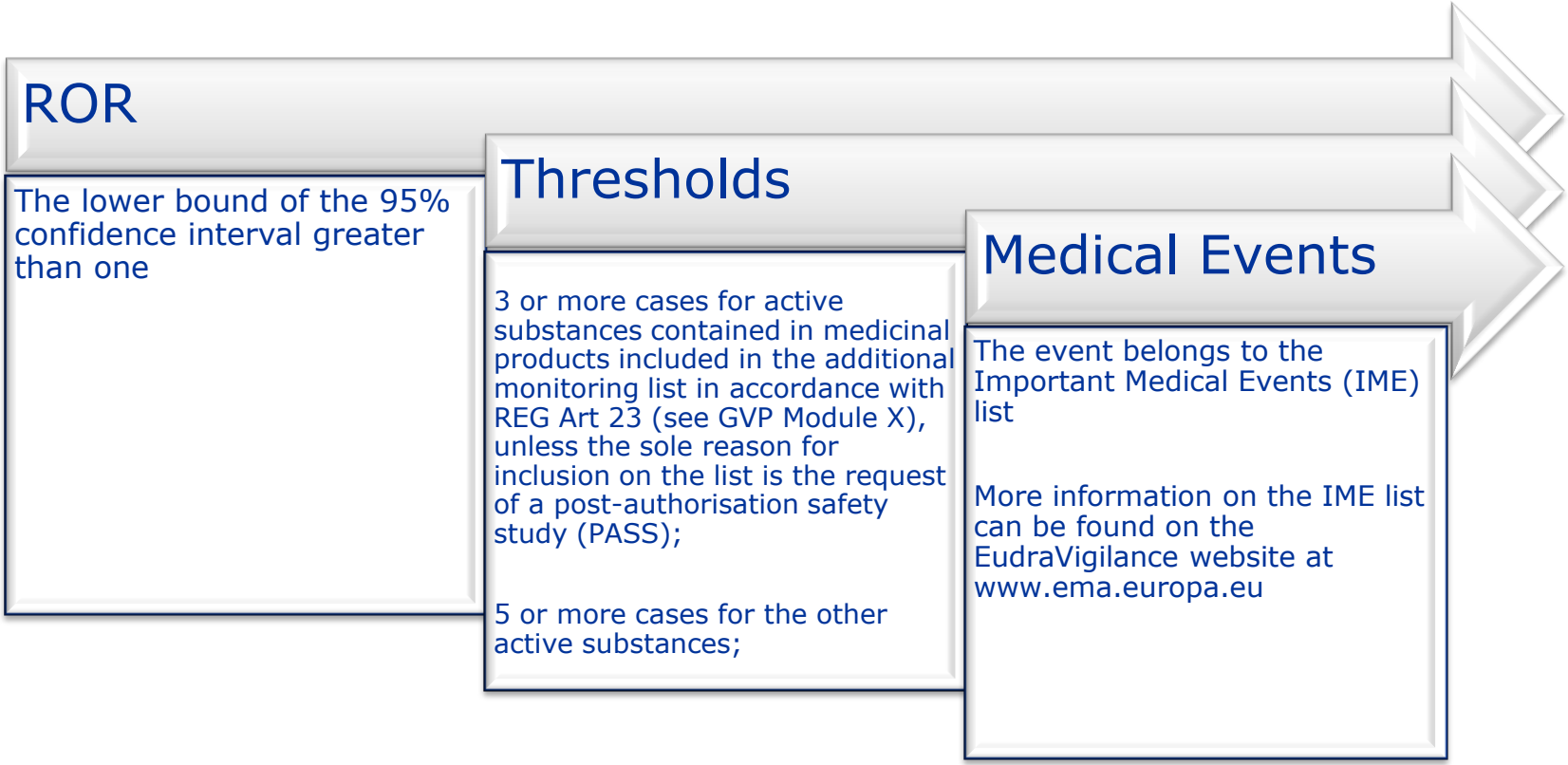
This example provides us with the 'idea' that nausea in relation to product X is reported 3 times more than expected

a	15 reports of nausea with the medicinal product X
b	100 reports with medicinal product X and no event of nausea
c	5,000 reports of nausea reported with all other medicinal products in the database (reports with medicinal X among other products are excluded)
d	100,000 reports with all other medicinal products in the database not including nausea (reports with medicinal X among other products are excluded)

Signals of disproportionate reporting – the concept

- A set of rules, based on the observed value of the disproportionality statistic and, usually, also on other statistics (e.g. number of cases reported), is applied in EVDAS to indicate when a given DEC should be highlighted for further analysis. When this occurs it is often referred to as a signal of disproportionate reporting (SDR).

Definition of an SDR in EV – General population

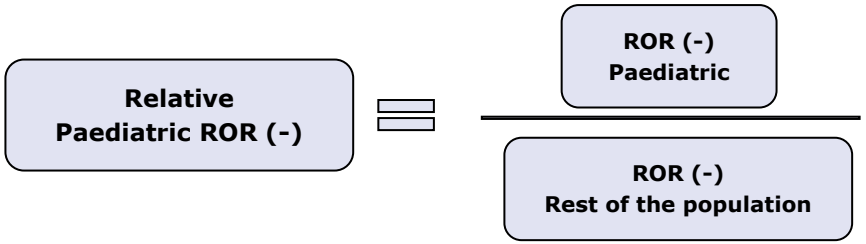


Subgroup analysis

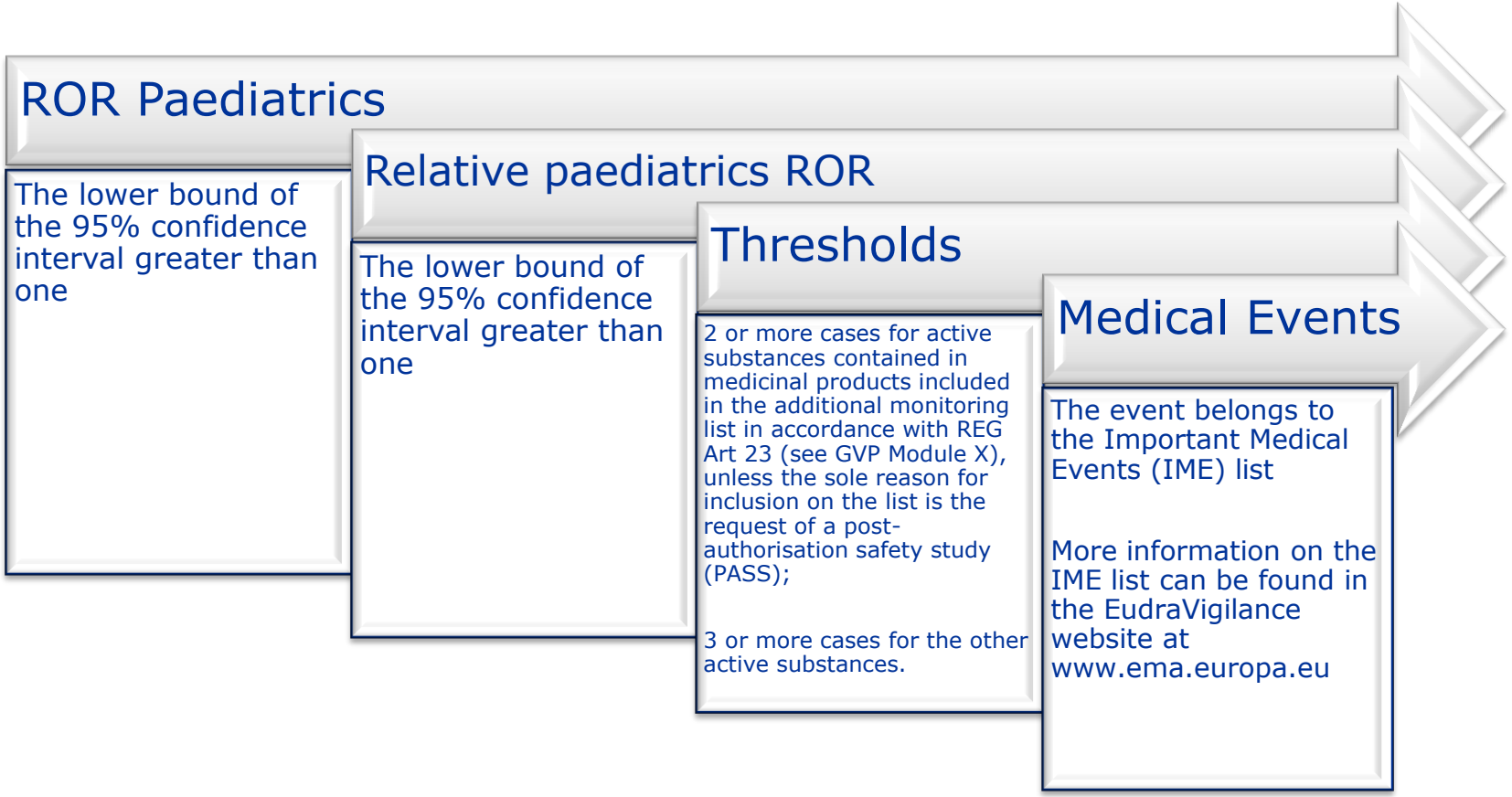
- The concept of subgrouping consists on calculating the disproportionality measure within each of the subgroups defined by the covariates. The aim is to consider the diversity and potential confounding factors within the dataset.
- An SDR is considered only when the conditions for an SDR are met within any subgroup.
- The exclusion of litigation cases and the use of subgrouping by geographical region is implemented in the eRMR. The ROR is calculated for the following regions: Europe, North America, Japan, Asia and Rest of the world.
- An SDR is considered in the eRMR when there is an SDR in at least one of those regions.

Specific patient populations – Paediatrics (< 18 year-old)

- Disproportionality analysis can be applied to cases relating to children in order to increase the ability to detect signals in the paediatric population.
- The method of disproportionality is also the ROR.
- Within-group disproportionality is also applied so only disproportionalities significantly higher than those in the non-paediatric group are considered.
- The relative paediatric ROR is calculated based on the following formula:

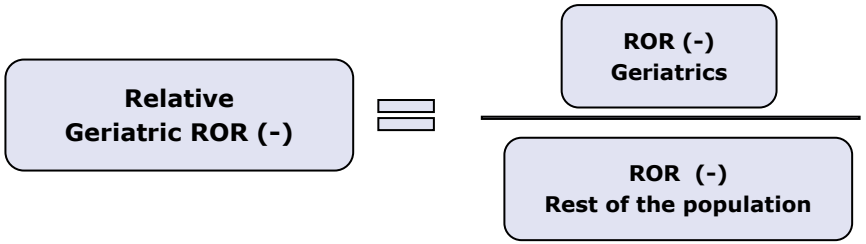


Definition of an SDR for the paediatric population

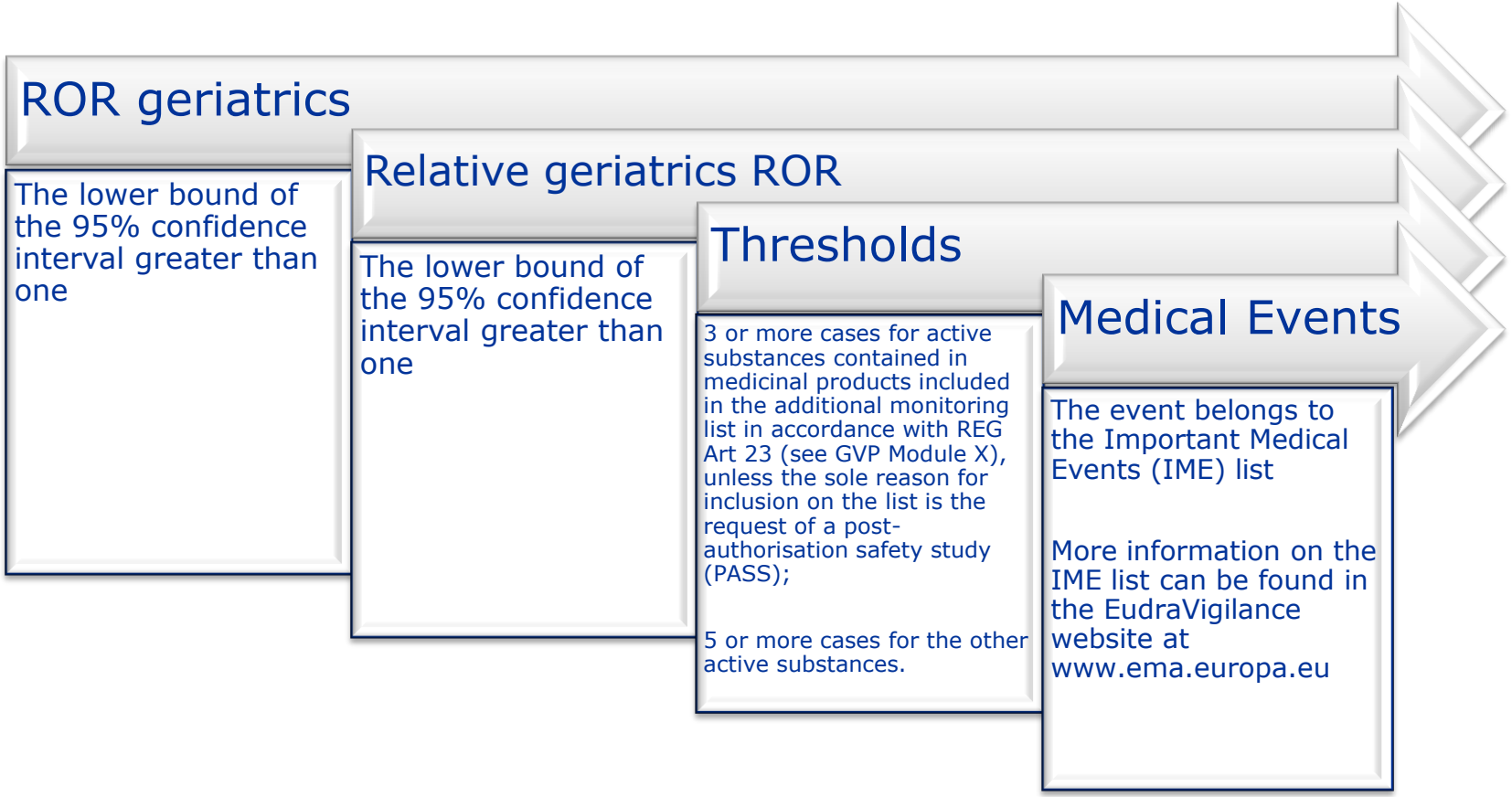


Specific patient population – Geriatrics

- Disproportionality analysis can be applied to cases relating to patients 65 years old or older in order to increase the ability to detect signals in the geriatric population.
- The method of disproportionality is also the ROR.
- Within-group disproportionality is also applied so only disproportionalities significantly higher than those in the non-geriatric group are considered.
- Relative geriatric ROR is calculated based on the following formula:



Definition of a SDR for the geriatric population



Other areas of interest

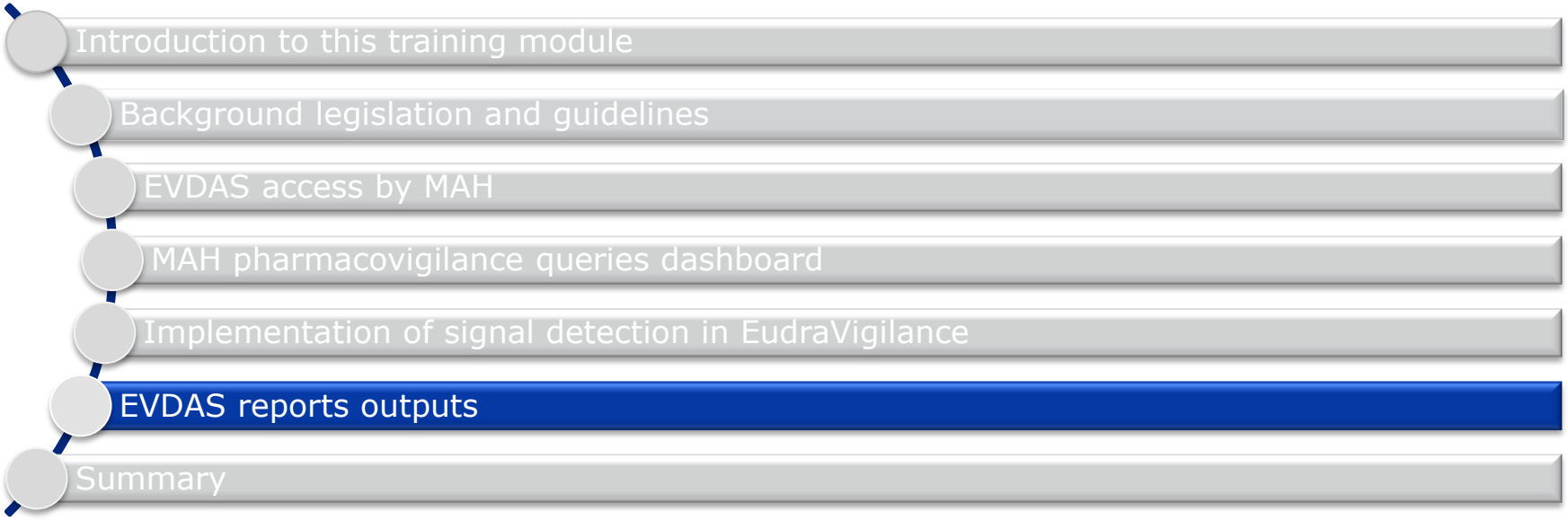
- In the eRMR, the following information is separately visualised and highlighted for each DEC when new reports are submitted:
  - Medication error
  - Positive re-challenge
  - Literature cases.

Section Summary

In this section you obtained an understanding of:

- How statistical signal detection is implemented in EudraVigilance
- The concept of the ROR
- Definitions of signals of disproportionate reporting (SDR)
- Approaches for special populations

Content Summary



Section Overview

- In this section we will explore in detail the EVDAS report outputs for you to get a better understanding of:
  - The eRMR as a tool for signal detection
  - The line listing and the fields included
  - How to retrieve the ICSR forms
  - Data included in the ICSR forms

The eRMR

The eRMR

- eRMR is a tool for signal detection in EudraVigilance and facilitates monitoring the safety of medicines.
- Displays summary statistics on both the new cases and cumulative cases and therefore permits for continuous monitoring of the database.

Be aware that the eRMR is not a tool for signal validation or evaluation for which more extensive review of the data and analysis are required.

The eRMR

- To take advantage of all the possibilities offered by the eRMR, users are advised to export the data in the available formats so that the data can be manipulated appropriately.
- The illustrations and instructions provided in this section are based on an eRMR exported in Excel format.

Be aware that the data provided in the following screenshots is only for the purpose of training and is not real data.

The eRMR - DEC

- The eRMR is structured at drug-event combination level (DEC), each line of the eRMR contains the name of the drug (active substance high level) and the name of the event/reaction (MedDRA PT).

Active Substances	SOCs	HLGTs	HLTs	SMQ Broad	SMQ Narrow	PTs
Cladribine	Gastr	Gastrointestinal Inflammatory Conditions	Gastritis (Excl Infective)		Gastro_nonspec_inflam & Dysf_cond	Gastritis
Cladribine	Gastr	Gastrointestinal Signs And Symptoms	Gastrointestinal And Abdominal Pains (Excl Oral And Throat)		Gastro_nonspec_inflam & Dysf_cond	Abdominal Pain
Cladribine	Gastr	Gastrointestinal Signs And Symptoms	Gastrointestinal And Abdominal Pains (Excl Oral And Throat)		Gastro_nonspec_inflam & Dysf_cond	Abdominal Pain Upper

eRMR - MedDRA

Active Substances	SOCs	HLGTs	HLTs	SMQ Broad	SMQ Narrow	PTs	IME / DME
Gefitinib	Gastr	Exocrine Pancreas Conditions	Acute And Chronic Pancreatitis	Drug reaction with eosinophilia and systemic symptoms syndrome	Acute Pancreatitis	Pancreatitis	Ime / Dme
Gefitinib	Gastr	Exocrine Pancreas Conditions	Acute And Chronic Pancreatitis	Drug reaction with eosinophilia and systemic symptoms syndrome	Acute Pancreatitis	Pancreatitis Acute	Ime / Dme
Gefitinib	Gastr	Gastrointestinal Inflammatory Conditions	Colitis (Excl Infective)		Agranulocytosis	Neutropenic Colitis	Ime / Dme

IME List

Important medical event list

The EudraVigilance Expert Working Group has coordinated the development of a list of important medical event (IME) terms, together with the criteria to facilitate its maintenance.

The list aims to facilitate the classification of suspected adverse reactions as well as aggregated data analysis and case assessment for the day-to-day pharmacovigilance activities of stakeholders in the EU. The list is for guidance purposes only. To submit any comments on the IME list, send an email to: medraimelist@ema.europa.eu.

- Important medical event terms list (MedDRA version 19.1)
- Inclusion and exclusion criteria for the "Important Medical Events" list

DEM list

Designated medical events (updated)

EMA has developed a list of designated medical events containing **medical conditions** that are inherently **serious** and often medicine-related:

EMA designated medical event list

It does not address product specific issues or medical conditions with high prevalence in the general population.

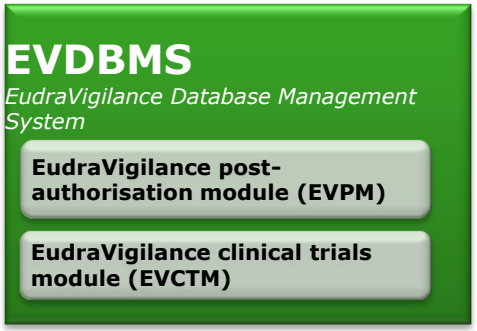
The list contains Medical Dictionary for Regulatory Activities (MedDRA) terms and serves as a **safety net in signal detection.** EMA and Member States use it to focus on reports of suspected adverse reactions that deserve special attention, irrespective of statistical criteria used to prioritise safety reviews.

The designated medical event list is one of the tools the European medicines regulatory network uses and is **not intended as a comprehensive list** of terms for signal detection activities.

EMA has published the list to ensure its approach is transparent. It is subject to review in light of further experience with its use.

eRMR – Number of cases

- The figures displayed in the columns of the eRMR are computed from the EudraVigilance Post-Authorisation Module (EVPM).



eRMR – Number of cases

New EVPM	Total EVPM	New EEA	Tot EEA	New HCP	Tot HCP	New Serious	Tot Serious	New Obs	Tot Obs	New Fatal	Tot Fatal	New Med Err	Tot Med Err	New + RC	Tot + RC	New Lit	Tot Lit
0	1	0	1	0	1	0	1	0	0	0	0	0	0	0	0	0	0
0	2	0	2	0	2	0	2	0	0	0	2	0	0	0	0	0	0
0	1	0	1	0	1	0	1	0	0	0	1	0	0	0	**0**	0	0
0	1	0	1	0	1	0	1	0	0	0	0	0	0	0	0	0	0

eRMR – Special population – paediatrics

- **'New Paed' / 'Tot Paed':** Number of cases referring to patients aged < 18 years;
- '**Ratio ROR(-) Paed vs Others**: lower bound of the 95% confidence interval of the ratio between the ROR for paediatrics and the ROR for the rest of the population;

➢ By selecting Paediatric SDR 'Yes', you will visualise all the SDRs for paediatrics according to the criteria previously described.

New Paed	Tot Paed	Ratio ROR (-) Paed vs Others	Paediatric SDR
2	5	3.26	Yes

eRMR – Special population – geriatrics

- **'New Geriatr' /'Tot Geriatr':** Number of cases referring to patients aged ≥ 65 years;
- **'Ratio ROR(-) Geriatr vs Others':** lower bound of the 95% confidence interval of the ratio between the ROR for geriatric and the ROR for the rest of the population;

➢ By selecting Geriatric SDR 'Yes', you will visualise all the SDRs for geriatrics according to the criteria previously described.

New Geriatr	Tot Geriatr	Ratio ROR (-) Geriatr vs Others	Geriatrics SDR
3	8	12.40	Yes

eRMR - ROR

- The columns with the total number of spontaneous cases per region for the concerned DEC, including the reference period, is used for the calculation of the 95% confidence interval bound of the ROR in the subsequent columns.
- ROR (-) all: 95% confidence interval lower bound of the ROR for the concerned DEC, using all the other DECs available in the database as reference.

New Spontaneous	Tot Sp. Europe	Tot Sp. North America	Tot Sp. Japan	Tot Sp. Asia	Tot Sp. Rest	Tot Spontaneous	ROR (-) Europe	ROR (-) North America	ROR (-) Japan	ROR (-) Asia	ROR (-) Rest	ROR (-) All

eRMR - SDR

- The column ‘SDR’ identifies the DECs with a signal of disproportionate reporting i.e. when the SDR criteria are met in at least one of the regions the SDR column will be populated as yes.
- This will allow the users to prioritise SDRs when screening the eRMR.

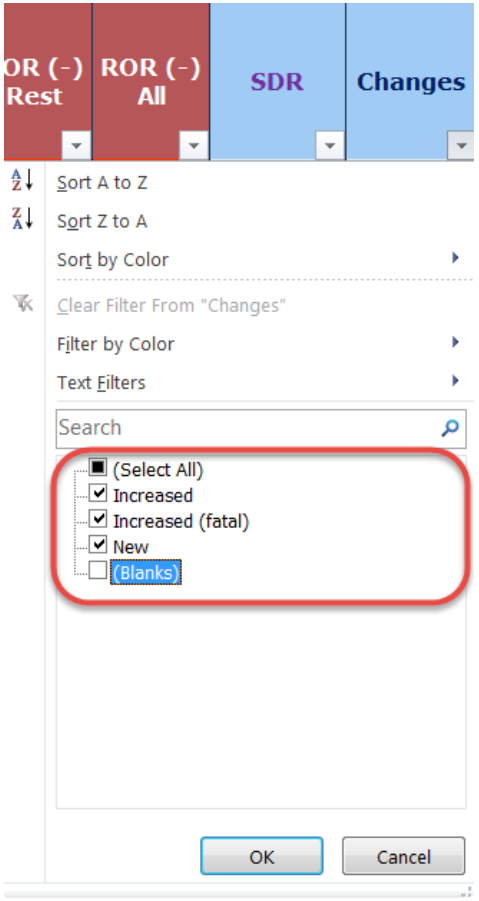
SDR
Yes
No
Yes
No
Yes
No

eRMR - Changes

- **'Changes':** This column indicates all DECs for which new ICSRs (initial or follow-up) or de-duplicated were received in EVPM during the reference period.
- By selecting a value in the drop-down list of the column "Changes", three different filters can be applied:

- **"New"**: DEC appearing in EVPM for the first time;
- **"Increased"**: DEC with an increased number of cases in the column 'Tot EVPM' or for which a follow-up report has been received or a master case (following de-duplication) has been created;
- **"Increased fatal"**: DEC with an increased number of fatal cases or for which a follow-up or a de-duplicated for a fatal case has been received;

- To select only the cases included in the reference period, untick the 'blanks' in the changes options



eRMR - Route Of Administration (ROA) and Indication For Use (IFU)

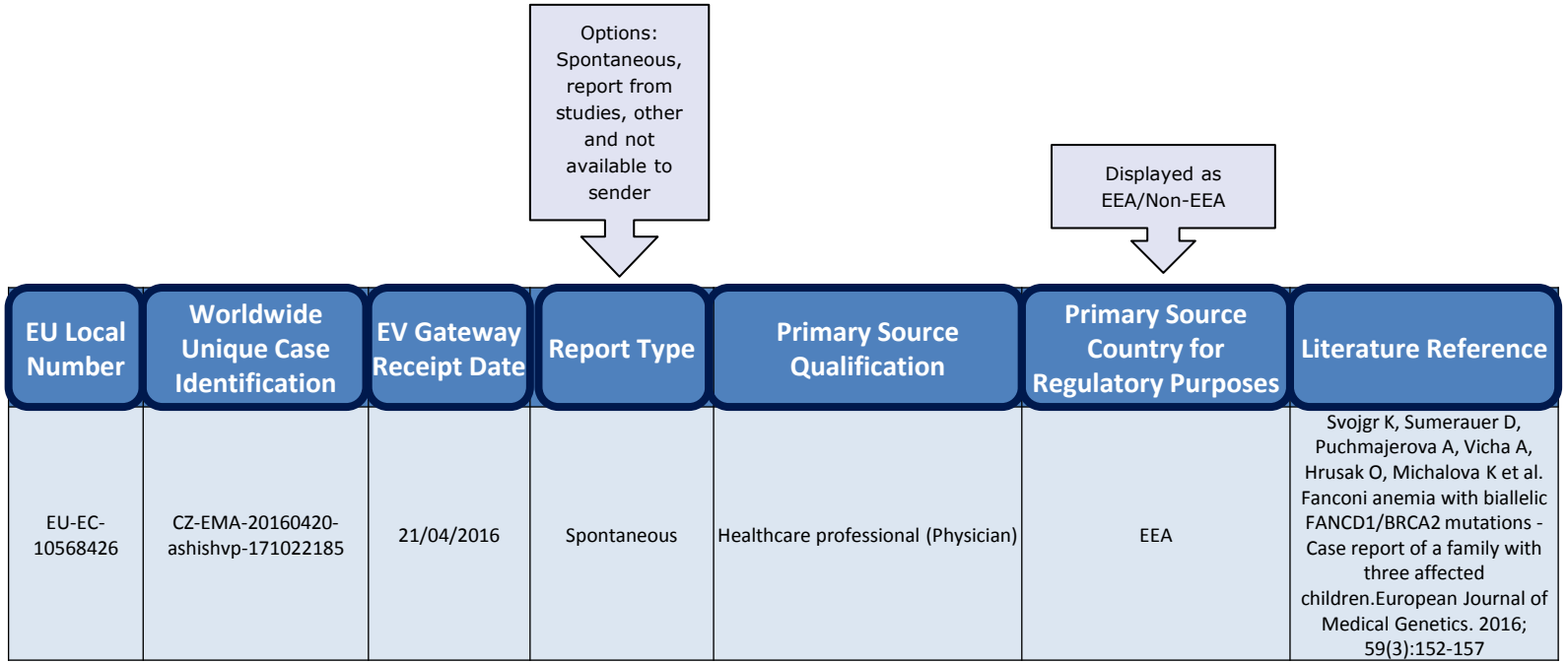
- The eRMR provides number of cases for the specific DECs stratified by ROA and IFU.
- This information should be used with caution as the ROA and IFU may not have been reported in some cases.
- The number of cases with unknown ROA/IFU are also provided.
- As there could be plenty of different routes of administrations and it would not be practical and useful to provide the number of cases per each of the reported ROA, only the number of cases using the 3 most common ROA reported are provided.
- The same approach is followed with the IFU which is provided at the level of the HLGT.

The Line Listing

The Line Listing

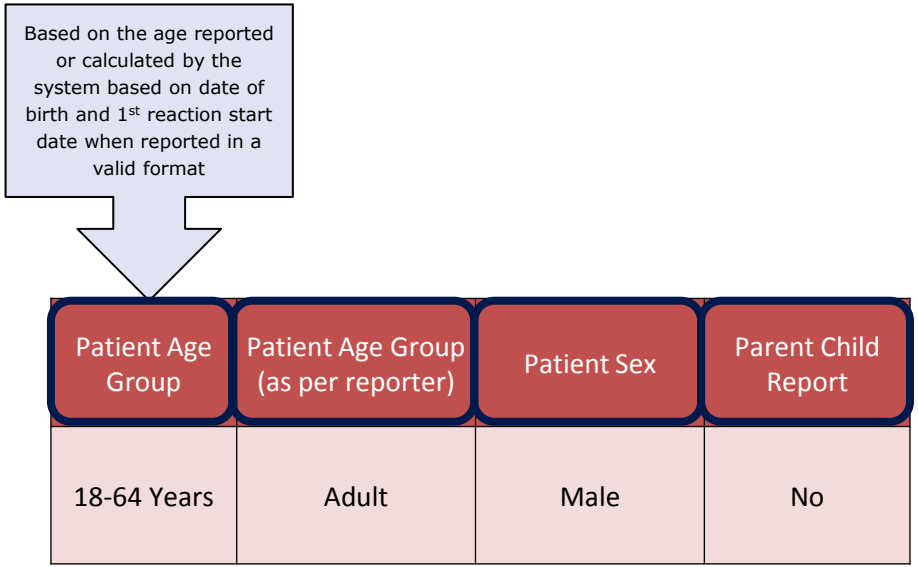
- The line listing provides details of the individual cases according to the EV access policy level 1

Line Listing fields



EU Local Number	Worldwide Unique Case Identification	EV Gateway Receipt Date	Report Type	Primary Source Qualification	Primary Source Country for Regulatory Purposes	Literature Reference
EU-EC-10568426	CZ-EMA-20160420-ashishvp-171022185	21/04/2016	Spontaneous	Healthcare professional (Physician)	EEA	Svojgr K, Sumerauer D, Puchmajerova A, Vicha A, Hrusak O, Michalova K et al. Fanconi anemia with biallelic FANCD1/BRCA2 mutations - Case report of a family with three affected children.European Journal of Medical Genetics. 2016; 59(3):152-157

Line Listing fields



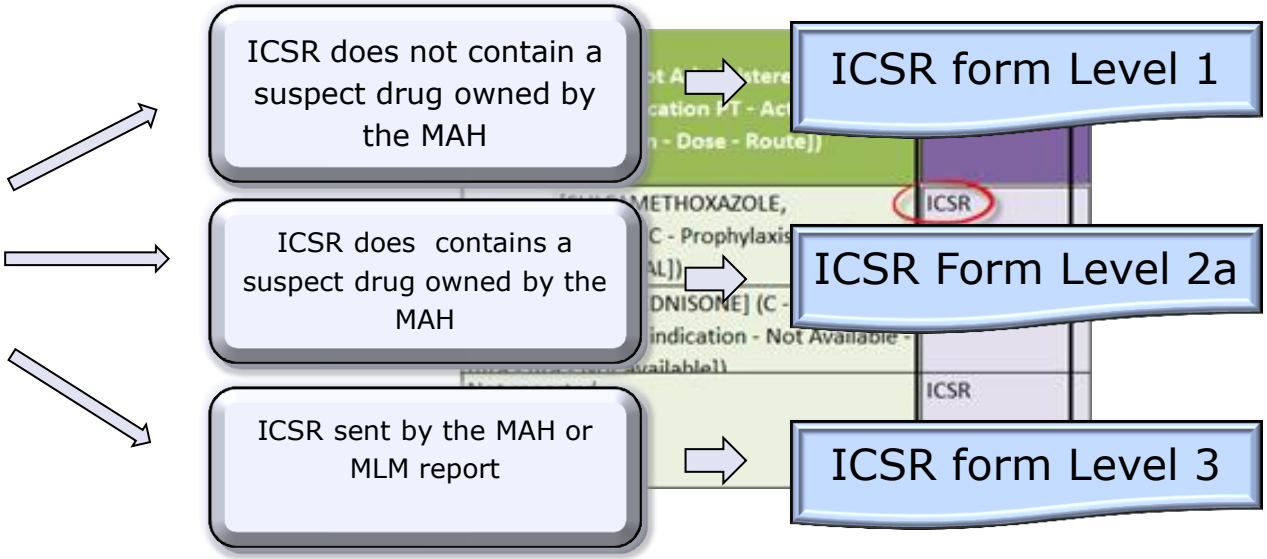
Line Listing fields

Drug characterisation is abbreviated to:
Suspect: S, Interacting: I, Concomitant: C, Drug not administered: N

Therapy duration is populated using the field duration of drug administration (G.k.4.r.6a/b) but if that is not available, then it is calculated from the therapy start date (G.k.4.r.4) and therapy stop date (G.k.4.r.5) provided that those dates are submitted in a complete format (DDMMYYYY).

Reaction List PT (Duration – Outcome - Seriousness Criteria)	Suspect/interacting Drug List (Drug Char - Indication PT - Action taken - [Duration - Dose - Route])	Concomitant/Not Administered Drug List (Drug Char - Indication PT - Action taken - [Duration - Dose - Route])
Nausea (n/a - Not Recovered/Not Resolved - Caused/Prolonged Hospitalisation) Vomiting (n/a - Not Recovered/Not Resolved - Caused/Prolonged Hospitalisation)	[MERCAPTOPURINE MONOHYDRATE] (S - Autoimmune hepatitis - Drug withdrawn - [n/a - n/a - Not available])	[SULFAMETHOXAZOLE, TRIMETHOPRIM] (C - Prophylaxis - Unknown - [n/a - 140mg - ORAL])

Link to ICSR form



The ICSR Form

ICSR form

- Following the implementation of the ICH-E2B(R3) format in EudraVigilance, the new ICSR form has been created to provide a readable format for the E2B(R3) data elements.
- The ICSR form replaces the CIOMS I previously retrieved from the database under R2 format.
- The ICSR form does not contain the reported information for all possible E2B data fields but rather a selection of fields considered most relevant for safety assessment.
- In general the data elements are populated in the form in the same way (text, numbers) as they have been reported, sometimes abbreviations are used. Moreover some fields are populated following a calculation of specific fields following the same rules as in the line listing (e.g. therapy duration).
- The ICSR is provided in PDF format.

ICSR Form – Format

- The data fields provided in the ICSR form are structured and displayed in a way that facilitates the analysis of the data and provides the user with the key elements to assess the temporal and causal association between the drugs and the ADRs.
- Fields are grouped into logical sections (e.g. drug, reaction, medical history), so that the user can easily visualise all the available information for a specific topic.
- All the ICSR forms follow the same format regardless of cases submitted under R2 or R3 terminology but users should consider when analysing the data that legacy cases were migrated to the new R3 format.

ICSR Form – Dynamism

- The are some core sections in the form that will always be present. This is to make the form consistent and recognisable by the users; these sections are: general information, Patient, Reaction, Drug and Case narrative.
- The rest of the sections follow a specific dynamism. That means that if no data has been provided for the entire section, that section is not populated in the form. This is to avoid having completely empty sections.
  - Example: If the case is not fatal and therefore no information is provided in the data elements related to death, the section "Death" is not populated.

ICSR form – Sections

- The following slides provide a general overview of the sections populated in the ICSR form level 2a

ICSR form Level 2a

EUROPEAN MEDICINES AGENCY

General information and Patient's details

General Information	
Worldwide Unique Case Identification Number	JP-Beta-lactam-3462832
Sender type	Pharmaceutical Company
Sender's Organisation	Beta-lactam antibiotics S.L.
Date Report Was First Received from Source	10/11/2002
Date of Most Recent Information	10/11/2002
Type of Report	Report from study
Primary source country	JP
Study registration number	983200163
Study Name	Study for mitocho opathies
Study Type	Other studies
Reporter's qualification	Physician, Consumer
Case serious?	Yes
Medically confirmed?	Yes

Fields on the study details do not appear in the spontaneous cases

Patient				
Age	**Age Group**	**Sex**	**Weight**	**Height**
10	Neonate	Female	53.25 kg	102 cm

ICSR form Level 2a

Reaction

As serious criteria is reported at reaction level in R3 format, the cases migrated from R2 will populate the seriousness criteria (reported at case level) for all the reactions reported in the case

Reaction / Event

MedDRA LLT	Start Date	Stop Date	Duration	Outcome	Seriousness*
Drug reaction with eosinophilia and systemic symptoms	01/08/2002	31/08/2002		not recovered/not resolved/ongoing	death, life threat., hospital., congen.
Mitochondrial encephalomyopathy with lactic acidosis and stroke-like episodes	05/06/1980			not recovered/not resolved/ongoing	death, life threat., congen.
End stage liver disease	20/08/2002			fatal	death, disability, other
B-immunoblastic lymphoma (Kiel Classification) refractory				recovered/resolved	life threat., other

ICSR form

Drug information

Dynamic field: The column is not populated if no data is reported

Dynamic field: Only for Parent/child reports

Drug Information

Role†	Drug	Start Date	S	uration	Dose	Uni	Action taken
S	Avastin 25 mg/ml RECODED	15/01/1992	0	15d	10 mg/kg		Drug withdrawn
C	Epilim Chrono 200 mg RECODED						Dose reduced

Based on R3 data elements G.k.10.r and G.k.11 (free text) to capture additional information not covered by other section [e.g. 1=counterfeit, 7=Medication error]

Drug Informat

Info‡	Drug		Cumul. dose to 1st Reaction	Pharm. Form	Route of Admin.	Parent Route of Admin.	Batch / Lot #
7	Avastin	cell	1200 mg	Concentrate for solution for infusion	transplacental	intravenous	AO852369
	Epilim Chrono 200 mg RECODED	Clonic seizures	15 g	Prolonged Release Tablets			123654PP

Additional Information on Drug
This was an unfortunate medication error

ICSR form

Temporal association

Reaction / Event					
MedDRA LLT	**Start Date**	**Stop Date**	**Duration**	**Outcome**	**Seriousness***
Drug reaction with eosinophilia and systemic symptoms	01/08/2002	31/08/2002	30d	not recovered/not resolved/ongoing	death, life threat., hospital., congen.
Mitochondrial encephalomyopathy with lactic acidosis and stroke-like episodes	05/06/1980			not recovered/not resolved/ongoing	death, life threat., congen.
End stage liver disease	20/08/2002			fatal	death, disability, other
B-immunoblastic lymphoma (Kiel Classification) refractory				recovered/resolved	life threat., other

Drug Information							
Role†	**Drug**	**Start Date**	**Stop Date**	**Duration**	**Dose**	**Units in Interval**	**Action taken**
S	Avastin 25 mg/ml RECODED	15/01/1992	01/02/1992	15d	10 mg/kg	1 per 2w	Drug withdrawn
C	Epilim Chrono 200 mg RECODED						Dose reduced

Time to onset and rechallenge

Calculation of the Time to Onset (TTO):

- Difference between the reaction start date (E.i.4) and earliest therapy start date (G.k.4.r.4).
- If the earliest therapy start date is not provided, or it is not provided in a valid format, but there are subsequent therapies valid dates provided, then the calculation of TTO will not take into account those consecutives dates, otherwise the information provided will not be a real TTO.
- If TTO cannot be calculated as above, the value for G.k.9.i.3.1a/b 'Time Interval between Beginning of Drug Administration and Start of Reaction / Event' is used to populate this field.

Time-to-Onset and Rechallenge matrix table

Reaction/Event (MedDRA LLT)	Drug	TTO	Rechallenge?/Reaction recurred?
Drug reaction with eosinophilia and systemic symptoms	Avastin 25 mg/ml Epilim Chrono 200 mg	187d 186d	No/NA Yes/Yes
Mitochondrial encephalomyopathy with lactic acidosis and stroke-like episodes	Avastin 25 mg/ml Epilim Chrono 200 mg	125d 140d	Yes/No No/NA
End stage liver disease	Avastin 25 mg/ml Epilim Chrono 200 mg	20d 123d	Yes/No No/NA
B-immunoblastic lymphoma (Kiel Classification) refractory	Avastin 25 mg/ml Epilim Chrono 200 mg	20 hours 123d	Yes/No No/NA

Medical history, concurrent conditions and past drug history

Relevant Medical History and Concurrent Conditions

MedDRA LLT	Start Date	End Date	Continuing	Family History	Comments
Atrial fibrillation	10/10/1995		Yes	Yes	The patient was diagnosed with atrial fibrillation in another hospital and no records are in our files
	04/01/1996		No		The pneumothorax was a spontaneous pneumothorax and the patient had to be intubated for more than a week.
Varicella		05/10/1999	No		It was unknown if the patient had been immunised against the virus

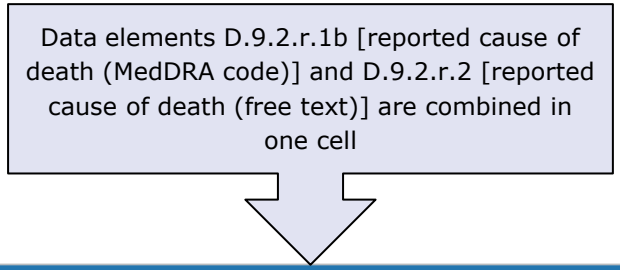
Dynamic field: captures information about other medical history that cannot be coded

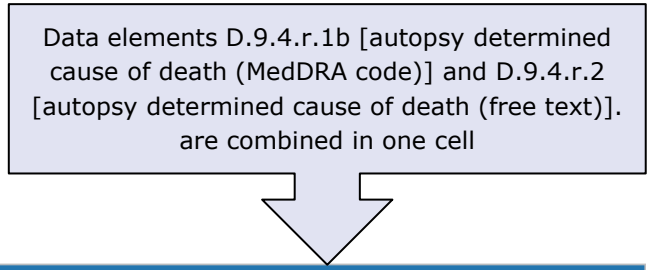
Text for Relevant Medical History and Concurrent Conditions (not including reaction / event)
Unclear if the patient had surgeries in the past

Past drug history

Drug	Start Date	End Date	Indication	Reaction
Cotrimoxazole	01/08/1994	31/09/1994	Acute pulmonary histoplasmosis	Eye disorder
Acetylsalicylic acid	05/05/1993		Headache	Gastrointestinal disorder

ICSR form
Death





Death			
Date of Death	**Reported Cause**	**Autopsy done?**	**Autopsy-determined Cause of Death**
31/08/2002	Pancreatic cancer	Yes	Pancreatic cancer resectable

ICSR form Level 2a – Main Sections

Literature and comments

Literature Reference

Mudalel ML, Dave KP, Humme JP, Solga SF. N-acetylcysteine treats intravenous amiodarone induced liver injury. World Journal of Gastroenterology 21: 2816-2819, No. 9, Mar 2015

Trikudanathan G, Arain M, Mallery S, Freeman M, Attam R. Endoscopic necrosectomy in children. Journal of Pediatric Gastroenterology and Nutrition 59: 270-273, No. 2, Aug 2014

Reporter's Comments

"Gloria statuitque simul uenarum finem castellum ad ostium tabernaculi. Byquinis reales, videre possent gypsy at digitis uenarum inspicere.""Removeatur Science has distantias», super Melquiades. ""Mox homoVides quid usquam gentium domi relicto. ""A meridieDemonstratio magnificantes vitrum cum giganteas incendio miram fecit: multum illiin medio plateae et paleas videlicet radios succenderuntsolar. José Buendía Arcadio qui ad consolacionem inriti magnetesIpse armatus Inuentionem multumque fatigatus noua belli usu. Melquiades rursus temptaret";

Sender's Diagnosis / Syndrome / or Reclassification of Reaction / Event (MedDRA LLT)

hepatic failure

Sender's Comments

hepatic failure

Laboratory test

populated using data elements F.r.3.2 [Test Result (value / qualifier)] combined with element F.r.3.2. [Result Unstructured Data (free text)] which is provided in brackets.

Laboratory Test

Test Name	Test Date	Results	Normal High Value	Normal Low Value	Comments
blood pressure	01/01/2009	90/170 mm[Hg]	70 mm[Hg]	140 mm[Hg]	hormally the blood pressure well controlled
Drug-induced lymphocyte stimulation test	15/08/2002	positive for bevacizumab			The test was done in another lab
Bilirubin conjugated	25/08/2002		17 umol/L	5 umol/L	
Platelet count	10/08/2002		410 10*9/L	150 10*9/L	maybe this could be a reaction to chemotherapy but we don't have baseline values

ICSR form Level 2a

Parent – child

Information Concerning the Parent for a Parent-Child/Foetus Report

Parent

Age	Weight	Height	Sex	Last Menstrual Period Date
30	65 kg	169 cm	Female	08/08/2001

Relevant Medical History and Concurrent Conditions of the Parent

MedDRA LLT	Start Date	End Date	Continuing	Comments
Malignant hypertension	01/06/1956		Yes	The mother had uncontrolled hypertension for several years
White coat hypertension	05/06/1980	18/09/1980	No	

Past Drug History of the Parent

Drug	Start Date	End Date	Indication (MedDRA Term)	Reaction (MedDRA LLT)
Alimta Recoded	01/01/2009	01/01/2009	Asbestosis	Breast external beam radiation therapy
Amiodarone tablets RECODED	15/12/1986	15/12/1989	Borderline hypertension	Pericoronitis
Avloclor 250 MG RECODED				

Text for Relevant Medical History and Concurrent Conditions of the parent (not including reaction / event)
Unclear if the parent had surgeries

ICSR form
Related reports

Related Reports	
Relation	**Case Identifier**
Duplicate	Hospital La Princesa
Duplicate	Red Cross International
Duplicate	FDA
Linked	GB-London- 987654
Linked	ES-Madrid-789456
Linked	IT-Rome-741258

Full description of the ICSR form is provided in the User Manual:

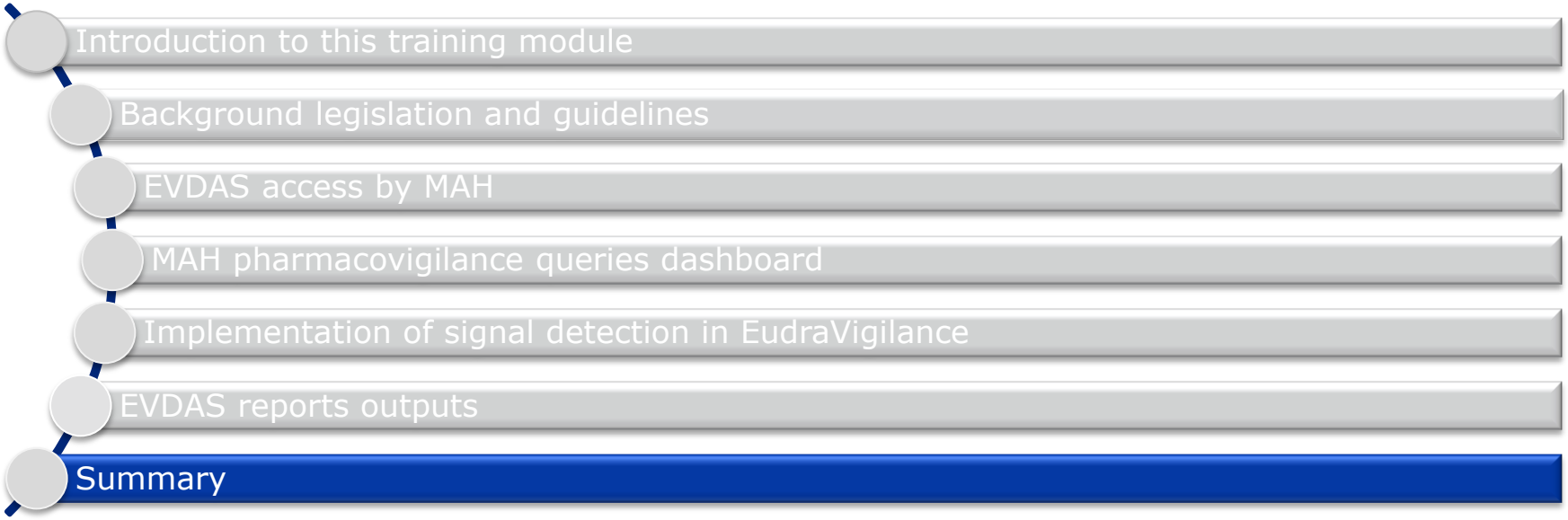
EV-G6 - ICSR Form

Section Summary

In this section you obtained an understanding of:

- The eRMR as a tool for screening the data in EudraVigilance
- Details of the line listing to assess the individual cases
- Details of the ICSR form

Content Summary



Summary of EV-M5b

We are now at the end of the training Module EV-M5b, which provided you the basis for:

- Access to EudraVigilance data by MAHs
- The EVDAS interface to retrieve the data in EudraVigilance
- The MAH Pharmacovigilance queries dashboard
- Understanding how statistical signal detection is implemented in EudraVigilance
- Understanding the eRMR, the line listing and the ICSR Form

Supporting Documents (1)

Documentation	Description
Guideline on good pharmacovigilance practices: Module IX – Signal management *Revision 1 in draft*	Describes the signal management process in the EU
Addendum I to GVP Module IX Draft	Details of the methodological aspects of signal detection from spontaneous reports of suspected adverse reactions

Supporting Documents (2)

Documentation	Description
Screening for adverse reactions in EudraVigilance	Describes the methods of statistical signal detection in EudraVigilance
EudraVigilance stakeholder change management plan	Details the changes taking place in the EudraVigilance system and to the process of reporting Individual Case Safety Reports (ICSRs)

Supporting Documents (3)

Documentation	Description
European Medicines Agency policy on access to EudraVigilance data for medicinal products for human use (EudraVigilance Access Policy)	• EMA has revised the EudraVigilance access policy ahead of implementing the new EudraVigilance system in 2017 • This revised access policy was adopted by the EMA Management Board in December 2015 and will enter into force six months after the Management Board announces that the EudraVigilance database has achieved full functionality, based on an independent audit report in 2017

Where can I get support if needed?

EudraVigilance Registration

- Email - eudravigilanceregistration@ema.europa.eu
- Tel - 44 (0) 20 3660 7523

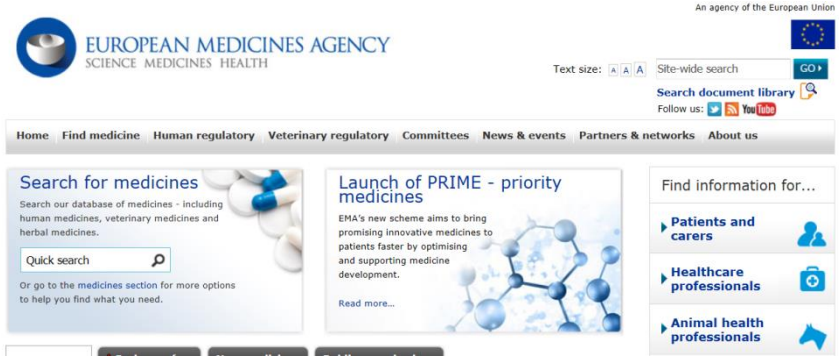
EudraVigilance Operations and IT Operations

- Visit the EMA Service Desk portal: https://servicedesk.ema.europa.eu
- Urgent helpline for technical enquiries: +44 (0)20 3660 8520

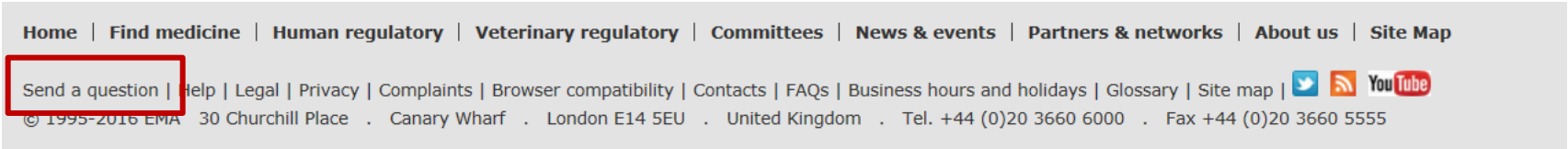
Where can I get support if needed?

Pharmacovigilance operations

- Send a question to EMA (accessible from the EMA homepage)



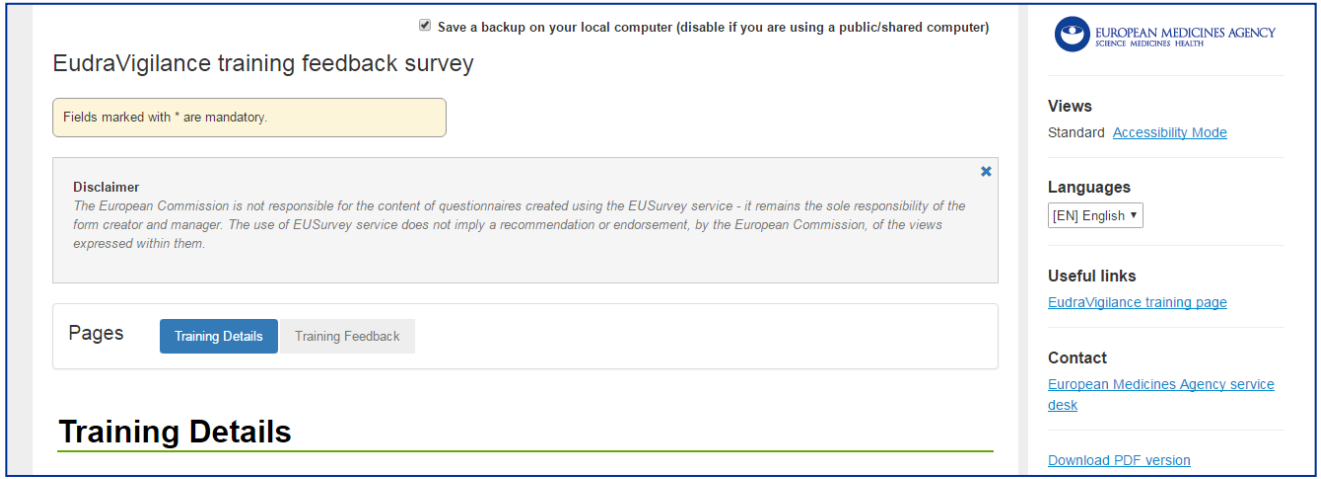
Web address:
http://www.ema.europa.eu/ema/index.jsp?curl=pages/about_us/landing/ask_ema_landing_page.jsp&mid=WC0b01ac05806499f0



Feedback

- Please provide us with feedback on this E-learning module and any attendant guidance documents you have viewed by taking the EMA training survey.

- The survey is accessible via this link.



Acronyms

Acronym	Description
ADR	Adverse Drug Reaction
CIOMS	Council for International Organizations of Medical Sciences
DEC	Drug Event Combination
DEM	Designated Medical Event
EEA	European Economic Area
EMA	European Medicines Agency
eRMR	Electronic Reaction Monitoring Report

Acronyms

Acronym	Description
EV	EudraVigilance
EVDAS	EudraVigilance Data Analysis System
EVPM	EudraVigilance Post-authorisation Module
EVWEB	EudraVigilance Web Application
Geriatr	Geriatric
GVP	Good Pharmacovigilance Practices
HCP	Healthcare Professional

Acronyms

Acronym	Description
HLT	High-Level Terms
ICH	International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use
ICSR	Individual Case Safety Report
IFU	Indication for Use
IME	Important Medical Event
IR	Commission implementing Regulation 520/2012
Lit	Literature

Acronyms

Acronym	Description
Med Err	Medication error
MedDRA	Medical Dictionary for Regulatory Activities
NCA	National Competent Authority
OBIEE	Oracle Business Intelligence Enterprise Edition
Obs	Observational
Paed	Paediatric
PASS	Post-authorisation Safety Study

Acronyms

Acronym	Description
PSUR	Periodic Safety Update Report
PT	Preferred Term
QPPV	Qualified Person for Pharmacovigilance
RC	Rechallenge
ROA	Route of Administration
ROR	Reporting Odds Ratio
SDR	Signal of disproportionate reporting

Acronyms

Acronym	Description
SOC	System Organ Class
Sp	Spontaneous
TTO	Time to Onset
xEVMPD	Extended EudraVigilance Medicinal Product Dictionary
SOC	System Organ Class

Thank you for your attention

Further information

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