EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

Work instructions

Title: Key activities when screening the electronic Reaction Monitoring Reports (eRMRs) for new signals		
Applies to: Signal & Incident Management Service (SIM) , Pharmacovigilance & Epidemiology Department		
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1. Changes since last revision

Update to reflect the new instructions in line with the Revision 1 of GVP Module IX and the User Manual User Manual of the electronic Reaction Monitoring Report (eRMR) for National Competent Authorities and EMA.

2. Records

- All eRMR files concerning centrally authorised products (CAPs) are stored in a DREAM folder called "IM RM CAP list" in the following locations: "*Cabinets/03. Pharmacovigilance/PhV - Human/3.3 Signal detection activities/01 Signal detection tracking tools/IM RM CAP list"*
- Signal Notifications sent by each Signal Management Lead (SML) are stored in electronic format in the mailbox: *Public Folders/All Public Folders/Chrono In/EMAILS/H-SD* (H-SD)
- All signals (both under review and already reviewed) are listed in the Signal Detection Tracking Table named "SDMB-IM_RM 2.xls" which is located in DREAM in: *"Cabinets\03. Pharmacovigilance\PhV – Human\3.3 Signal detection activities\01 Signal detection tracking tools\IM RM CAP list*".

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3. Instructions

This WIN provides the general instructions on the main activities to follow before, during and after the screening of the Excel eRMR files and refers to:

- SOP/H/3065 - Periodic signal detection for centrally authorised products based on reaction monitoring reports - which states that the screening of the eRMR is performed by SMLs.
- WIN/H/3287 – Validation of signals from the review of individual cases
- WIN/H/3268 - Maintenance of Signal Detection tracking table
- User Manual on how to screen the electronic Reaction Monitoring Report for National Competent Authorities and EMA – Description of the structure, content and use of the tool for signal detection in EudraVigilance data

This WIN also provides instructions on how to send Signal Notifications in a standardised format to the H-SD mailbox for validation.

These instructions are applicable to once-monthly monitored (RM), every two-week monitored (IM) substances and weekly monitored products in special situation (i.e. pandemic).

3.1. Excel eRMR File Management

The eRMRs files are generated by the Data Standardisation and Analytics (DSA) manager of the I-BD-DSA service and forwarded to the Signal & Incident Management Service (SIM) administrative support for IM or RM substances in line with the agreed time schedule (i.e. dates are planned yearly). The SIM administrative support saves and updates the Excel eRMR files for each Signal Management Leads (SMLs) following the steps described below:

3.1.1. Receiving the eRMR .csv unformatted files by SIM administrative support

When the new non-formatted .csv eRMRs files are created by the I-BD-DSA service, an e-mail is sent to SIM administrative support by the DSA manager. The message contains the locator to the folder in DREAM which contains all non-formatted eRMRs files. The updated eRMRs include the new cases received in EudraVigilance (EV) during the reference period (mentioned in the subject of the email). In case of a technical problem, the DSA Manager informs SIM administrative support of the delay.

3.1.2. Updating the eRMRs in DREAM

SIM administrative support updates the formatted Excel eRMR file saved in DREAM for each SML using the non-formatted eRMRs. Once the files are updated, the SIM administrative support sends an e-mail to all SMLs and lets them know that the Excel eRMRs files are ready for the screening.

3.1.3. Check-out and Check–in the Excel eRMR file in DREAM

Each SML checks-out the Excel eRMR file in DREAM for editing. Once the screening is finalised, the SML checks-in the Excel eRMR file in DREAM. It is a good DREAM practice and it is advisable that SMLs keep the Excel eRMR files checked-in while not working on them to avoid any inconvenience in case of absence.

3.1.4. Exporting the eRMRs to the G:drive

The SIM administrative support sends a reminder via Outlook to all SMLs specifying by when all Excel eRMR files have to be checked-in for the update. The SIM administrative support double-checks whether or not all files are checked-in in DREAM and, should this not be the case, the SIM administrative support re-contacts the concerned SML with a new reminder. Once all Excel eRMRs files are checked-in, the SIM administrative support saves them on the G: drive and informs I-BD-DSA service accordingly.

3.2. Periodicity

The non-formatted .csv eRMR files are produced with the new data corresponding to the period of interest – the so called 'reference period'. The folder contains one file for each SML. The files are named:

- "TO_EXPORT_SML name".XLS

and saved in DREAM in the following location: *"Cabinets/13. Programmes and Projects/zz. Closed projects 2004-2014/EudraVigilance - NEW STRUCTURE/Pharmacovigilance/Data Analysis/SAS analysis/Signal Validation Team - Reaction Monitoring Reports/eRMR_SMI"*

The formatted Excel eRMR files to be used for screening for new signals are named:

- For every two-week monitored products (IM): "IM_SML name".xls
- For once-monthly monitored products (RM): "RM_SML name".xls

and saved in DREAM in the following location: "*Cabinets\03.Pharmacovigilance/PhV – Human/3.3 Signal detection activities/01 Signal detection tracking tools/IM RM CAP list*

3.3. SML's key activities when screening the eRMR

3.3.1. Check-out/Check-in of the Excel eRMR file:

Following the email sent-out by the SIM administrative support (informing that the Excel eRMRs files are updated) the SML can start screening the files.

In line with the timelines set up by the SIM administrative support, the SML ensures the Excel eRMR file is checked in to allow an update of the data. The SIM administrative support will send a reminder by when the eRMR files have to be checked in for the next update (see above section 3.1.4. Exporting the eRMRs to the G: drive)

3.3.2. Retrieving Drug Event Combinations (DECs) flagged as priorities in the eRMR

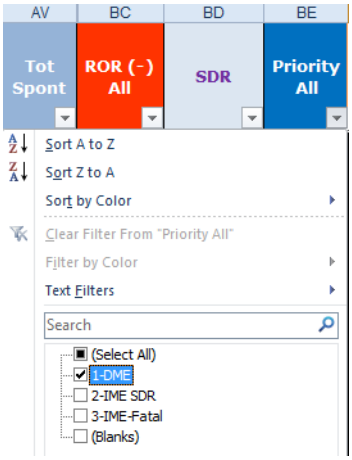
The screening of DECs presented in the eRMR is prioritised according to established criteria e.g. seriousness, high drug attributable risk, previous awareness, statistical relevance etc. (in line with the guidance on 'Screening for adverse reaction in EudraVigilance')[1].

The eRMR contains three "Priority" columns that are designed to facilitate the retrieval of the most relevant DECs for paediatric, geriatric and total population respectively (see eRMR user manual for details on the structure and content of the eRMR files)[2]. Applying filters in these columns enable users

[1] https://www.ema.europa.eu/documents/other/screening-adverse-reactions-eudravigilance_en.pdf
[2] http://bi.eudra.org/templates/PHV%20EVDAS/eRMR%20user%20manual.pdf

to focus on all ADRs of special interests that are received during the reference period and that require to be screening with priority for the identification of a new potential safety signal.

Some DECs are classified with the highest level of priority (i.e. DMEs). For these, SMLs should enter a signal status or a comment in the column BH “comments”. If none of the labels for the column ‘Signal Status’ is applicable (as per the eRMR user manual[3]), a review of the cases or a justification in the column BH ’comments’ (for instance to postpone the review until additional cases/supportive elements become available) is needed. The DME list has been developed to allow the identification of a cluster of reactions that are considered the most important ones to be investigated; thus, this is a mandatory step for all eRMRs.



3.3.3. *Screening the remaining Priorities*

All remaining priorities can be retrieved in the following columns: ‘Priority All’ (2.IME-SDR, 3.IME-Fatal), ‘Priority Paediatrics’ (1.TMEs, 2.IME-SDR) and “Priority Geriatrics” (1.IME-SDR).

Investigation and justification of the DECs classified with these priorities are based on the SML’s clinical judgement.

SOC	SMQ Narrow	PT	IME/ DME	New EV	Tot EV	Tot Fatal	AM OM O	Tot +RC	Tot Lit	Priority Paed	Priority Geriatr	Priority All
Resp	Cardiac Failure - Haemod_oedem _ Eff & Fluid_overload	Acute Pulmonary Oedema	Ime	1	19	8	---	0	3			3-IME-Fatal
Gastr	Haemod_oedem _ Eff & Fluid_overload - Hepatic Disorders	Ascites	Ime	1	74	26	---	1	35	2-IME SDR		3-IME-Fatal

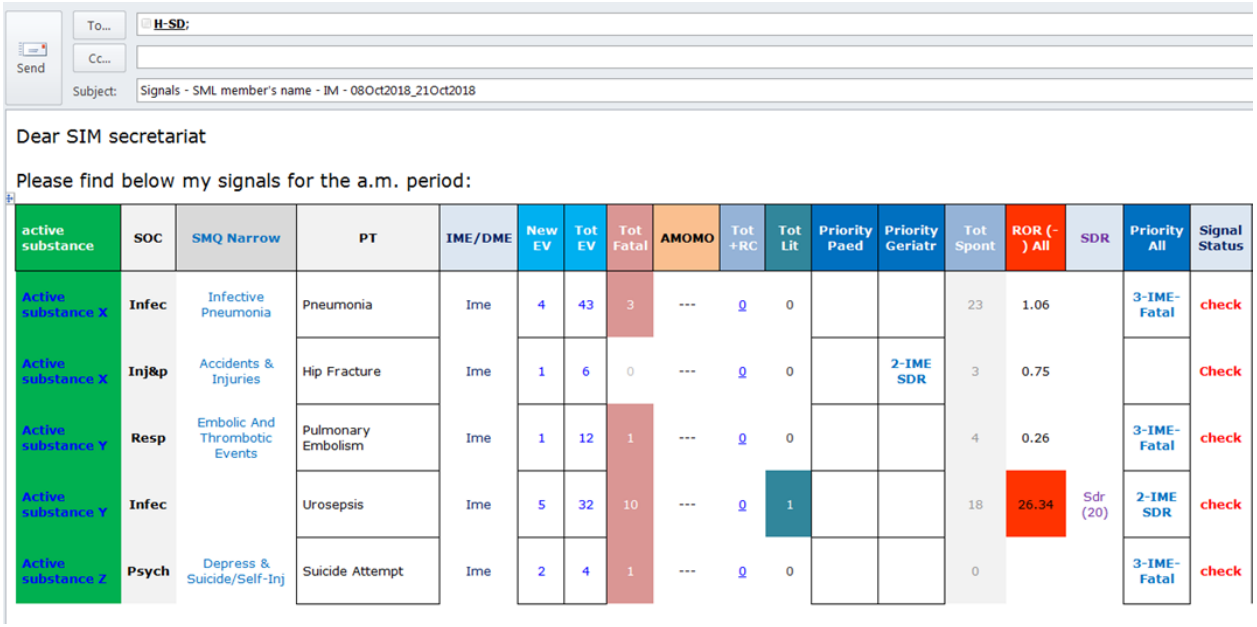
N.B. Identification of signals should be based on all available information in the eRMR received during the reference period and not limited to the priorities. Judgment should be exercised and information of clinical relevance should be identified, even if it does not represent an IME/DME or a SDR.

[3] http://bi.eudra.org/templates/PHV%20EVDAS/eRMR%20user%20manual.pdf

3.3.4. *Transmission of Signal Notification to H-SD*

When the screening of the eRMR is finalised and the Signal Status 'Check' was selected, a review of the cases is expected. In the eRMR set the filters on 'Check' in the column "Signal Status" to select all DECs of interest for which further investigation is required.

To open a PT-signal in H-SD, select the row of the eRMR and include below columns; copy and paste (not as an image) in an email to be sent to H-SD. In order to facilitate the work of the SIM administrative support and the retrieval of messages, indicate in the Subject of the email: Signals - SML's name - RM or IM – Reference period.



active substance	SOC	SMQ Narrow	PT	IME/DME	New EV	Tot EV	Tot Fatal	AMOMO	Tot +RC	Tot Lit	Priority Paed	Priority Geriatr	Tot Spont	ROR (-) All	SDR	Priority All	Signal Status
Active substance X	Infec	Infective Pneumonia	Pneumonia	Ime	4	43	3	---	0	0			23	1.06		3-IME-Fatal	check
Active substance X	Inj&p	Accidents & Injuries	Hip Fracture	Ime	1	6	0	---	0	0		2-IME SDR	3	0.75			Check
Active substance Y	Resp	Embolic And Thrombotic Events	Pulmonary Embolism	Ime	1	12	1	---	0	0			4	0.26		3-IME-Fatal	check
Active substance Y	Infec		Urosepsis	Ime	5	32	10	---	0	1			18	26.34	Sdr (20)	2-IME SDR	check
Active substance Z	Psych	Depress & Suicide/Self-Inj	Suicide Attempt	Ime	2	4	1	---	0	0			0			3-IME-Fatal	check

3.3.5. *Updating the eRMR file column 'Status' and 'Comments':*

Following the review of the cases, the Excel eRMR files need to be updated in line with the conclusions adopted for the concerned signals. The column "Signal Status" should reflect the outcome. The column "Comments" should include the case retrieval date and reflect the conclusion sent to H-SD in the report.

3.4. *Timelines*

3.4.1. *Screening eRMR files*

The eRMR files should be promptly screened in line with the periodicity of the products under monitoring. In case of absence or conflicting priorities or delays, see chapter below (3.7 processes in place in case of SML's absence).

3.4.2. *Signals under review*

The SML should prioritise the finalisation of signal under review (called in the eRMR 'ongoing signals') based on a risk proportionate approach taking into account all the elements supporting causality and seriousness (e.g. when the term is a DME, presence of fatal cases, presence of cases with positive re-challenge etc.)

3.5. Opening signals using overarching MedDRA and non-MedDRA terms

The screening of the eRMR files is generally performed at MedDRA-Preferred Term (PT) level in line with IMI-PROTECT (package 3) recommendation[4].

Therefore, when opening signals triggered by other data sources (e.g. other Regulatory Agency, Literature etc.), the SML should attempt to identify the MedDRA term that corresponds best to the safety concern.

However, in some instances, i.e. to strengthen the signal evaluation strategy, it may be more appropriate to open a signal at a different MedDRA grouping level (i.e. High Level Term (HLT), High Level Group Term (HLGT), System organ class (SOC), or Standardised MedDRA query (SMQ)) or by using a combination of MedDRA terms and/or non-MedDRA terms. In those situations, the use of MedDRA and non-MedDRA overarching terms by the SML can be done to open a signal. The term used to open the signal should be included in the subject field of the email to send the signal validation report to H-SD mailbox

3.6. Internal Audit

In accordance with the agreed improvement action plan following the audit of signal detection in 2010, routine checks are performed every year on an eRMR reference period for each SML, during which he/she was present. The goal of this check is to ensure the quality of the eRMR's review (e.g. double-check that potential signals are not missed)

Below are the key steps:

- The comments received from the eRMR audit are sent directly to the concerned SML.
- The SML can provide justification/explanations with one of the following approch:
    - Open a signal for investigation (in this case, H-SD must be copied so that SIM administrative support can enter the signal in the tracking table, as for any standard signal). SML should clearly instruct the SIM administrative support to open a signal indicating the corresponding MedDRA terms. In this case the process follows the normal course of action when opening signals for review.
    - Provide directly reasons/justifications for not reviewing the concerning signals, as a reply to the audit email, adding : "*No action needed*".
- As a general principle, all reviews/explanations should be documented in the eRMR for regulatory memory.

3.7. Process in case of SML's absence

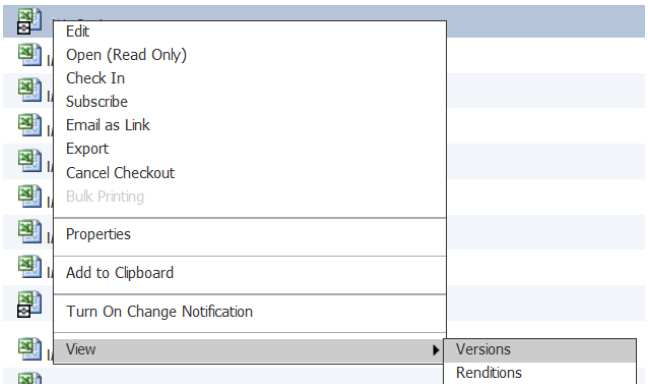
This process applies when the SML is absent for one or more weeks. The SIM administrative support saves in DREAM on a regular basis following earlier agreed schedule the updated version of the Excel eRMR file sent to SIM administrative support by the DSA manager. When the SML is absent during the review of a specific eRMR the retrieval of previous versions is possible following one of the two options below:

[4] http://www.imi-protect.eu/methodsPub.shtml

3.7.1. *Retrieval from DREAM*

The SML visualises and selects from DREAM the version of interest that needs to be screened.

[*Right-click on the Excel eRMR File -> View -> Versions-> Select the version of interest*]



3.7.2. *Retrieval from email*

Prior to the absence, the SML informs the SIM administrative support specifying which version of the Excel eRMR file has to be sent as an attachment by email. When the Excel eRMR file is updated in DREAM with the new data, the SIM administrative support then sends an email to the absent SML with the attached version requested.

Once the SML is back, the different Excel eRMR file versions are retrieved and the screening should be done separately. These versions can also be printed for the review on paper as follow:

[*Select the area of interest -> file -> print area -> set print area -> control + p*]

In order to save 'signal status' and 'comments' to the latest version of the eRMR saved in DREAM, update it with the results obtained from the screening of the previous version/s of the eRMR/s.