22 November 2017
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Information Management Division

EudraVigilance stakeholder change management plan

Project Maintenance Group 1 (for consultation)	15 July 2015
EudraVigilance Expert Working Group (for consultation)	23 September 2015
Signal Management Review Technical Working Group (SMART WG) – Work Stream 1 (for consultation)	7-10 September 2015
Pharmacovigilance Risk Assessment Committee (PRAC) (for consultation)	7-10 September 2015
Implementation Group (IG) (for information)	14 September 2015
IT Directors (for information)	22 October 2015
EU Telematics Management Board (EUTMB) (for information)	15 September 2015
Endorsement by European Risk Management Facilitation Group (ERMS-FG)	12 October 2015
Heads of Medicines Agencies (HMA) (for information)	22 October 2015

30 Churchill Place ● Canary Wharf ● London E14 5EU ● United Kingdom
Telephone +44 (0)20 3660 6000 **Facsimile** +44 (0)20 3660 5555
Send a question via our website www.ema.europa.eu/contact

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Versions

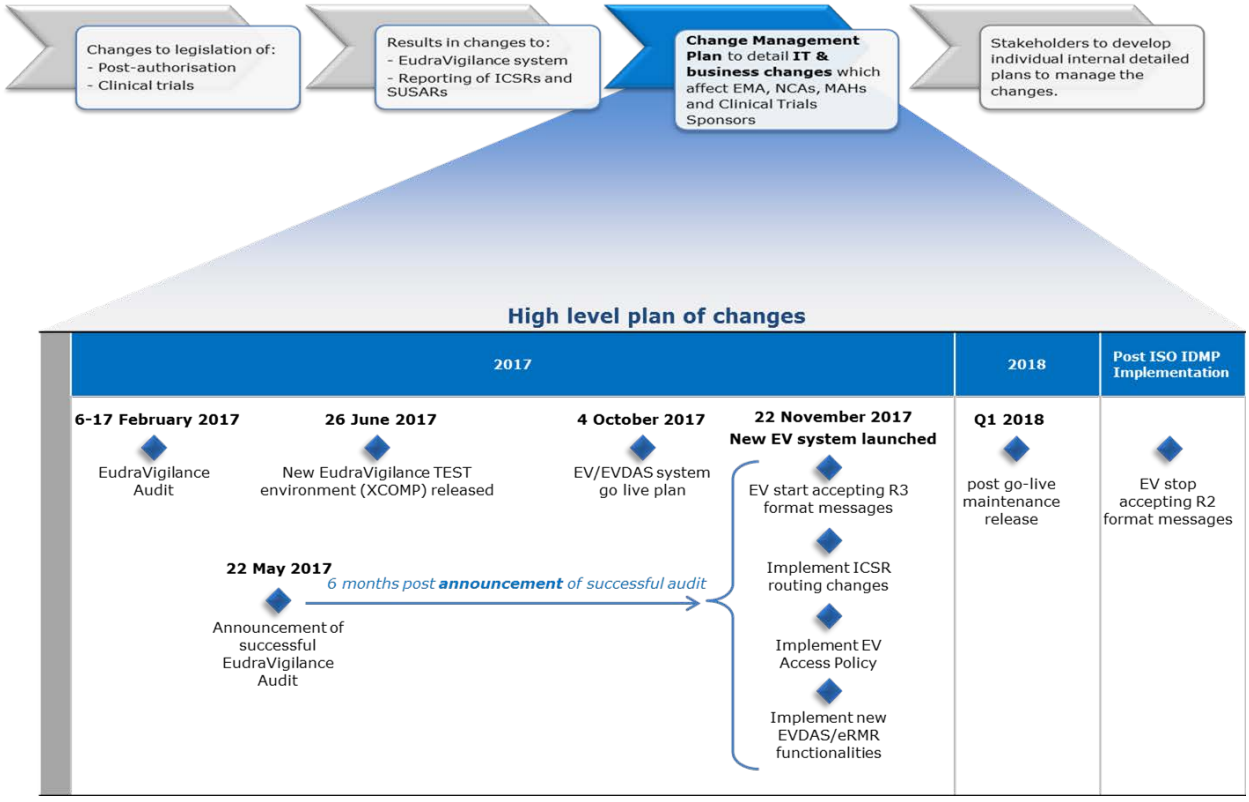
Date	Version number	Summary of changes
26 October 2015		Original document.
1 August 2016	1.0	The first revision of the document has been carried out to include clarifications and updates to: • The EudraVigilance project timeframes • New section on Benefits of the new system • Availability of training materials • The new EudraVigilance helpdesk • Connection of the SPOR project (including ISO IDMP) with EudraVigilance.
23 June 2017	2.0	The second revision of the document has been carried out to include: • Updates on the EudraVigilance project timeframes (high level plan of changes, implementation roadmap, go-live plan) based on the announcement of the EMA Management Board on 22 May 2017 that EudraVigilance has achieved full functionality • Updates on testing with the new EudraVigilance system and user training • Updates on the availability of training materials • A new section dedicated to the EudraVigilance Technical Support Plan and NCA checklist • New sections dedicated to the EudraVigilance testing instructions and checklist for Marketing Authorisation Holders and Sponsors of Clinical Trials in the EEA.
22 November 2017	3.0	The third revision of the document has been carried out to include: • Administrative updates brought by the new EudraVigilance system launch on 22 November 2017 • Introduction of links to the recently published GVP modules, the EudraVigilance go-live plan and the technical note • Update on transitional arrangements for MAHs signal validation process.

1. Executive summary

This document details the changes which were implemented in the EudraVigilance system and changes to the process of reporting Individual Case Safety Reports (ICSRs) as well as Suspected Unexpected Serious Adverse Reactions (SUSARs) related to medicinal products. These changes were brought about by changes to the post-authorisation legislation.

The intended audience of this document were the National Competent Authorities (NCAs), Marketing Authorisation Holders (MAHs), sponsors of clinical trials and the EMA. This document details the IT and business changes that have been made at both European and stakeholder level.

Organisations were advised to use this document as a starting point to develop their own internal plans to manage the changes that occurred on 22 November 2017, once the new EudraVigilance system was moved into production. Following the implementation of the enhanced EudraVigilance system this document will no longer be updated and will be kept for reference purposes.



2. Changes to legislation

This section provides an overview of the main changes introduced through updates to the legislation concerning the EudraVigilance and associated systems.

2.1. Legal requirements

Regulation (EC) No 726/2004, Directive 2001/83/EC, Directive 2001/20/EC, and Regulation (EU) No 536/2014 outline the electronic reporting requirements to EudraVigilance, the data processing network and management system for reporting and evaluating suspected adverse reactions during the

development and following the marketing authorisation of medicinal products in the European Economic Area (EEA).

2.1.1. Post authorisation legal requirement changes

In December 2010 the pharmacovigilance legislation was updated through amendments to Regulation (EC) No 726/2004 and Directive 2001/83/EC. This was followed by the addition of Commission Implementing Regulation (EU) No 520/2012[1] in June 2012.

The main changes to electronic reporting requirements that have been brought about by these amendments to the legislation are:

- Usage of ISO standards in the reporting of ICSRs, ISO ICSR standard 27953-2:2011
- Usage of ISO IDMP terminologies, once available, in the submission of ISO ICSR messages
- EMA medical literature monitoring service
- The audit of the EudraVigilance system
- Simplification of reporting of ICSRs in the EU and forwarding of national cases to the relevant NCA.

There is currently no date from which E2B(R2) cannot be used in the EU, therefore organisations may continue receive and send E2B(R2) as well as E2B(R3) format messages following the new EudraVigilance system implementation.

2.1.2. Clinical trials

There will be no changes to the reporting of suspected unexpected serious adverse reactions during clinical trials until the application of the new Clinical Trial Regulation.

The Clinical Trials Regulation (Regulation (EU) No 536/2014) will apply as from six months after the publication of the Commission notice about the full functionality of the EU portal and database. According to Article 40 of the Regulation (EU) No 536/2014, the Agency shall set up and maintain an electronic database for the reporting of suspected unexpected serious adverse reactions (SUSARs) and annual safety reports. The database shall be a module of the EudraVigilance database.

The main changes to electronic reporting requirements that are planned in relation to clinical trials are:

- Usage of ISO standards in the reporting of SUSARs, ISO ICSR standard 27953-2:2011
- Usage of ISO IDMP set of standards and terminologies, once available, in the submission of ISO ICSR messages
- Simplification of reporting SUSARs in the EU
- Development of a standard web-based structured form for the SUSARs reporting by sponsors to EudraVigilance; this form would be ISO ICSR 27953-2:2011 (E2B(R3)) compliant.

3. Benefits of EudraVigilance 8

The EudraVigilance 8 system will deliver significant benefits to stakeholders including:

[1] http://eur-lex.europa.eu/LexUriServ/LexUriServ.do?uri=OJ:L:2012:159:0005:0025:EN:PDF

New feature	Benefit
• Enhanced signal-detection and data-analysis tools to support safety monitoring directly by Member States and marketing authorisation holders	• Better detection of new or changing safety issues, enabling rapid action to protect public health
• Improved quality and completeness of ICSR data	• Better searchability and more efficient data analysis
• Enhanced performance/scalability of the EudraVigilance system	• Able to support an increased number of ICSRs due to the new requirement to report non-serious cases to EudraVigilance
• Simplified reporting of ICSRs to EudraVigilance and the rerouting of ICSRs to Member States	• Reduced duplication of efforts • Marketing authorisation holders no longer have to provide ICSRs to national competent authorities, but only to EudraVigilance only
• Provision of data to the World Health Organization (WHO) Uppsala Monitoring Centre directly from EudraVigilance	• Enhanced collaboration between EMA and WHO • Member States will no longer need to carry out this task
• Provision of an e-learning curriculum to train users on the new system	• Accessible online training available to all users at any time, tailored to the different users needs (Pharmacovigilance operation, EudraVigilance operation, IT operation)

The Agency will carry out a benefits assessment with stakeholders in the months following implementation. EMA intend to make the benefits report available in 2018.

4. Business Process Change Management

It was suggested that all impacted organisations should prepare plans concerning the launch of the new EudraVigilance system on 22 November 2017 and the resulting changes that occurred to reporting, downloading and analysis of data.

This section highlights the main changes the new system has brought to business processes for all stakeholders. Section 6. provides more detailed guidance specific to each stakeholder group.

4.1. Submission of ICSRs within the EEA

Up until the implementation of the new EudraVigilance system there was no change to the process for the submission of ICSRs for either authorised medicinal products or investigational medicinal products. Following the implementation of the new EudraVigilance system on 22 November 2017, ICSR submissions in the EEA should only be made to the EudraVigilance to meet reporting compliance; this applies to NCAs and MAHs. Therefore, submissions from MAHs to NCAs and from NCAs to MAHs should have stopped from this point forward, for SUSAR submissions see section 4.2. below for details.

The EudraVigilance gateway does not prevent stakeholders from sending ICSR to each other. However, it should be noted that these types of exchanges are made outside of official support by the EMA. Exceptions may apply e.g. NCAs to regional pharmacovigilance centres.

With regards to the post-authorisation pharmacovigilance requirements, in addition to the simplified reporting of serious cases, EEA non-serious cases should also be reported to EudraVigilance within 90-days of receipt in order to meet reporting obligations. Non-serious non-EEA case should not be reported to EudraVigilance unless a case that was previously reported as serious is being amended to a non-serious case. It should also be noted that in E2B(R3), seriousness is reported at event level rather than at case level in E2B(R2), therefore if any event is considered serious then the whole case should be considered serious.

4.2. Clinical trial SUSAR reporting

Until the Clinical Trial Regulation is applicable there is no change to the current process for the reporting of suspected unexpected serious adverse reactions during clinical trials[2].

The clinical trials regulation will become applicable six months after the European Commission publishes a notice in the Official Journal that the clinical trials EU portal and the EU clinical trials database have achieved full functionality and the systems meet the functional specifications. The clinical trials regulation will start to apply from this “Application Date”.

Clinical trials already approved through the clinical trials directive 2001/20/EC will continue to have the same SUSAR reporting requirements as specified in the directive for a transition period of 3 years after the clinical trials regulation is applicable.

In addition, in the 12 months following the clinical trials regulation application date, a sponsor can choose to have their trial approved through the clinical trials Directive rather than through the Regulation. If so that trial and SUSAR reporting responsibilities will follow the clinical trials Directive for up to three years after the clinical trials regulation application date.

Sponsors that have a clinical trial approved through the Clinical Trials Regulation are normally required to send SUSARs to EudraVigilance only. The EudraVigilance system will then automatically reroute the SUSARs to the concerned NCAs. However, the option remains for small organisations to report SUSARs directly to the NCA that has approved the trial through establishing an agreement between the sponsor and the NCA concerned. The NCA will then forward any SUSARs reported to them under such agreements to the EudraVigilance system.

4.3. EEA case submissions to the WHO UMC

Until the implementation of the new EudraVigilance system there was no change to the process for the submission of ICSRs from NCAs to the WHO-UMC. Following the implementation of the new EudraVigilance system, ICSR submissions for cases occurring in the EEA should only be made by the EudraVigilance system to WHO-UMC. Therefore, NCAs should have stopped their own processes for submitting ICSRs to the WHO-UMC after the new EudraVigilance system launch on 22 November 2017.

4.4. Signal Management

Authorised users of the EudraVigilance Data Analysis System (EVDAS) are expected to retrieve data and use the available predefined reports included in the newly implemented functionalities to meet

[2] Directive 2001/83/EC of the European Parliament and of the Council of 6 November 2001 on the Community code relating to medicinal products for human use (OJ L 311, 28.11.2001, p. 67).

their data analysis and signal detection obligations. User manuals and training materials were made available to support all users of the system. A process has changed for MAHs as they are now granted access to the EVWEB and EVDAS to support their obligation to monitor EudraVigilance, detect and validate safety signals for the products and substances for which they hold a marketing authorisation. In the event of identifying and validating a safety signal, these safety signals should be reported in accordance to the revised Good pharmacovigilance practices (GVP) Module IX on "Signal Management" (EMA/827661/2011).

The guidance "Screening for adverse reactions in EudraVigilance" (EMA/849944/2016) was published in December 2016 and describes routine signal detection methods in EudraVigilance '.

5. EudraVigilance system implementation plan

The EudraVigilance system has been updated to become ISO ICSR 27953-2:2011 (ICH E2B(R3)) compliant.

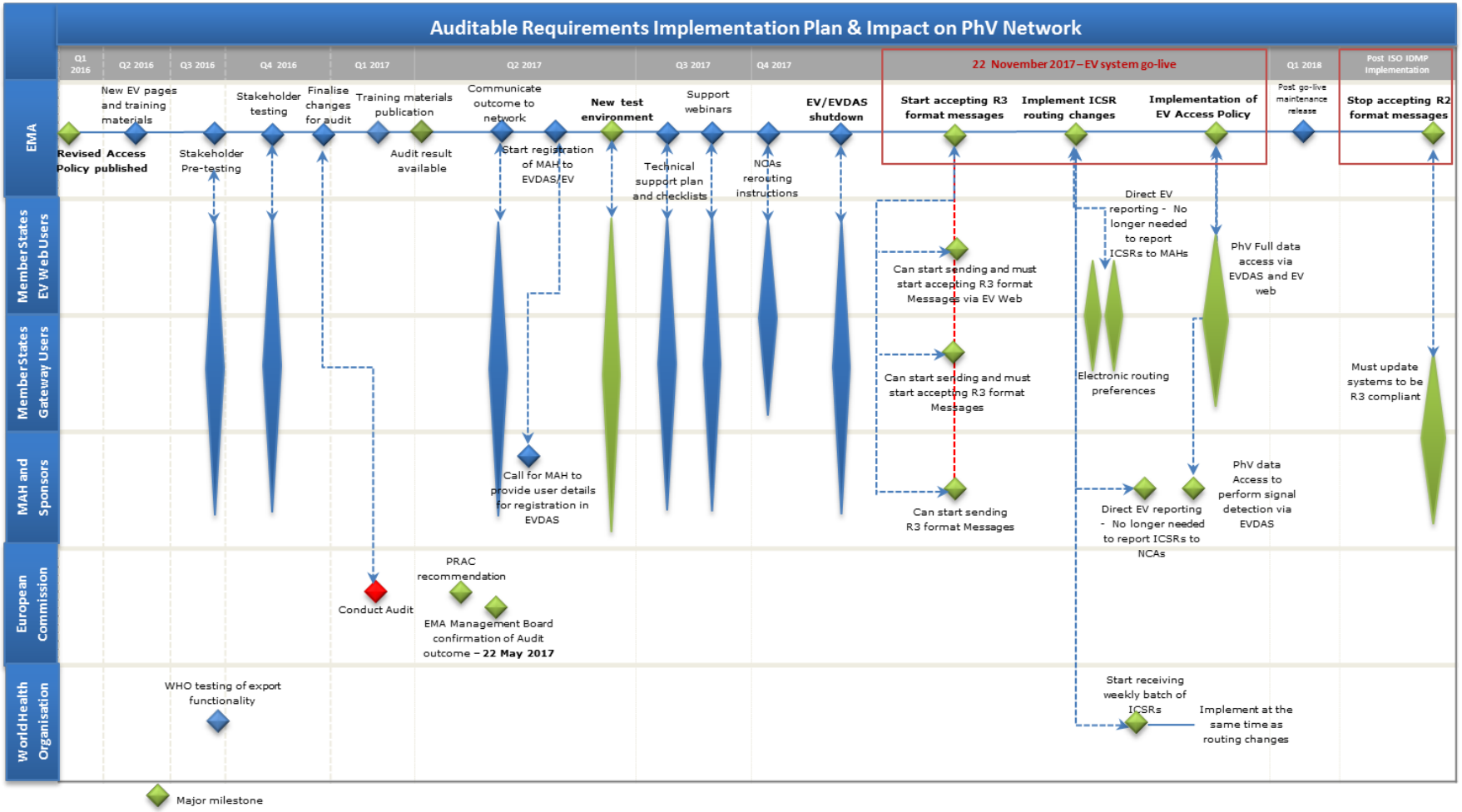
On 22 May 2017 EMA Management Board confirmed and announced that the EudraVigilance database has achieved full functionality and the system meets the functional specifications that were adopted by the Pharmacovigilance Risk Assessment Committee (PRAC) and the Management Board in December 2013. The confirmation and announcement by the EMA Management Board is based on an independent audit and a subsequent favourable recommendation from the PRAC concluding that the updated EudraVigilance system is fully functional. Six months after the announcement of the EMA management board, the move to simplified reporting took effect, i.e. the enhanced EudraVigilance system was launched on 22 November 2017.

There will be no changes to the reporting of suspected unexpected serious adverse reactions during clinical trials[1] until the application of the Clinical Trial Regulation.

The use of ISO IDMP terminologies will only apply when they become available; therefore these terminologies were not part of the new EudraVigilance System update on 22 November 2017. In line with the ICH E2B(R3) Implementation Guide, the E2B(R2) code lists or free text (where an E2B(R2) code list does not exist) is used in the interim period. Once the terminologies related to the ISO IDMP standards will be available, these new terminologies will be implemented in EudraVigilance.

5.1. Implementation roadmap

The diagram below illustrates the sequence of planned IT and business process changes to the EudraVigilance (transactional system and EVDAS) and the impact of these on the EudraVigilance stakeholders.



5.2. EudraVigilance system changes

The previous EudraVigilance system was made of the following components that have been amended as part of the auditable requirements:

- EV organisation and user management;
- EV gateway;
- EV database management system;
- EVWEB reporting application;
- EV data analysis system, including the European database of suspected adverse drug reaction reports (http://www.adrreports.eu/);
- EudraVigilance duplicate detection and management system;
- EudraVigilance medicinal product recoding application.

Three new components have been added to the system:

- EV rerouting rules engine;
- WHO-UMC forwarding functionality;
- ICSR download functionality for MAHs.

The eXtended EV Medicinal Product Dictionary (XEVMPD) component is no longer an integral part of the EudraVigilance system and instead has become an independent system that the EudraVigilance system and XEVMPD users can access for information on medicinal products.

5.2.1. EudraVigilance organisation and user management

The EudraVigilance registration process has been simplified with the implementation of the new system and published on the dedicated EudraVigilance: how to register webpage. Existing organisation and user registrations were automatically transferred to the new system. A new registration process for EVDAS users of MAHs has also been implemented.

5.2.2. EudraVigilance gateway

The EudraVigilance gateway has been be configured to accept E2B(R3) files. After the 22 November 2017, the transmission of ICSRs by MAHs through the gateway to National Competent Authorities (NCAs) is no longer supported by the EMA. Gateway users are not prevented from sending ICSRs through the gateway to other registered organisations that are connected to the gateway. However, organisations performing such transmissions are not able to contact the EMA gateway helpdesk for support if issues occur with these transmissions. Following the implementation, organisations should be aware that only submissions of ICSRs to the EudraVigilance system are being considered as fulfilling the legal obligations of the sender. Therefore, organisations should have ensured that the transition to simplified reporting was coordinated with the new system implementation.

5.2.3. EudraVigilance database management system (EVDBMS)

The EudraVigilance database management system has been subject to significant changes as the database was updated to support the ICH E2B(R3) structure and data fields. All existing ICH E2B(R2) data have been migrated into this new database.

The XML parser[3] has been replaced and is able to process both E2B(R2) and E2B(R3) messages. If an E2B(R2) message is sent to the EudraVigilance system, an E2B(R2) acknowledgement message is returned. Likewise, an E2B(R3) acknowledgment is returned for E2B(R3) ICSR messages. **If an invalid XML message is sent to EudraVigilance, an E2B(R3) acknowledgment will be returned.**

EudraVigilance applications for Medicinal Product Recoding and Duplicate Detection and management have been amended to support the ICH E2B(R3) format. Master cases that are produced by the EMA in response to identifying duplicated ICSR in the EudraVigilance system are being produced in E2B(R3) format only.

5.2.4. EVWEB reporting application

The EVWEB application has been redesigned using a different technology which enables the application to work in additional browsers rather than being restricted to specific versions of Internet Explorer. The supported browsers are the latest version of Firefox, Chrome and Internet Explorer; other browsers may work with the application but are not supported by the Agency.

The functionalities of the application have been upgraded to only support E2B(R3) ICSR data entry. Although the application has similar ICSR functionalities, the user interface has a different appearance and the E2B(R3) standard itself introduced additional data elements as well as different ways of structuring data. These changes required users of the previous system to undertake training to become familiar with these changes. E-learning modules EV-M3b, EV-M3c, EV-M3d and EV-M3e) should have been followed. In addition, face-to-face training courses were/are offered to familiarise with the new EVWEB functionalities and the use of the new ICH E2B(R3) format based on various case scenarios. Training offerings and support were published at the EudraVigilance training and support webpage.

5.2.5. EV data analysis system (EVDAS)

The EVDAS has been updated to the new E2B(R3) data structure. In addition, a new set of functionalities and predefined reports (as per level of access defined in the revised EudraVigilance Access Policy) were implemented. The subsequent sections provide details on what functionality is available for specific stakeholder groups.

5.2.5.1. Healthcare professionals and general public

The European database of suspected adverse drug reaction reports (http://www.adrreports.eu/) has been updated and improved to include:

- Weekly refresh of published data;
- Publication of data for non-serious cases received in EudraVigilance;
- Publication of 'country' data (in aggregated dashboard);
- Publication of additional data elements via line listing reports and a new ICSR form.

Please note that several safeguards have been put in place to ensure full compliance with personal data protection i.e. to prevent patient identification.

[3]An application that processes and loads the data held within an XML file into the database

5.2.5.2. Marketing Authorisation Holders

Access is extended to MAHs for to use the EVDAS signal detection and analytical/reporting functions to the extent necessary to comply with their pharmacovigilance obligations. Such functions include:

- The electronic Reaction Monitoring Report (eRMR) based on the eRMR used within the EU network and the EMA for signal detection activities;
- The individual case line listing and ICSR form.

The level of access to each ICSR and data elements has been implemented as defined in the revised EudraVigilance Access Policy. Several safeguards have been put in place to ensure compliance with personal data protection i.e. to prevent patient identification. EVDAS is accessible to MAHs as of 22 November 2017.

5.2.5.3. Commission, NCAs in the EEA and the EMA

New functionalities and predefined reports have been implemented in EVDAS to support:

- Signal detection and management activities including eRMRs;
- ICSR data quality monitoring;
- Use of Article 57 data.

5.2.6. EudraVigilance rerouting rules engine

The EudraVigilance rerouting rules engine is a new component that forwards ICSRs to the relevant NCAs depending on a set of conditions defined by NCAs. As per the EU Individual Case Safety Report (ICSR) Implementation Guide, the EudraVigilance system reroutes ICSRs in the format received i.e. no conversions are being applied. The rerouting of recoded ICSRs will be put in place as part of the implementation of the ISO IDMP terminologies, in a future upgrade of the EudraVigilance system.

5.2.7. ICSR download function for MAHs

After the switch to simplified reporting on 22 November 2017, MAHs are no longer receiving ICSRs directly from NCAs. For MAHs to receive ICSRs concerning their medicinal products, the ICSR download functionality should be used.

In line with the revised EudraVigilance Access Policy MAHs are able to access ICSRs (Access Policy Level 2A) for any substance and medicinal product that has been reported as a suspect or interacting drug. The data elements provided for the ICSRs include the elements as defined in the revised EudraVigilance Access Policy for Level 2A. Level 2A access is determined on the basis of the active substance grouping based on the Article 57 substance and product information submitted to the XEVMPD by MAHs.

In addition to Level 2A access to ICSR data, MAHs are able to request the extended Level 2B access in support of their pharmacovigilance obligations and signal evaluation (Level 2B includes case narrative data elements as per revised EudraVigilance Access Policy) as detailed in the GVP modules VI and IX. Requests made by authorised user will be log and the requester will be asked to provide details of the reason of such request. In addition, they will be asked to confirm that they will adhere to the EudraVigilance Access Policy Confidentiality Undertaking.

ICSRs provided via the EudraVigilance ICSR download functionality are only available in ICH E2B(R3) format.

The download function is available as part of the new EVWEB application.

5.2.8. EudraVigilance duplicate detection and management system

The change to ICH E2B(R3) did not affect the logic of the duplicate detection algorithm as the data elements used did not change between ICH E2B(R2) and E2B(R3). The duplicate detection client has been amended to handle duplicates existing in both ICH E2B(R2) and E2B(R3) formats and to produce valid ICH E2B(R3) messages. The duplicate detection client generates valid ICH E2B(R3) master messages including the cluster information.

The management of duplicates required training of EMA staff and its contractors in the new ICH E2B(R3) data elements and format along with changes to the duplicate management interface.

NCAs and MAHs were not affected by changes to the system apart from having access to Master cases in EudraVigilance created by the EMA in ICH E2B(R3) format.

5.2.9. EudraVigilance medicinal product recoding application

The change to ICH E2B(R3) did not affect the recoding process as the XEVMPD continues to be used until ISO IDMP terminologies are available and implemented. The data elements used to describe medicinal products and substances did not change between ICH E2B(R2) and E2B(R3) format. However, an additional data element for capturing device components of advanced therapies has been implemented. The recoding application has been amended to handle both ICH E2B(R2) and E2B(R3) formats and the interface has been updated to the new software technology.

These updates to the recoding application required training of EMA staff and its contractors in the new ICH E2B(R3) fields, format and the new interface.

The automated recoding also required updates to the new EudraVigilance database structure to reflect the changes to data elements and data structures.

NCAs and MAHs were not affected by these changes to the system.

5.2.10. Nullification requests

When an organisation submits a nullification report, EudraVigilance automatically marks an ICSR as nullified if the pre-existing case has been submitted by the same organisation or one of its affiliates. These nullification reports have the report classification “Nullified report”.

If a nullification request is received for a case that was previously sent by another organisation the following two processes applies:

i. If the **nullification concerns an EEA case**, the nullification report is stored and the nullification retransmitted to the concerned NCA. The concerned NCA should then review the nullification. If the nullification is for a valid reason, the NCA should submit nullification for the individual case they have previously submitted to EudraVigilance. The nullification reports from the sending organisation have the report classification “EEA Nullification request”;

ii. If the **case is from outside the EEA**, the case ID must match a case ID that already exists in the EudraVigilance database. If no matching case ID exists, the nullification report is rejected. If a matching case ID is found, the nullification is accepted and stored with the report classification “Nullification request”. The EMA then reviews the nullification request

and if the nullification is for a valid reason, the EMA marks the associated ICSRs as nullified through changing the report classification of the appropriate ICSRs to “Nullified report”.

The first of these two processes (point i) does not require EMA involvement unless the concerned NCA has requested not to receive re-routed ICSRs. In such situation, the EMA periodically provides those NCAs with details of the nullification requests so that the NCA can submit nullifications if appropriate.

The second process (point ii) does require EMA involvement to approve the nullification of cases held in EudraVigilance. Limited training was required at the level of the EMA to support this process. However, the number of these types of nullification requests is expected to be low.

5.3. Supporting documentation for stakeholders

ICH E2B(R3) documentation provides the basis for the implementation of the ISO ICSR standard with two main documents downloadable from the ICH ESTRI website http://estri.ich.org.

In addition to the ICH Implementation Guide, an EU ICSR Implementation Guide has been developed and published. Associated supporting documents, including user guides, training material and guidelines have also been developed or updated and are described below. Together these documents provide additional information on specific EU regional requirements that are not provided in the ICH documentation and are published on the dedicated EudraVigilance: electronic reporting webpage.

Documentation	Description	Date available
ICH implementation guidance		
ICH Implementation guide package	A set of documents including the ICH ICSR implementation guide, backwards and forwards compatibility recommendations and element mapping	Available now - ICH Implementation guide package
ICH E2B(R3) Questions & Answers (Q&As)	A question and answer document relevant for technical E2B questions	Available now - ICH E2B(R3) Questions & Answers (Q&As)
EU implementation guidance		
EU Individual Case Safety Report (ICSR) implementation guide	A guide which describes the additional EU specific requirements to generate a valid ICSR and Message acknowledgment to implement EN ISO ICSR in accordance with ICH E2B(R3)	Available now - EU Individual Case Safety Report (ICSR) implementation guide
EU ICSR implementation guide business rules spreadsheet	This spreadsheet includes all the ICH E2B(R3) and EU specific business rules in a format to help system developers	Available now – EU ICSR implementation guide business rules spreadsheet
EU backwards forwards conversion element mapping spreadsheet	This document describes the relationship between EU specific data elements in E2B(R3) and E2B(R2). This	Available now – EU backwards forwards

Documentation	Description	Date available
	document is an addition to the ICH backwards forward conversion rules. It covers additional EU specific rules for the conversion back and forth between E2B(R2) and E2B(R3).	conversion element mapping spreadsheet
EU backwards forwards conversion tool v.2.5	Based on the ICH BFC tool it includes the additional EU specific data fields	Available now - EU backwards forwards conversion tool
EU E2B(R3) code lists	The list of codes for EU specific data fields	Available now - EU E2B(R3) code lists
EU reference instance	ICH reference instance amended to include the EU specific data fields	Available now - EU reference instance
EU example instances	Additional example instances to be used for testing ICH E2B(R3) transmission to the enhanced EudraVigilance system	Available now - EU example instances
EudraVigilance Access Policy		
EudraVigilance Access Policy (Rev3)	The revised EudraVigilance Access Policy, which governs the level of access different stakeholder groups have to adverse drug reactions reports.	Available now – EudraVigilance Access Policy
Overview of comments received on 'Draft revision of EudraVigilance access policy for medicines for human use'	The comments received on the draft revision of the EudraVigilance access policy during its public consultation between 4 August and 15 September 2014.	Available now - Overview of comments received on 'Draft revision of EudraVigilance access policy for medicines for human use'
Good pharmacovigilance practice (GVP) guidance		
GVP Module VI	This module addressees the management and reporting of adverse reactions to medicinal products	Available now – GVP Module VI Revision 2
GVP Module IX	This module describes the general guidance and requirements on structures and processes involved in signal management and how they are applied in the setting of the EU pharmacovigilance and regulatory	Available now - GVP Module IX Revision 1

Documentation	Description	Date available
	network	

5.4. E2B(R3) Stakeholder implementation considerations

Once an organisation submits an ICH E2B(R3) ICSR, it is not permitted for that organisation to submit a follow-up to that ICSR in the previous E2B(R2) format. This is to prevent inconsistencies that would occur between the two submission formats.

After the new EudraVigilance system launch on 22 November 2017, organisations can submit ICSRs in both ICH E2B(R2) and E2B(R3) formats. However, access to ICSR XML data held within EudraVigilance is provided in ICH E2B(R3) format only. Organisations should therefore make sure that they have systems in place that can process E2B(R3) files. This can be done either by implementing native E2B(R3) support in their own pharmacovigilance system or by implementing the published Backwards/Forwards conversion (BFC) tool to convert E2B(R3) files into E2B(R2) files. An extended version of the ICH E2B(R3) BFC tool that includes the additional EU specific data fields specified in the EU implementation guide has been made available in the EU and published on the dedicated EudraVigilance: electronic reporting webpage.

5.5. Testing with the new EudraVigilance system and user training

The execution of stakeholder testing with selected MAHs and NCAs occurred in November 2016. Following this testing and successful completion of the independent audit, the EudraVigilance test system XCOMP was launched on 26 June 2017. All organisations with a registered EudraVigilance test account were automatically granted access to the XCOMP environment and could start sending ICH E2B(R3) ICSRs as well as downloading ICH E2B(R3) ICSRs based on test data. In addition, users could have started using the new EVWEB interface in the XCOMP environment. The go-live of the external testing system on 26 June 2017 allowed for a five month period until 22 November 2017 for organisations to become familiar with the new system and test their local pharmacovigilance/safety IT system and their interoperability with the new EudraVigilance system.

Testing instructions were provided on the EudraVigilance change management webpage and the EudraVigilance: electronic reporting webpage.

5.5.1. Testing process for E2B(R3) & E2B(R2) submissions

A set of E2B(R3) example test files as described in the EU ICSR Implementation Guide are available on the EudraVigilance: electronic reporting webpage. Testing organisations were expected to upload these files into their own pharmacovigilance system and then resubmit these cases to the EudraVigilance system. EMA then checked that the original file and resubmitted file were identical in all the fields apart from those that can be changed by a re-transmitter e.g. administrative field.

Organisations wishing to test ICH E2B(R2) submissions for a new pharmacovigilance system or following a major upgrade of their system also have example test files available and testing follows the same process as described above.

Testing instructions published on the EudraVigilance: electronic reporting webpage. A specific testing time slot can be booked by contacting EMA at gattesting@ema.europa.eu.

5.5.2. New EVWEB application user training

As described in section 5.5. the new EVWEB application was made available in the XCOMP environment as of 26 June 2017. Therefore, organisations which have been using EVWEB and were intending to use EVWEB in the future had a period of 5 months to familiarise with the new functionalities.

Users and organisations that have already attended and passed the EVWEB training course did not need to re-attend the course. The EMA has published a user guide, online eLearning videos, release notes and offers support webinars. In addition, face-to-face training courses were also available since 12 June 2017. The training materials explained the new E2B(R3) format including the new data elements and the new EVWEB functionalities. For users that have never used EVWEB a more comprehensive training course to provide a more in depth training of the EVWEB tool was made available in the continuation of what was done for the previous EudraVigilance system. The user manual, release notes, training materials and face-to-face training courses on the new EudraVigilance system are available and published on the EudraVigilance training and support webpage.

5.5.3. EVDAS user training

The EVDAS user manual for pharmacovigilance reports was published on 22 November 2017.

eLearning videos have been created for EVDAS users to highlight new functionalities/reports.

In addition, in 2017 the Agency have organised two dedicated “train-the-trainer” courses for NCAs in the EEA on the new EVDAS functionalities.

The materials are available on the EudraVigilance training and support webpage.

5.6. Art 57 – XEVMPD

The new EVWEB application for ICSRs does not include a component for creating and sending XEVPRM messages to the Art 57 database. The previous version 7 of the EVWEB application is kept in place for the submission of Art 57 data with the same URL. The ICSR related functionalities have been removed from EVWEB version 7 at the time of the new EudraVigilance System launch.

The EudraVigilance go-live plan and the Technical Note on the planned EudraVigilance downtime from 8 to 21 November 2017 were published by the Agency on 4 October 2017. Documents outlined the steps, which had been followed during the transition from the previous to the current EudraVigilance system.

A separate project to replace the XEVMPD data format with the ISO IDMP format will be considered bu EMA in due time.

No changes to the business process or resource requirements are expected until the ISO IDMP format is implemented.

5.7. What to do in case of system failure

The process to follow in case of a failure of submission of ICSRs occurring at the sending organisation side or at the level of the EMA has changed after the new system was implemented. If the failure occurs at the sender’s side, the process of submission of CIOMS forms via fax or other methods is no longer supported, and the organisation must submit the cases electronically to EudraVigilance as soon as their system is available again. Manual recoding of the official receipt dates by the EMA to the data of the fax CIOMS form are no longer continue.

If the failure is occurring at the level of EudraVigilance, organisations will need to submit cases within two business days after the system failure has been resolved. Cases received late due to the system failure at the level of the EudraVigilance system will be excluded from reporting compliance by setting the official receive date of the cases submitted in this period within EudraVigilance to the date the system became non-available or the Receipt date (A.1.7 E2B(R2) or C.1.5 E2B(R3)), whichever is greater. Instructions are also provided at the on the EudraVigilance: electronic reporting webpage.

5.8. EudraVigilance go-live planning

To release the new system in production it was planned that the EudraVigilance production system would be unavailable for a defined period of time as described in section 6.1.1. During that period, all the data of the previous EudraVigilance production system were migrated to the current EudraVigilance system. Following the completion, the new EudraVigilance system components have been installed to the production environment and configuration changes have been implemented on the EudraVigilance gateway. The new functionalities of EVDAS have also been made available.

During that period, several IT systems were partially disrupted or non-available at all.

To facilitate the transition, the EU Regulatory network's pharmacovigilance business team has prepared a EudraVigilance go-live plan and a technical note in consultation with the Pharmacovigilance Risk Assessment Committee (PRAC), the Clinical Trials Facilitation Group (CTFG) and the EudraVigilance Expert Working Group.

The plan outlines a set of detailed, sequenced tasks and activities required to launch the new EudraVigilance production system, explains the process for handling the legacy data resulting from the downtime and describes temporary arrangements.

During the new system implementation period, organisations should have had reconfigured their systems to ensure that post-authorisation submissions were made to the EudraVigilance system (EVPM) only as it has become the central reporting system for the EEA. Any reports that were required submitting during that period of non-availability should have been transmitted electronically to EudraVigilance (EVPM) only, as soon as the system was made available again on 22 November 2017.

Further instructions, including detailed information on measures, which were put in place by organisations during the EudraVigilance downtime, were published on 4 October 2017, as part of the EudraVigilance Go-Live Plan and the Technical note.

5.9. Planned future updates to the EudraVigilance 8 system

The ISO IDMP set of standards and their resulting terminologies were not fully available at the time of implementation of the new EudraVigilance system. However, ISO IDMP integration will be planned for through a subsequent project. In addition, the Agency will also change the way organisations and users are registered to access IT systems and services which will replace the current EudraVigilance registration process. Further details on these updates will be discussed with stakeholders in the future.

More details on the ISO IDMP project can be found by clicking on this link. In addition the SPOR roadmap can be found by clicking on this link.

6. Stakeholder Implementation planning

This section provides detailed guidance to each stakeholder group on what activities should have been planned for the new EudraVigilance system launch on 22 November 2017.

6.1. EMA change management planning

This section of the change management plan focuses on the IT and business process changes that had been considered by the EMA for the period of time leading up to and after implementation of the new EudraVigilance system.

6.1.1. EMA IT implementation plan

6.1.1.1. EudraVigilance Testing

In addition to the internal testing performed at the level of the EMA, external testing was conducted in November 2016 with a selected number of stakeholders. The organisations participating in the external testing were chosen through a call for volunteers via the EudraVigilance Expert Working Group and the Pharmacovigilance Business Team. This testing was performed in advance of the independent audit of the EV system. Following this testing, the successful completion of the independent audit and the EMA Management Board announcement that the EudraVigilance system meets the required functional specifications, the XCOMP environment was released to all stakeholders on 26 June 2017.

6.1.1.2. System Implementation

All ICSRs from the EudraVigilance system have been migrated to the new ICH E2B(R3) compliant database.

All registered users at the time of the new EudraVigilance system launch were automatically granted access to the new system and therefore there was no action required by existing users. New users will need to follow the registration process as described at the EudraVigilance: how to register webpage.

The previously implemented gateway is also used for the new ICH E2B(R3) compliant system. The ICH E2B(R2) gateway community also remained the same. For the submission of E2B(R3) messages the gateway configuration at the EMA has been updated; these updates may have required organisations wishing to submit ICH E2B(R3) messages to also update their own gateway configuration.

The EudraVigilance helpdesk contact details have changed to the following:

- **EudraVigilance Registration**

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

- **EudraVigilance Helpdesk**

  EMA IT Service Desk (For support with EudraVigilance and EMA gateway / webclient)

  Tel.: +44 (0)20 3660 8520 (for urgent technical matters)

Information on how to raise a query through each support method can be found in the EudraVigilance Support Guide.

No changes have been made to the existing XEVMPD tool and therefore the functionalities and interface remain the same.

The new URL for the new EVWEB reporting application for ICSR(s) is as follows: https://eudravigilance-human.ema.europa.eu.

6.1.2. Business process changes and resourcing requirements

The changes relating to business processes, which occurred after the implementation of the new EudraVigilance system are summarised in section 4. The following sections describe these changes in relation to the EMA and the potential changes in work load and internal process ownership.

In addition, relevant SOPs and working instructions associated with the business processes described in this section have been reviewed and amended.

6.1.2.1. Re-routing of ICSRs from EudraVigilance to NCAs

The configurations of rerouting rules are being directly maintained by the NCAs using the EVWEB interface. NCAs have been contacted by the EMA to collect their rerouting requirements so that the initial configuration of the rerouting rules could be implemented in advance of the EudraVigilance system going live. The re-routing rules as defined by each NCA were available to test from 26 June 2017 when the XCOMP environment was made available. After the initial configuration settings have been entered in the production system by the Agency, little additional work was expected from this activity. This initial set up have been performed by EMA.

6.1.2.2. Access to data held in EudraVigilance by MAHs

MAHs have tools to download and analyse data held within EudraVigilance, training materials and user manuals were made available at the EudraVigilance training and support webpage. It was therefore expected that external organisations would prepare themselves using these published materials and through regular communications sent out by the EMA. However, there was an increase in helpdesk queries, which led up to the new system implementation and is very likely to continue for a period of several months after implementation.

6.1.2.3. EudraVigilance registration requests

The registered users for EudraVigilance were migrated to the new EudraVigilance system with the same configuration settings for accessing EVWEB and the secure area of EudraVigilance.

As per updates to the EudraVigilance Access Policy, MAHs have been granted access to the EVDAS. MAHs therefore were required to assign specific users the permission to access the EVDAS system in addition to EVWEB and the secure area of EudraVigilance. A phased registration approach was initiated with EVDAS registration of MAH users starting in 1 June 2017. The effect of this additional work on EMA resources had been planned for, taking into account recent improvements to the functionalities to user and organisation management.

Additional registrations for the new XCOMP (EVTEST) system occurred, following the new XCOMP environment release on 26 June 2017.

The EudraVigilance training environment used in support of face to face training courses has also been updated and the process for providing training accounts to the training courses defined.

The organisation and user registration for the submission of XEVMPD data continues with no changes.

The registration process is being performed by the Data and Information Lifecycle Management service.

6.1.2.4. Access to data requests

Access to data requests received from the public, healthcare professionals, research organisations and other international regulatory authorities are handled in the same way as the previous process. The EudraVigilance Access Policy is being used to identify the data elements that can be provided for such requests.

A significant increase in volume of requests is not expected, following the new system implementation. The answering of these requests is being performed by the Signal Management service.

6.1.2.5. MAH signal validation and management process

With the access to EudraVigilance MAHs have obligations to monitor the data available in the system in accordance with the principles set out in GVP Module IX and to inform the Agency and NCAs about validated signals. However, EMA and the European Commission have agreed transitional arrangements to streamline the monitoring of EudraVigilance by MAHs.

During a pilot period of one year, MAHs of the active substances included in the list of active substances involved in the pilot on signal detection in EudraVigilance will have to monitor them in EudraVigilance and inform EMA and national competent authorities of validated signals with their medicines.

This requirement will only start on 22 February 2018, effectively granting those MAHs a three-month 'grace period' to familiarise themselves with the new EudraVigilance system, the new tools to support EudraVigilance monitoring and to finalise their own processes.

These transitional arrangements do not apply to obligations on simplified reporting and management of individual case safety reports (see Good pharmacovigilance practices (GVP) Module VI and EudraVigilance change management).

All other MAHs also have access to EudraVigilance data and are able to integrate the data into their own signal management processes. However, during the pilot period they will have no obligation to continuously monitor EudraVigilance and inform the regulatory authorities of validated signals.

After one year, EMA will base the next phase of implementation on experience gained through the pilot. For updates and further information please visit dedicated Signal Management webpage .

6.1.2.6. Recoding application

The recoding process does not change significantly with the system updates; this will however need to be reviewed when ISO IDMP is implemented. The new ICH E2B(R3) format did introduce new data elements such as Device ID for advanced therapies and therefore the recoding application has been updated. As this process is carried out by a contractor, training had been planned for the contractor. This has been carried out through Train the Trainer sessions and webinars.

The activities of monitoring the contractor and providing their training are being performed by the Data Standardisation and Analytics service. Apart from the set-up phase, no change to resource requirements was foreseen.

6.1.2.7. Duplicate detection

The duplicate detection process does not change with the system updates. The new ICH E2B(R3) format including the new data elements and the subsequent changes to the duplicate detection tool do

need to be appropriately managed. As this process is carried out by a contractor, training has been planned for the contractor. This was being carried out through Train the Trainer sessions and webinars.

The activities of monitoring the contractor and providing their training are being performed by the Data Standardisation and Analytics service. Apart from the set-up phase, no change to resource requirements was foreseen.

6.1.2.8. Data quality review

The data quality review process currently does not change with the system updates. The new ICH E2B(R3) format including the new data elements and the subsequent changes to the EVWEB tool do need to be appropriately managed. As this process is carried out by a contractor training has been planned for the contractor on both EVWEB and the changes brought in through the implementation of ICH E2B(R3). In addition, as data continue to be submitted in ICH E2B(R2) format and the EVWEB displays the content in ICH E2B(R3) format, the data quality reviewers required specific training. This training provided a detailed understanding on how to assess these two different submission formats in a review tool. The training was being carried out through Train the Trainer sessions and followed up with webinars.

The activities of monitoring the contractor and providing their training are being performed by the Data Standardisation and Analytics service. Apart from the set-up phase, no change to resource requirements was foreseen.

6.1.2.9. EudraVigilance testing with organisations

The method for testing of submission of ICSR to EudraVigilance has been simplified. The instructions published on the webpage EudraVigilance: electronic reporting should have been followed. The EMA has provided a set of sample ICSR files to be uploaded and transmitted to the EudraVigilance external testing system along with a testing script to be followed by the testing organisations.

In addition, the test data were made available in a human readable format for manual data entry and submission where applicable. The set of sample files cover a range of different reporting scenarios to ensure that the sending system has been correctly implemented, including the additional EU specific requirements. This applies to organisations testing updates to systems using the ICH E2B(R2) specification or for systems that have implemented the ISO ICSR 27953-2:2011 (ICH E2B(R3)) standard.

The organisation performing the testing is expected to upload these sample files into their pharmacovigilance system and follow the test script. Once uploaded, these test files should be transmitted to the EudraVigilance external testing system for review by the EMA. Unexpected differences between the sample set of ICSR files and the information processed by XCOMP is communicated to the testing organisation. Any issues identified are to be addressed before allowing the testing organisation to enter into production.

These testing activities are being performed by the Data Standardisation and Analytics service. This new testing process should lead to a reduction of work. However, there was a significant rise in testing as new pharmacovigilance systems were implemented by MAHs and NCAs.

6.1.2.10. Medical Literature Monitoring Service

The Medical Literature Monitoring Service does not change with the system updates. The new ICH E2B(R3) format including the new data elements and the subsequent changes to the EVWEB application do need to be appropriately managed. As this process is carried out by a contractor using

EVWEB, training has been planned for the contractor. This was carried out through Train the Trainer sessions and webinars.

The activities of monitoring the contractor and providing their training are being performed by the Data Standardisation and Analytics service. Apart from the set-up phase, no change to resource requirements was foreseen.

6.1.2.11. WHO-UMC reporting

The reporting of EEA ICSRs to the WHO-UMC is a new process for the EMA as the new EudraVigilance system is forwarding relevant ICSRs automatically using a set of predefined rules. Apart from the set-up phase, the automation that was put in place means that only limited resources are required to support this process. Some checking and monitoring is needed to ensure the successful forwarding of ICSRs to the WHO-UMC; in addition, helpdesk support for WHO-UMC queries has been planned although the expected workload is very low.

This process is performed by the Data Standardisation and Analytics service. Apart from the set-up phase and the annual reconciliation activities, no significant increase in resource requirements was foreseen.

6.1.2.12. Helpdesk - business support

No changes were expected to the helpdesk process for EudraVigilance business support. However, an increase in queries, leading up to the EudraVigilance system implementation and for several months after the implementation, was expected. The following query topics were anticipated:

- Submission of ICSRs in E2B(R3) format;
- Testing E2B(R3) submissions;
- Simplified reporting;
- MAH downloading of ICSRs;
- MAH signal reporting;
- MAH & NCA EudraVigilance data analysis (including eRMR & Art 57 substance groupings);
- EudraVigilance registrations;
- New EVWEB interface;
- European database of suspected adverse drug reaction reports Adrreports.eu.

More EMA resources have been planned for the support of helpdesk activities, however additional staff was required to monitor the work, coordinate and train the additional resources. Data Standardisation and Analytics service is providing standard answers and links to documents to facilitate the handling of helpdesk queries. Additional staff was required to support and coordinate the additional resources.

6.1.2.13. Helpdesk Second-line (IT operations) Support

No changes were expected to the helpdesk process for EudraVigilance (including EVDAS and ADR website) second-line support. However, an increase in queries relating to potential system issues at the level of the users and the EMA was expected after the new test EV system (XCOMP) implementation and again in the period after the production system implementation.

More EMA resources were planned for the support of helpdesk activities.

6.1.2.14. EVDAS

The main change for EMA users was the implementation of several new functionalities and predefined reports in EVDAS to support:

- Pharmacovigilance activities, including the implementation of a new measure of disproportionality (reporting odds ratio), new functionalities for sub-group analyses and new data elements;
- Data quality monitoring, including reports on organisations reporting to EudraVigilance, safety report monitoring, expedited reporting timelines compliance monitoring, safety reports data quality;
- Publication of Article 57 data, including reports on authorised medicinal products, legal entity (MAH) and Qualified Person Responsible for Pharmacovigilance (QPPV) details, approved substances, pharmacovigilance system master file and listings on authorised medicinal products;
- The eRMR, including the integration with EVDAS, the improvement of data visualisation and the clarification on methodology.

Support to the users was performed by the Data Standardisation and Analytics (DSA).

6.1.3. EMA training

The EVDAS user manual for pharmacovigilance reports has been updated and new user manuals for Article 57 reports and data quality reports have been created.

eLearning videos has been created for EMA users of EVDAS that highlight new functionalities/reports or changes that have been made to pre-existing reports.

New EMA users will be trained as part of the standard EVDAS training provided to NCAs by the signal management service. Training materials has been updated accordingly.

6.1.4. EMA communications plan

A communication plan has been developed to ensure that the necessary information was circulated to relevant stakeholders at the appropriate time and to ensure that impacted parties were aware of the modifications to the EudraVigilance system. This was to ensure that they are prepared for the IT and business changes. Communications were undertaken through both general update communications and targeted communications based on key project milestones. Key project milestones and a summary of associated communication activities are available at the EudraVigilance change management webpage.

6.1.4.1. General update communications

Regular updates on the development and progress of the changes to the EudraVigilance system have been/will be communicated via the bulletin 'What's new in Pharmacovigilance?' This bulletin is distributed to both pharmaceutical industry and Member State stakeholders i.e., to Industry Associations, Qualified Persons for Pharmacovigilance (QPPVs), Heads of Medicines Agency (HMA), the Pharmacovigilance Business team, EU Commission, international partners, ENCePP. The bulletins can be accessed at the Agency's Newsletter webpage.

6.1.4.2. Targeted communications based on key milestones

Information on key milestones had been disseminated to relevant stakeholders through the following channels:

- Publication of EMA News Items on the Agency corporate website (shard in advance with NCAs to preparation of local communication at the level of the NCA);
- Tailored emails to the registered EudraVigilance users;
- Presentations and teleconferences with Pharmacovigilance Business team, the Pharmacovigilance Risk Assessment Committee (PRAC), the EudraVigilance Expert Working Group (EV-EWG), EU Network Pharmacovigilance Oversight Group (EU-POG), IT Directors Group and the Heads of Medicines Agencies (HMA).

The key project milestones around which the communications had been anchored were/are:

- The audit of EudraVigilance system;
- The availability of the conversion tool for ICH E2B(R2)/(R3);
- The EMA Management Board announcement of results of audit of EudraVigilance system;
- The availability of the EudraVigilance XCOMP test environment;
- The publication of the EudraVigilance go-live plan;
- The move to the ICSR simplified reporting;
- The availability of the new EVDAS functionalities;
- The mandatory reporting requirement of non-serious cases in EudraVigilance;
- The commencement of Agency reporting to WHO;
- The ability of the EudraVigilance system to receive E2B(R3) messages;
- The enabling of the EudraVigilance ICSR re-routing;
- End date of accepting ICH E2B(R2) messages.

Additionally, targeted information announcing e.g. training dates and information days had been provided to relevant stakeholders.

Information on key project milestones and the associated communications plan was provided in the Key project milestones and summary of associated communication activities.

6.1.4.3. Dedicated EudraVigilance information on the EMA corporate website

The public area of the EudraVigilance website has been decommissioned as of July 2016 and all the content has been rewritten into the EMA website.

The restricted area of the EudraVigilance website was switched on 22 November 2017 to a existing URL.

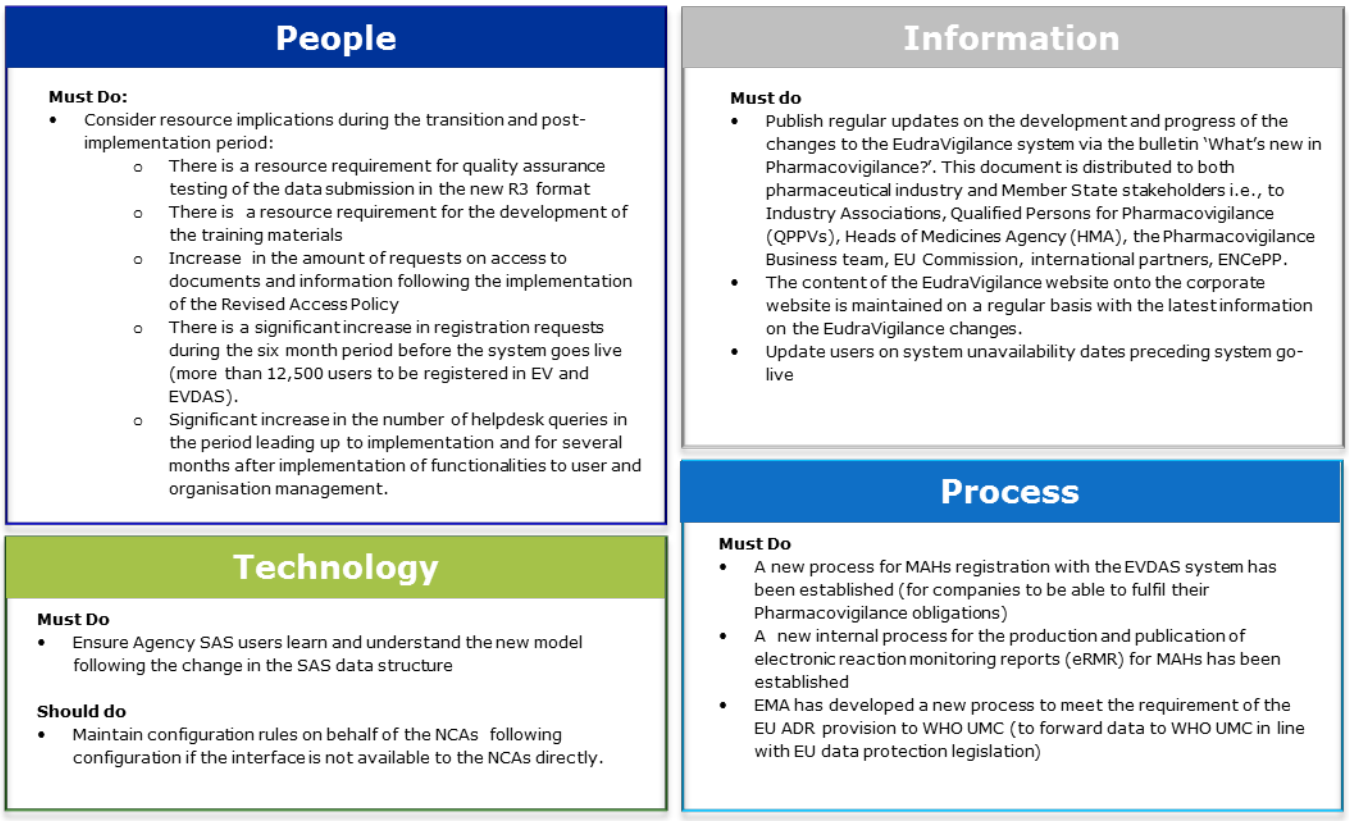
The content from the EudraVigilance website can be found in the section dedicated to EudraVigilance which can be accessed following the path: Human Regulatory > Pharmacovigilance > EudraVigilance

The pages related to EudraVigilance include:

- System overview: provides an overview of EudraVigilance system components, system functionality, and processes supporting EudraVigilance.
- Electronic reporting: Provides an introduction to electronic reporting requirements and supporting information for stakeholders e.g. documentation for E2B(R3) implementation.
- Registration: provides an explanation of the registration process that stakeholders must undergo to use EudraVigilance for the electronic data interchange of pharmacovigilance information.
- Change management: Provides information regarding changes related to EudraVigilance enhancements e.g. change management plan, communication plan, stakeholder impact.
- Access to data: Provides information regarding changes related to EudraVigilance enhancements e.g. change management plan, communication plan, stakeholder impact.
- EudraVigilance training and support: Provides an overview of the EudraVigilance training plan, and details of all existing and upcoming training materials.
- Security principles and responsibilities: Provides information on the **security and confidentiality** principles that stakeholders using EudraVigilance need to comply with.

6.1.5. EMA change management planning

The following EMA actions have been grouped by area and whether they were obligatory or recommended actions.



6.2. NCA change management planning

This section of the change management plan focuses on the IT and business process changes that should have been considered by NCAs in the period of time leading up to and after implementation of the new EudraVigilance system.

6.2.1. NCA IT changes

The implementation of the new EudraVigilance system required the adaptation of existing national IT systems to support the use of the new ISO ICSR standard and to process the data. The sections below cover specific IT system components that should have been considered at a national level.

6.2.1.1. Implementing ISO ICSR (E2B(R3)) in national pharmacovigilance systems

Following the launch of the new EudraVigilance system, all stakeholders are able to start using the ISO ICSR (E2B(R3)) format for the submission of ICSRs. Organisations are also able to use the ICH E2B(R2) format for the submission of ICSRs after the 22 November 2017. Those organisations which have not implemented fully compliant ISO ICSR system needs to support the receipt and processing of ICSRs in the new format. The reason for this is that when cases are forwarded by the EudraVigilance system to the NCA that requests them, the format of the message received is not being changed. In addition, data processed and entered into EudraVigilance by the EMA (such as Master cases for duplicates, cases identified in the Medical Literature and in the future ICSRs recoded against the ISO IDMP terminologies) are made available to NCAs in the ISO ICSR (ICH E2B(R3)) format only.

NCAs therefore needed to either implement support for ISO ICSR (ICH E2B(R3)) in their systems or implement a backwards/forwards conversion tool to be able to process ICSR messages in the ISO ICSR (E2B(R3)) format.

6.2.1.2. EudraVigilance Gateway

NCAs using a local installation of the gateway software provided by the EMA did not need to replace this software. Guidance for making configuration changes was provided as part of the EudraVigilance Checklist for national Competent Authorities in the EEA and by EMA gateway support.

As of 22 November 2017, the transmission of ICSRs between MAHs and NCAs is no longer supported by the EMA. However, the gateway does not prevent organisations exchanging ICSRs, e.g. between NCAs and their regional pharmacovigilance centres.

As of 22 November 2017, organisations should be aware that only submissions of ICSRs to the EudraVigilance system are being considered as fulfilling the legal obligations of the sender. Therefore NCAs should ensure that the transition to simplified reporting is communicated with MAHs within their territory.

6.2.1.3. EVWEB

NCAs using EVWEB needed to prepare for the implementation of the new version of the application. The application has been upgraded to only support ICH E2B(R3) ICSR data entry. ICH E2B(R3) introduced additional data elements and different ways of structuring the data, therefore the user interface reflects this and has a different appearance.

These changes required the users within the NCA to undertake training to become familiar with the new EVWEB functionalities. Training materials and online training is available at the EudraVigilance training and support webpage; please see section 5.5. for details.

Face to face training courses for NCA users was planned for 2017 based on a survey conducted by EMA in March 2017.

6.2.1.4. EudraVigilance rerouting rules engine

The configurations of rerouting rules are being directly maintained by the NCAs using the EVWEB interface. NCAs were contacted by the EMA to set up the configuration of the rerouting rules in advance of the EudraVigilance system going live. NCAs were therefore invited to decide in advance which ICSRs they wish to have forwarded and to test the re-routing in XCOMP as of 26 June 2017. Details on the options for rerouting are described in the EU ICSR Implementation Guide.

NCAs are able to update the rerouting rules at any time as of 22 November 2017; however it should be noted that changes made may require a few hours to be applied and become active in the system.

6.2.1.5. EudraVigilance duplicate detection and management system

Additional message types have been introduced as part of the EU implementation of the ICH E2B(R3) format to support the forwarding of cases created or modified by the EMA e.g. the creation of Master cases for identified duplicate cases. NCAs should be aware that these message types did not exist in the E2B(R2) specifications and the EU backwards-forwards conversion tool is converting the message type for master cases to “masterichicsr” in the field M.1.1 when downgrading an E2B(R3) master case message.

6.2.1.6. NCA Testing

As NCAs receive cases rerouted by EudraVigilance, no testing was required with MAHs or sponsors of clinical trials that submit cases directly to the new EudraVigilance system. For those NCAs that have eSUSAR reporting forms, testing should have been planned to ensure that they are able to send those SUSARs without issues to the new EudraVigilance system.

The testing process with the EudraVigilance system has been simplified in accordance with the details provided in the EU ICSR Implementation Guide. The EMA has published a set of sample ICSR files to be uploaded and transmitted to the EudraVigilance external testing system along with a testing script to be followed by the organisation performing the testing.

NCAs were required to test once they were ready to implement a new system supporting the submission of ICH E2B(R3) ICSRs. Testing of existing their E2B(R2) system with the new EudraVigilance system was not required, however it was encouraged to be performed in advance of 22 November 2017 to identify any potential issues in the sending or receiving of ICSRs.

Instructions published on the webpage EudraVigilance: electronic reporting should have been followed. Please also refer to section 6.2.6. ‘EudraVigilance Technical Support Plan and NCA checklist’.

6.2.2. NCA business process changes

6.2.2.1. Simplified reporting of ICSRs to EudraVigilance

The main change to NCA business processes was that MAHs are no longer submitting ICSRs directly to NCAs; instead these cases are being reported to EudraVigilance before being automatically forwarded to the concerned NCA depending on the NCA re-routing settings.

Communication planning should have been put in place at national level to inform MAHs about this change and to ensure that MAHs are able to report directly to EudraVigilance in advance of the move to simplified reporting.

In addition to the reporting of serious cases to EudraVigilance system within 15-days, non-serious cases also need to be submitted by the concerned NCAs within 90-days of receipt.

NCAs using EVWEB needed to plan for an increase in resources for the manual data entry of non-serious cases into EudraVigilance taking into account that the number of non-serious cases received is generally higher than those of serious cases. However, it should be noted that with the implementation of simplified reporting, NCAs no longer need to provide ICSRs to MAHs.

6.2.2.2. Reporting of SUSARs to EudraVigilance

Until the clinical trials regulation is applicable there is no change to the current process for the submission of SUSARs for clinical trials.

Sponsors that will have a clinical trial approved through the clinical trials regulation will normally be required to send SUSARs to EudraVigilance only. Clinical trials approved through the clinical trials Directive 2001/20/EC will continue to have the same SUSAR reporting requirements as specified in the Directive for a transition period of three-years after the clinical trials regulation is applicable. The EudraVigilance system will then automatically reroute SUSARs to the concerned NCAs. However, the option will remain for small organisations to report SUSARs directly to the NCA that has approved the trial through establishing an agreement between the sponsor and the NCA concerned. The NCA will then forward any SUSARs reported to them under such agreements to the EudraVigilance system.

Planning should also be put in place at national level to inform sponsors of these changes and what is required at national level for SUSAR reporting once applicable.

6.2.2.3. Nullification requests

As NCAs have previously transmitted cases originally from MAHs, nullification requests may be received by EudraVigilance from those MAHs directly for cases that are marked in the system as being sent by an NCA. The business rules in the previous EudraVigilance system did not permit such nullifications to occur and therefore the new EudraVigilance system has amended rules to not reject such submissions.

When an organisation submits a nullification report, the new EudraVigilance system automatically marks an ICSR as nullified if the pre-existing case has been submitted by the same organisation or one of its affiliates.

If nullification is received for an EEA case where no pre-existing case from the same organisation or one of its affiliates is found in EudraVigilance, then the nullification report is stored and the nullification retransmitted to the concerned NCA. If an NCA has elected not to receive re-routed cases the EMA is periodically providing the details of nullification requests as a report via e-mail to the NCA. The concerned NCA should then review the nullification requests; if nullification is for a valid reason, the NCA should submit nullification for the case they have previously submitted to EudraVigilance.

Therefore, NCAs needed to establish processes to check if they need to nullify cases they have previously forwarded to EudraVigilance.

6.2.2.4. MAH Signal validation and management process

As described in section 6.1.2.5. the transitional arrangements to streamline the monitoring of EudraVigilance by MAHs have been agreed. During a pilot period of one year, MAHs of the active substances included in the list of active substances involved in the pilot on signal detection in EudraVigilance will have to monitor them in EudraVigilance and inform EMA and national competent authorities of validated signals with their medicines. This requirement will only start on 22 February 2018.

These transitional arrangements do not apply to obligations on simplified reporting and management of individual case safety reports (see Good pharmacovigilance practices (GVP Module VI)).

All other MAHs also have access to EudraVigilance data and are able to integrate the data into their own signal management processes. However, during the pilot period they will have no obligation to continuously monitor EudraVigilance and inform the regulatory authorities of validated signals.

After one year, EMA will base the next phase of implementation on experience gained through the pilot. For updates and further information please visit dedicated Signal Management webpage .

6.2.2.5. NCAs reporting to WHO-UMC

The reporting of ICSRs occurring in the EEA to the WHO-UMC is now performed by the EMA instead of directly by the NCAs. These ICSRs are being forwarded automatically using predefined rules that have been agreed with WHO-UMC as of 22 November 2017.

The main change for NCAs was that they no longer need to perform this activity. NCAs should have planned for the last submission of data to occur around the time of the switch to simplified reporting so that any data for the WHO-UMC covers the period up until the switch to simplified reporting. EudraVigilance submits data prospectively from 22 November 2017.

6.2.2.6. EVDAS

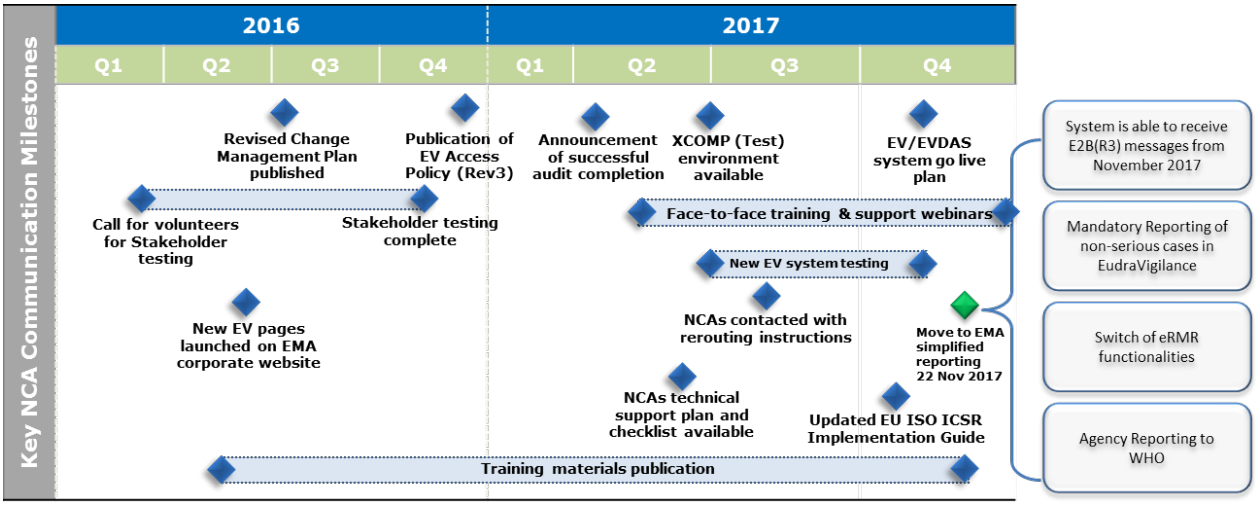
The main change for NCAs was the implementation of several new functionalities and predefined reports in EVDAS to support:

- Pharmacovigilance activities including the implementation of a new measure of disproportionality (reporting odds ratio), new functionalities for sub-group analyses, new reports and new data elements;
- Data quality monitoring, including reports on organisation reporting to EudraVigilance, safety report monitoring, expedited reporting timelines compliance monitoring;
- Access to Article 57 data, including reports on authorised medicinal products, legal entity (MAH) and QPPV details, approved substances, pharmacovigilance system master file and listings on authorised medicinal products;
- The eRMR, including the integration with EVDAS, the improvement of data visualisation and the clarification on methodology.

6.2.3. NCA communications

NCAs needed to develop a communications plan to ensure that the necessary information was circulated to their relevant stakeholders at the appropriate time so that impacted parties were aware of the changes to the reporting requirements and associated business process. They should have also

informed their stakeholders of the need to be prepared for the associated IT changes that were required.



6.2.4. NCA training

Training should have been planned for NCA staff on the new business process and new IT systems to be ready once the new system is going live on 22 November 2017. If NCAs provided training to its stakeholders, these training courses and training materials should have been updated accordingly along with plans for when the new training materials were implemented.

A EudraVigilance training plan has been produced by the Agency and published on the EMA website, outlining recommended and supporting learning for each stakeholder group. These were categorised by subject matter into 3 areas.

- Pharmacovigilance Operations – modules detailing the key changes in pharmacovigilance legislation, standards and guidelines and the impact of these on pharmacovigilance activities. It includes e-learning on the EudraVigilance Access Policy, the pharmacovigilance legislation, and revised GVP guidelines VI and IX.
- EudraVigilance Operations – modules describing the EudraVigilance and EVDAS functionalities and components, as well as the various data analysis, submission, visualisation and reporting options. Includes e-learning and user manuals on registration in EudraVigilance and EVDAS, using EVWEB to submit, visualise and export ICSRs and using EVDAS to analyse data.

IT Systems Operations – modules providing instructions on the modifications required to prepare local systems for the EudraVigilance system enhancements. It included e-learning on IT development and ICSR testing.

NCAs were advised to follow all the recommended e-learnings in each area whether they are new or existing users.

In addition to the training modules, optional quizzes have been made available for some training modules, allowing users to verify their e-learning. The majority of the training modules and supporting material has been published on the EudraVigilance Training and Support webpage.

6.2.5. NCA change management plan summary

The following NCA actions have been grouped by area and whether they were obligatory or recommended actions.

People

Must Do

- Staff to undergo training on:
  - Use of the new ICH E2B(R3) format
  - EVDAS
  - GVP Modules VI (revision 2)
  - GVP Modules IX (revision 1)
  - EudraVigilance Access Policy

  Refer to detailed training catalogue for all training modules

Should Do

- Undertake training on EVWEB to become familiar with application changes;
- Complete testing of existing systems six to three months prior to the new system going live;
- Consider resource and budget implications associated with the implementation of the ISO ICSR standard and supporting the receipt of ICH E2B(R3) messages. This concerns the work of IT system developers in particular.

Information

Should Do

- Prepare a communication plan to keep local stakeholders informed about the switch to the simplified reporting and the process changes related to signal management
- Ensure that the transition to simplified reporting to EV is communicated to marketing-authorisation holders within their territory

Technology

Must Do:

- Upgrade the local pharmacovigilance system to be able to generate and process ICSRs in the ICH E2B(R3) format
- Ad interim, install a backwards/forwards conversion tool (where applicable).

Should Do:

- Prepare internal plans in relation to the implementation of the new EudraVigilance system and the resulting changes in electronic reporting, downloading and analysis of data.

Process

Must Do:

Update existing processes:

- To receive ICSRs reported by marketing-authorisation holders and rerouted by EudraVigilance;
- To stop sending reports from healthcare professionals and patients to marketing-authorisation holders;
- To stop sending ICSRs to WHO UMC;
- To start reporting of suspected non-serious adverse reactions to EudraVigilance within 90 days of receipt;
- To comply with the provisions set out in revision 2 of GVP Module VI;
- To perform signal detection and validation in line with revision 1 of GVP Module IX and the new EVDAS reports and data outputs;
- To support the submission of validated signals by marketing-authorisation holders.

Should Do:

- Coordinate the transition to the simplified reporting with the new system's implementation and all stakeholders involved;
- Ad interim during the transition, follow the specific nullification (to indicate that a case is no longer valid) process as outlined in the EU ICSR Implementation Guide

6.2.6. EudraVigilance Technical Support Plan and NCA checklist

To further assist NCAs in preparing for the go-live of the new EudraVigilance (EV) system on 22 November 2017, the Agency has released a 'EudraVigilance Technical Support Plan' and 'EudraVigilance Checklist for national Competent Authorities in the EEA'.

The technical support plan described the testing and support activities, while the checklist outlined easy to follow steps to assist NCAs in preparing for the technical and business process changes.

The technical support plan and the checklist are complimentary to this EudraVigilance Stakeholder Change Management Plan and should have been read in conjunction.

6.3. MAH Change management planning

This section of the change management plan focuses on the IT and business process changes that should have been considered by MAHs in the period of time leading up to and after the implementation of the new EudraVigilance system.

6.3.1. MAH IT changes

The implementation of the new EudraVigilance system required the adaption of existing IT systems at the level of MAHs to support the new ISO ICSR standard and to the changes to the processing of the data. The sections below cover specific IT system components that should have been considered by MAHs.

6.3.1.1. Implementing ISO ICSR (E2B(R3)) format in MAH's phV systems

Following the new EudraVigilance system launch on 22 November 2017, MAHs have the choice to start using the ISO ICSR (E2B(R3)) format for the submission of ICSRs, assuming that all testing has been completed beforehand. MAHs can continue to use the ICH E2B(R2) format for the submission of ICSRs after the new system implementation. However, MAHs that chose not to implement a fully compliant ISO ICSR system need to support the ability to process the new format. The reason for this is that when ICSRs are made available for MAHs to download from EudraVigilance in accordance with the EudraVigilance Access Policy, these are in the E2B(R3) format only.

MAHs needed to consider implementing a fully ISO ICSR compliant system or to use a backwards/forwards conversion tool to support the processing of ICSRs in the ICH E2B(R3) format and the ICSR acknowledgements.

6.3.1.2. Electronic gateway

MAHs using an electronic gateway solution did not need to replace their current software solution. However, configuration changes may have been required in order to support the processing of E2B(R3) messages including the acknowledgments returned (EudraVigilance will only return E2B(R3) acknowledgments). Further guidance was provided as part of the EudraVigilance testing instructions and checklist for Marketing Authorisation Holders and Sponsors of Clinical Trials in the EEA published at EudraVigilance change management webpage.

With simplified reporting effective, the transmission of ICSRs between MAHs and NCAs is no longer supported by the EMA. However, the gateway does not prevent MAHs exchanging ICSRs with other MAHs or sponsors of clinical trials. It should be noted that, organisations performing such transmissions are not able to contact the gateway helpdesk for support if issues occur with these transmissions.

Following the implementation MAHs should be aware that only submissions of ICSRs to the EudraVigilance system are considered as fulfilling the MAH's legal obligations. Therefore, MAHs should have ensured that modifications to their submission systems were configured and tested well in advance of the planned implementation.

6.3.1.3. EVWEB

MAHs using EVWEB needed to prepare for the implementation of the new version of the application. The application has been updated to only support E2B(R3) ICSR data entry. The E2B(R3) standard has introduced additional data elements and different ways of structuring the data; therefore the user interface has been changed and has a different appearance.

These changes required the users within the MAH organisation to undertake training to become familiar with the new system. Training materials, release notes and online training have been made available and published on the EudraVigilance training and support webpage (please see section 5.5. for details).

It was recommended that MAHs plan to start training their staff well in advance of the new system being implemented.

The results of queries performed in EVWEB are based on access levels defined in the EudraVigilance Access Policy.

6.3.1.4. EV downloading ICSRs concerning MAH's products/substance related products

After the switch to simplified reporting, MAHs no longer receive ICSRs directly from NCAs. In order for MAHs to receive ICSRs concerning their products or substances contained in one of their products, the ICSR download functionality of EVWEB should be used.

In line with the EudraVigilance Access Policy MAHs are able to request ICSRs (Access Policy Level 2A) for any substance contained in one of their medicinal products that have been reported as a suspect or interacting drug. The data elements that are provided for the ICSRs are based on the data elements as defined in the EudraVigilance Access Policy. The access levels for MAHs of a particular substance are determined based on the Article 57 substance and medicinal product information submitted to the XEVMPD or future ISO IDMP system.

In addition to Level 2A access to ICSR data, MAHs are able to obtain Level 2B access (including the case narrative data elements) in the context of performing signal evaluation as detailed in GVP modules VI & IX. Requests made by authorised user are logged and the requester is asked to provide details of the signal being evaluated. In addition the requestor has to confirm that they adhere to the EudraVigilance Access Policy Confidentiality Undertaking.

It should be noted that the ICSRs that are provided via this download functionality are only available in E2B(R3) format.

The download function was made available through the new EVWEB application.

6.3.1.5. Downloading MLM ICSRs

The MLM ICSR Export manager was replaced with the download functionality in the new EVWEB application as outlined above. The interface looks different to the previous one, and users needed to explicitly choose to include MLM Service cases as part of the download functionality. Otherwise the same filtering criteria as previously are available and users can download zip files containing xml versions of the cases for further processing in their local pharmacovigilance database as applicable.

6.3.1.6. MAH Testing

As MAHs only send cases to EudraVigilance, no testing was required with NCAs.

The testing process with the EudraVigilance system has been simplified in accordance with the details provided in the EU ICSR Implementation Guide. The EMA has published a set of sample ICSR files to be uploaded and transmitted to XCOMP along with a testing script to be followed by the organisation testing.

MAHs were required to test once they were ready to implement the new system supporting the submission of E2B(R3) ICSRs. Testing of existing E2B(R2) systems with the new EudraVigilance system was not required, however it was encouraged in advance of the new system going live to identify any potential issues in advance. Therefore, MAHs should have planned to complete any testing of their existing systems prior to the new system going live to give time for any issues to be addressed.

Instructions published on the webpage EudraVigilance: electronic reporting should have been followed. Please also refer to section 6.3.6. 'Checklist and testing instructions for MAHs and Sponsors of Clinical Trials in the EEA'.

A specific testing time slot can be booked by contacting EMA at gattesting@ema.europa.eu. This applies only where the testing refers to a new ICH E2B(R3) compliant system or a major update of an existing E2B(R2) compliant system that would require retesting with EudraVigilance.

6.3.2. MAH business process changes

6.3.2.1. Simplified reporting of ICSRs to EudraVigilance

The main change to MAH business processes was that MAHs are no longer providing ICSRs directly to NCAs. MAHs needed to ensure that all reportable ICSRs were submitted to EudraVigilance only as of 22 November 2017. In addition to the reporting of serious cases to EudraVigilance within 15-days, non-serious cases that occurred in the EEA need to be submitted within 90-days of receipt.

Planning should have been put in place by each MAH to ensure that they are able to report directly to EudraVigilance in advance of the move to simplified reporting. Any submissions made by MAHs to NCAs after the move to simplified reporting will result in the MAH of not being compliant with their legal obligations.

MAHs using EVWEB needed to plan for an increase in resources for the manual data entry of non-serious EEA cases into EudraVigilance, taking into account that the number of non-serious cases received is generally higher than serious cases.

6.3.2.2. MAH signal validation and management process

The new process for signals validated by MAHs has been designed, discussed and consulted on during the first revision of the GVP Module IX on signal management. The revision of GVP Module IX describes the MAH signal validation and management process, including information on:

- MAH responsibility to continuously monitor the safety of their medicinal products and inform the authorities of any new information that might have an impact on the marketing authorisation [DIR Art 23(2), REG Art 16(2)];

- MAH responsibility to keep product information up-to-date in the light of scientific knowledge, including the assessments and recommendations made public via the European medicines web-portal [IR Art 11(1)(f), DIR Art 23(3), REG Art 16(3)];
- Periodicity of monitoring of EudraVigilance data;
- Notifications and procedural options for signals validated by the MAHs in the EU.

As described in section 6.1.2.5., EMA and the European Commission have agreed transitional arrangements to streamline the monitoring of EudraVigilance by MAHs.

During a pilot period of one year, MAHs of the active substances included in the list of active substances involved in the pilot on signal detection in EudraVigilance will have to monitor them in EudraVigilance and inform EMA and national competent authorities of validated signals with their medicines.

This requirement will only start on 22 February 2018, effectively granting those MAHs a three-month 'grace period' to familiarise themselves with the new EudraVigilance system, the new tools to support EudraVigilance monitoring and to finalise their own processes.

These transitional arrangements do not apply to obligations on simplified reporting and management of individual case safety reports (see Good pharmacovigilance practices (GVP) Module VI and EudraVigilance change management).

All other MAHs also have access to EudraVigilance data and are able to integrate the data into their own signal management processes. However, during the pilot period they will have no obligation to continuously monitor EudraVigilance and inform the regulatory authorities of validated signals.

After one year, EMA will base the next phase of implementation on experience gained through the pilot. For updates and further information please visit dedicated Signal Management webpage .

6.3.2.3. EVDAS

Access was granted to EVDAS by MAHs for the use of signal detection and analytical/reporting functions to the extent necessary to comply with their pharmacovigilance obligations. Such functions include:

- eRMRs based on the eRMR used within the EU network and the EMA for signal detection activities;
- Substance groupings for medicinal products for which MAHs hold a marketing authorisation;
- Individual case line listings and ICSR forms.

6.3.3. MAH training

Training should have been planned for MAH staff on the new business process and new EudraVigilance System functionalities to be ready when the EudraVigilance system launch on 22 November 2017. It was advised to start training well in advance of the new system being implemented with refresher training planned at regular intervals in the months leading up to implementation.

A EudraVigilance training plan has been produced by the Agency, outlining recommended and supporting learning for each stakeholder group. These were categorised by subject matter into 3 areas.

- Pharmacovigilance Operations – modules detailing the key changes in pharmacovigilance legislation, standards and guidelines and the impact of these on pharmacovigilance activities. This

included e-learnings on the EudraVigilance Access Policy, pharmacovigilance legislation, and the revised GVP guidelines.

- EudraVigilance Operations – modules describing the EudraVigilance and EVDAS functionalities and components, as well as the various data analysis, submission, visualisation and reporting options. This includes e-learning and user manuals on registration in EudraVigilance and EVDAS, using EVWEB to submit, visualise and export ICSRs and using EVDAS to analyse data. Dedicated modules have been created for MAH users for self-learning on how to access EVDAS and how to use the eRMR in the context of signal detection/validation.
- IT Systems Operations – modules providing instructions on the modifications required to prepare internal systems for the EudraVigilance system enhancements. This include e-learning on IT development and ICSR testing.

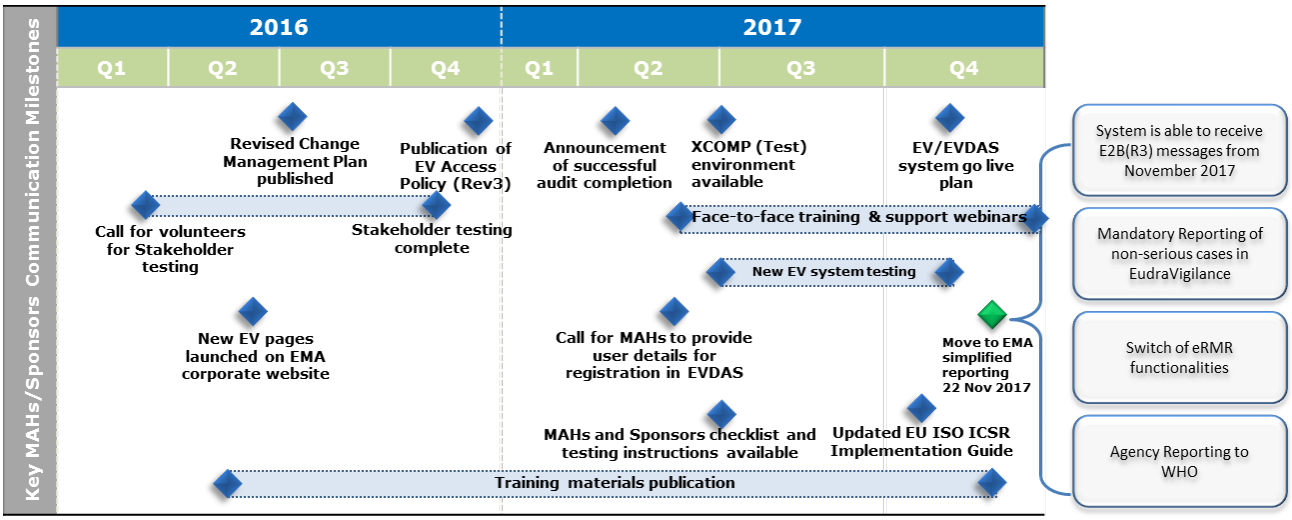
MAHs were advised to follow all the recommended e-learnings in each area whether they are new or existing users.

In addition to the training materials, optional quizzes have been made available when relevant for some training modules, allowing users to verify their learning.

The key training materials have already been made available on the EudraVigilance Training and Support webpage. User manuals were released in the second quarter of 2017.

6.3.4. MAH communications

MAHs should have considered developing a communication plan to ensure that the necessary information was circulated within their own organisation and with other organisations that they work with. These communications should have been made at appropriate times to ensure that impacted parties were aware of the changes to the reporting requirements and associated business process. They should have also informed their IT departments of the need to be prepared for the associated IT changes that were required to be made.



6.3.5. MAH change management summary

The following MAH actions have been grouped by area and whether they were obligatory or recommended actions.

People

Must Do:

- Assign specific users the permission to access EVDAS and register those users line with the EudraVigilance registration process;
- Staff to undergo training on:
  - Use of the new ICH E2B(R3) format
  - EVDAS
  - GVP Modules VI (revision 2)
  - GVP Modules IX (revision 1)
  - EudraVigilance Access Policy

  Refer to detailed training catalogue for all training modules

Should Do:

- Undertake training on EVWEB to become familiar with new functionalities and changes;
- Consider resource implications associated with the implementation of the ISO ICSR standard and supporting the receipt of R3 messages as well as the operation of a backwards/forwards conversion tool ad interim and where necessary.
- EMA foresees that new requirements may necessitate an increase in resources, including:
  - Meeting the new signal management requirements using EudraVigilance data and screening electronic reaction monitoring reports;
  - The legal requirement to report non-serious cases in EudraVigilance;
  - The mechanism for searching and downloading ICSRs using the ICSR download functionality of EudraVigilance to obtain access to ICSRs from national competent authorities in the EEA;
  - Training of staff.

Technology

Must Do:

- Configure, where applicable, the local Gateway to support ICH E2B(R3) messages. It is not necessary to replace the software;
- Ad interim, install a backwards/forwards conversion tool if the ICH E2B(R3) format cannot be processed yet locally;
- Upgrade and move to an ICSR ICH E2B(R3) compliant systems.

Should Do:

- Familiarise with electronic transmission format based on the ISO ICSR standard
- Plan for testing of local pharmacovigilance system adaptations.

Information

Must Do:

- Monitor data available in the system and to inform EMA and national competent authorities about safety signals validated to contain sufficient evidence to necessitate further analysis.

Should Do:

- Prepare a communication plan to inform affiliates, contractual partners and other stakeholders about the changes to take place with the launch of the new EudraVigilance system and related process changes.

Process

Must Do:

Update existing processes:

- To download ICSRs from national competent authorities in the EEA using the EudraVigilance ICSR download functionality;
- To stop sending ICSRs to national competent authorities in the EEA;
- To start reporting of suspected non-serious adverse reactions to EudraVigilance within 90 days of receipt;
- To comply with the provisions set out in revision 2 of GVP Module VI;
- To perform signal detection and validation in line with revision 1 of GVP Module IX and the new EVDAS reports and data outputs;
- To support the submission of validated signals to national competent authorities in the EEA.

Should Do:

- Align reporting of ICSRs (for medicinal products authorised in the EEA) occurring within or outside the EEA so that these reports are transmitted only to EudraVigilance in compliance with the pharmacovigilance legislation;
- Ensure that the transition to simplified reporting is coordinated in line with the guidance and communication provided by EMA and NCAs in EEA Member States.

6.3.6. MAH checklist and testing instructions

To further assist MAHs in preparing for the go-live of the new EudraVigilance (EV) system on 22 November 2017, the Agency has released a 'Checklist and testing instructions for Marketing Authorisation Holders and Sponsors of Clinical Trials in the EEA'.

This document provided some general testing instructions, easy to follow steps to assist MAHs and sponsors in preparing for the technical and business process changes. Reference was also made to the training and support offerings, which are available at the dedicated EudraVigilance training and support webpage, which provided detailed learnings on how to prepare for the changes to come. The checklist is complimentary to this EudraVigilance Stakeholder Change Management Plan and should have been read in conjunction.

6.4. Sponsors of clinical trials change management planning

This section of the change management plan focuses on the IT and business process changes that should have been considered by sponsors of clinical trials in the period of time leading up to and after implementation of the EudraVigilance 8 system.

6.4.1. Sponsor of clinical trials IT changes

6.4.1.1. Implementing ISO ICSR (E2B(R3)) support in clinical trial systems

Following the new EudraVigilance System launch on 22 November 2017, sponsors of clinical trials have the choice to start using the ISO ICSR (E2B(R3)) format for the submission of ICSRs, assuming that all testing has been completed beforehand.

It should be noted that sponsors can continue to use E2B(R2) for the submission of SUSARs. However, sponsors of clinical trials should have planned to develop their systems to support the new format.

6.4.1.2. Electronic gateway

Sponsors of clinical trials using an electronic gateway solution did not need to replace their current software solution. However, configuration changes may have been required in order to support the processing of E2B(R3) messages including the acknowledgments returned (EudraVigilance will only return E2B(R3) acknowledgments). Guidance was provided in the 'Checklist and testing instructions for Marketing Authorisation Holders and Sponsors of Clinical Trials in the EEA'.

With simplified reporting effective in accordance with the Clinical Trials Regulation, the gateway does not prevent sponsors of clinical trials exchanging SUSARs with MAHs or other sponsors of clinical trials; however, this type of exchange is not supported by the EMA. It should be noted that organisations performing such transmissions are not able to contact the gateway helpdesk for support if issues occur with these transmissions.

When the Clinical Trials Regulation becomes applicable, sponsors of clinical trials should be aware that for trials approved through the clinical trials regulation, only electronic submissions of SUSARs to the EudraVigilance system will be considered as fulfilling their legal obligations, unless the sponsor has a prior agreement with the concerned NCAs to submit those SUSARs through national systems. Sponsors should ensure that modifications to their submission systems are configured and tested well in advance of the planned implementation.

6.4.1.3. EVWEB

Sponsors of clinical trials using EVWEB needed to prepare for the implementation of the new version of the application. The application has been updated to only support E2B(R3) ICSR data entry. The E2B(R3) standard introduced additional data elements and different ways of structuring the data; therefore the user interface has been updated and has a different appearance.

These changes required the users within the sponsor's organisation to undertake training to become familiar with the new system. Training materials and online training has been made available and published on the dedicated EudraVigilance training and support webpage; please see section 3.6. for details.

It was recommended that sponsors plan to start training their staff six months in advance of the new system being implemented, followed by regular refresher training.

6.4.2. Sponsor of clinical trials business process changes

6.4.2.1. Reporting of SUSARs to EudraVigilance

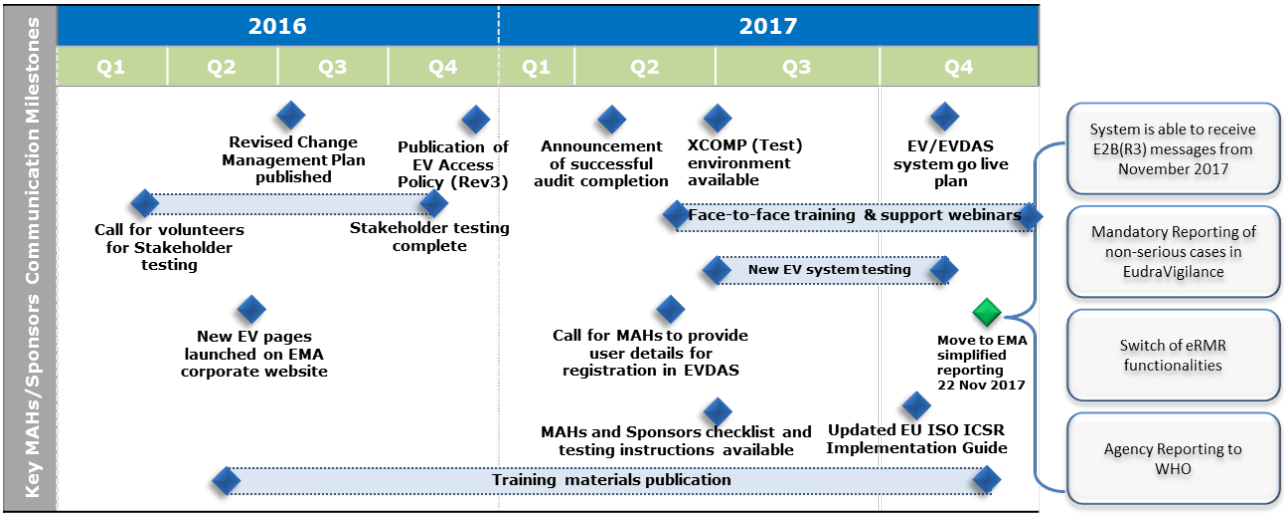
Until the clinical trials regulation (EU No 536/2014) is applicable there is no change to the current process for the submission of SUSARs for clinical trials authorised under the clinical trials directive 2001/20/EC.

Clinical trials authorised under the clinical trials directive 2001/20/EC will continue to have the same SUSAR reporting requirements as specified in the directive for a transition period of 3 years after the clinical trials regulation is applicable.

Sponsors that have a clinical trial authorised under the clinical trials regulation are normally required to send SUSARs to EudraVigilance only. The EudraVigilance system will then automatically reroute the SUSARs to the concerned NCAs. However, the option remains for small organisations to report SUSARs directly to the NCA that has approved the trial through establishing an agreement between the sponsor and the NCA concerned. The NCA will then forward any SUSARs reported to them under such agreements to the EudraVigilance system. It is expected that this will be for the submission of SUSARs by small organisations that are not able to create electronic submissions and do not have the resources to use EVWEB. The majority of SUSAR submissions are expected to occur through the simplified reporting to EudraVigilance and a set of business rules will be put in place for the automated forwarding of these SUSARs to the NCA requesting them.

6.4.3. Sponsor of clinical trials communications

Sponsors should have considered developing a communication plan to ensure that the necessary information was circulated within their own organisation and with other organisations that they work with. These communications should have been made at appropriate times to ensure that impacted parties were aware of the changes to the reporting requirements and associated business process. They should have also informed their IT departments of the need to be prepared for the associated IT changes that were required to be made.



6.4.4. Sponsor of clinical trials training

Training should have been planned for the staff of sponsors to explain the changes to IT systems to be ready for the go-live of the new EudraVigilance System on 22 November 2017. It was advised to start training well in advance along with refresher training planned at regular intervals in the months leading up to implementation.

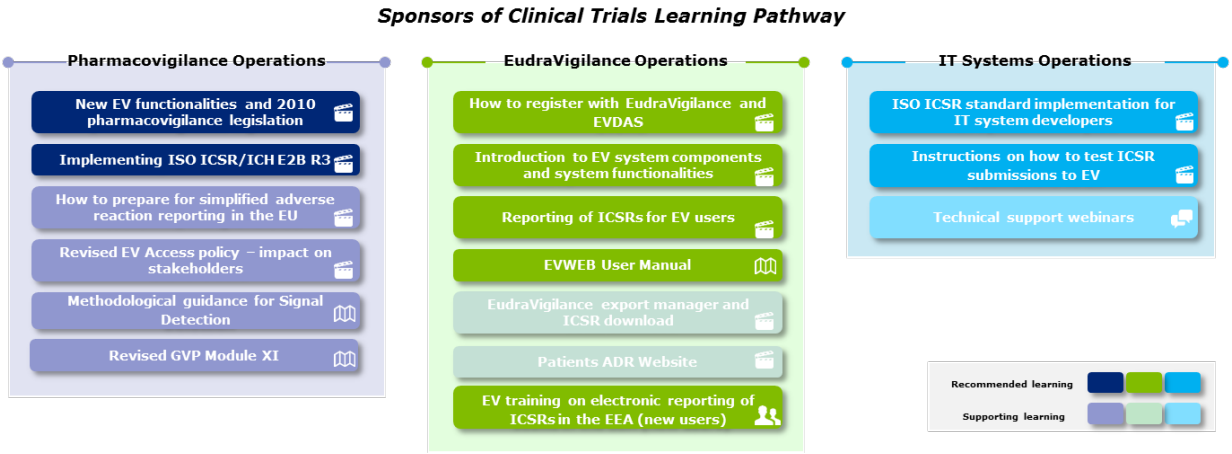
A EudraVigilance training plan has been produced by the Agency, outlining recommended and supporting learning for each stakeholder group. These were categorised by subject matter into 3 areas.

- Pharmacovigilance Operations – modules detailing the key changes in pharmacovigilance legislation, standards and guidelines and the impact of these on pharmacovigilance activities. It was recommended that sponsors focus on the new EudraVigilance functionalities and implementing the ISO ICSR/ICH E2B(R3) standard.
- EudraVigilance Operations – modules describing the EudraVigilance and EVDAS functionalities and components, as well as the various data analysis, submission, visualisation and reporting options. It was recommended to focus on modules related to EVWEB and the reporting of ICSRs.
- IT Systems Operations – modules providing instructions on the modifications required to prepare internal systems for the EudraVigilance system enhancements. It included e-learning on IT development and ICSR testing.

Sponsors of clinical trials were advised to follow all the recommended learnings in each area whether they are new or existing users.

In addition to the training materials, optional quizzes have been made available for some training modules, allowing users to verify their learning.

The key training materials have been made available on the EudraVigilance Training and Support page.



6.4.5. Sponsor of clinical trials change management summary

The following Sponsor actions have been grouped by area and whether they were obligatory or recommended actions.

People

Should Do:

- Ensure that users of EVWEB undertake training to become familiar with the new system; Refer to detailed training catalogue for all training modules
- Plan training for staff six months prior to the implementation of the new system. This should be followed up by regular refresher trainings, at least three months and two weeks before implementation.

Information

Should Do:

- Consider developing a communication plan to ensure that information on changes is circulated internally and partners and inform IT departments of associated IT change requirements.

Technology

Should Do:

- Plan to develop systems to support the ICH E2B(R3) format; submissions of SUSARs will be possible in the E2B(R2) format even after the implementation of the new system;
- Configure, where applicable, the local Gateway to support ICH E2B(R3) messages. It is not necessary to replace the software;
- Ensure that modifications to submission systems are configured and tested well in advance of the planned implementation.

Process

Should Do:

- Continue to report SUSARs for clinical trials authorised under Directive 2001/20/EC in accordance with the currently established process;
- Adapt their processes of reporting in line with the new ICH E2B(R3) format, data elements and business rules if they use EVWEB for SUSAR reporting;
- Adapt their business processes in line with the communication and instructions provided on the dedicated Clinical trials in human medicines webpage of the Agency

6.4.6. Sponsors of clinical trials checklist and testing instructions

To further assist sponsors of clinical trials (sponsors) in preparing for the go-live of the new EudraVigilance (EV) system on 22 November 2017, the Agency has released a '[Checklist and testing instructions for Marketing Authorisation Holders and Sponsors of Clinical Trials in the EEA]'.

This document provided some general testing instructions, easy to follow steps to assist MAHs and sponsors in preparing for the technical and business process changes. Reference was also made to the training and support offerings, which are available at the dedicated [EudraVigilance training and support webpage], which provided detailed learnings on how to prepare for the changes to come. The checklist is complimentary to this EudraVigilance Stakeholder Change Management Plan and should have been read in conjunction.

6.5. WHO-UMC change management planning

This section of the change management plan focuses on the IT and business process changes that should have been considered by the WHO-UMC in the period of time leading up to and after implementation of the new EudraVigilance system.

6.5.1. Implementing ISO ICSR (E2B(R3))

As of 22 November 2017, the WHO started to receive ISO ICSR E2B(R3)) format messages from the EMA for ICSRs originating in the EEA. Therefore, the WHO-UMC should have ensured that support for the new format was implemented and testing conducted before hand.

6.5.2. Business process change

The reporting of ICSRs occurring in the EEA to the WHO-UMC is performed by the EMA instead of directly by NCAs. These ICSRs are being forwarded automatically using predefined rules.

The main change for WHO-UMC was that they no longer need to receive ICSRs from EEA NCAs. The NCAs provided a last submission of data around the time of the switch to simplified reporting. The WHO-UMC received EEA data for the period up until the switch to simplified reporting from EEA NCAs and as of 22 November 2017 EudraVigilance submits EEA data to the WHO-UMC prospectively.