

# **SCOPE Work Package 5 Signal Management**

## **Best Practice Guide**

June 2016



**SCOPE**

# SCOPE Work Package 5

## Signal Management

### Best Practice Guide



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## 1. Introduction

### 1.1 Purpose of the document

The Strengthening Collaboration for Operating Pharmacovigilance in Europe (SCOPE) Joint Action has been established to maximise the effective implementation of the European Pharmacovigilance legislation that came into effect in June 2012 by the National Competent Authorities (NCAs) in European Union (EU) Member States (MSs). Funded by the Consumers, Health and Food Executive Agency (CHAFEA), with contributions from the MS partners, SCOPE aims to provide practical tools and guidance. SCOPE aims to deliver sustainable outcomes for MSs that last beyond the end of the three-year project through the creation of training materials, living documents and templates, which can be reviewed and adapted periodically.

SCOPE is divided into eight separate Work Packages (WPs). Three of these are focused on more practical aspects – coordination, dissemination and evaluation – spanning all areas of the project. The other five WPs focus on pharmacovigilance topics to deliver specific and measurable objectives, ranging from improvements in Adverse Drug Reaction (ADR) reporting to assessment of quality management systems for NCAs.

SCOPE Work Package 5 (WP5) seeks to further improve signal management within the network of EU Medicines NCAs.

Within WP5, the partners have been working on four topics:

1. Signal detection – lead: Medicines Evaluation Board (MEB).
2. Signal validation and prioritisation – lead: Agencia Española de Medicamentos y Productos Sanitarios (AEMPS).
3. Signal confirmation and assessment – lead: Danish Medicines Agency (DKMA).
4. Reports of special interest – lead: Medicines and Healthcare Products Regulatory Agency (MHRA).

Additionally, the Swedish Medical Products Agency (MPA) was actively involved in WP5.

Questionnaires have been used to gather information on all aspects of signal management: signal detection, validation, prioritisation, confirmation, assessment and management of signals raised from reports of special interest, including medication error and misuse/abuse of medicines. Using the available data and information, this best practice guidance has been developed for the European Network and will be complemented with training sessions. The overall objective of the activities of WP5 are to implement a shared understanding of best practice in signal management across the EU network, in order to document and deliver recommendations regarding the timely detection, management and assessment of safety signals across the EU network. There is a focus on signals of special interest and medication error.

In addition, SCOPE WP5 identified areas for future research and development.

## 1.2 Definitions and abbreviations

Terminology	Description
ADR	Adverse Drug Reaction
AE	Adverse Event
AEMPS	Agencia Española de Medicamentos y Productos Sanitarios
ATC	Anatomic Therapeutic Chemical Classification
BPG	Best Practice Guide
CAP	Centrally Authorised Product
CIOMS	Council for International Organizations of Medical Sciences
CHAFAEA	Consumer, Health and Food Executive Agency
CHMP	Committee for Medicinal Products for Human Use
CMDh	Coordination Group for Mutual Recognition and Decentralised Procedures – Human
CPRD	Clinical Practice Research Datalink
CSP	Core Safety Profile
DKMA	Danish Medicines Agency
DHPC	Direct Healthcare Professional Communication
DME	Designated Medical Event
EBGM	Empirical Bayes Geometric Mean
EC	European Commission
EMA	European Medicines Agency
ENCePP	European Network of Centres for Pharmacoepidemiology and Pharmacovigilance
EPITT	European Pharmacovigilance Issues Tracking Tool
eRMR	electronic Reaction Monitoring Report
EU	European Union
EUNTC	EU Network Training Centre
EVDAS	EudraVigilance Data Analysis System
FAERS	FDA Adverse Event Reporting System
FDA	Food and Drug Administration
GAB	General Advisory Board
GVP	Guideline on good pharmacovigilance practices

Terminology	Description
HLGT	High Level Group Term
HLT	High Level Term
IC	Information Component
ICSR	Individual Case Safety Report
IME	Important Medical Event
IMI	Innovative Medicines Initiative
IR	Implementing Regulation
IRN	Incident Review Network
LMS	Lead Member State
MAH	Marketing Authorisation Holder
MEB	Medicines Evaluation Board
MedDRA	Medical Dictionary for Regulatory Activities
MHRA	Medicines and Healthcare products Regulatory Agency
MPA	Medical Products Agency
MS	Member State
NAP	Nationally Authorised Product
NCA	National Competent Authority
NUI	Non Urgent Information
PASS	Post Authorisation Safety Study
PRAC	Pharmacovigilance Risk Assessment Committee
PRR	Proportional Reporting Ratio
PSUR	Periodic Safety Update Report
PT	Preferred Term
PROTECT	Pharmacoepidemiological Research on Outcomes of Therapeutics
RA	Rapid Alert
RMP	Risk Management Plan
ROR	Reporting Odds Ratio
RPPS	Regulatory Pharmacovigilance Prioritisation System
SCOPE	Strengthening Collaboration for Operating Pharmacovigilance in Europe
SmPC	Summary of Product Characteristics

Terminology	Description
SMART	Signal Management Review Technical Working Group
SMQ	Standardised MedDRA Query
SOC	System Organ Class
SOP	Standard Operating Procedure
WHO	World Health Organization
WP	Work Package
WPL	Work Package Lead

## 1.3 Background

The objectives of WP5 of the SCOPE Joint Action were defined at the start of the project as:

*‘to create, document and deliver recommendations for consistent and timely procedures for the timely management of safety signals across the EU network. There is an additional focus on detection and management of signals of special interest, such as those arising from medication errors, drug abuse, misuse, off label use and from the use of biological medicines.’*

Signal management is a key activity in pharmacovigilance. The signal management process is a set of activities performed to determine whether, based on an examination of individual case safety reports (ICSRs), aggregated data from active surveillance systems or studies, literature information or other data sources, there are new risks associated with an active substance or a medicinal product or whether risks have changed (1).

The EU legislation, implemented in 2012, introduced an EU-wide process for signal management overseen by the Pharmacovigilance Risk Assessment Committee (PRAC) with specific responsibilities and interactions between all stakeholders involved.

The EU legislation that includes provisions for signal management comprises:

- Regulation (EU) No 1235/2010 amending Regulation (EC) No 726/2004(2)
- Directive 2010/84/EU amending Directive 2001/83/EC (3)
- Commission Implementing Regulation (EU) No 520/2012 on the Performance of Pharmacovigilance Activities Provided for in Regulation (EC) No 726/2004 and Directive 2001/83/EC (4)

This legislation is supported by the ‘Guideline on good pharmacovigilance practices (GVP) Module IX Signal management’ (5) and a European Medicines Agency (EMA) Questions and Answers document (6). This Best Practice Guidance (BPG) is based on the guidance applicable at the time of finalisation of this document and any reference in this document to GVP Module IX refers to the version dated 22nd June 2012. Of note, GVP Module IX is under revision at the time of finalisation of this document. This revision will provide more streamlined information on scientific aspects of signal management as well as clarifications on terminology, roles and responsibilities and processes, updated guidance on the periodicity of monitoring of EudraVigilance, procedural options for signals validated by marketing authorisation holders, revised definitions and processes for emerging safety issues. Also, an addendum on methodological aspects of signal detection from spontaneous reports has been developed by the EMA that provides useful information.

The pharmacovigilance legislation (2012) has had an impact on already existing systems at national level. A way to facilitate signal management, as described in the legislation, is to further develop a common understanding and tools that could be used at the level of NCAs.

This BPG is a deliverable of WP5, together with a training plan covering signal management, with a primary focus on the process in the MSs. It provides recommendations for efficient and effective signal management at MS level. The majority of these recommendations are based upon the results of a survey conducted amongst MSs, during which best practices were identified (7). Recommendations are also supported by literature and expertise within WP5, the SCOPE project team, the SCOPE General Advisory Board (GAB) and the EMA.

The BPG builds upon the Report of the Council for International Organisations of Medical Sciences (CIOMS) Working group VIII ‘Practical Aspects of Signal Detection in Pharmacovigilance’, which contextualises different signal detection approaches within a holistic signal management perspective (8).

At the level of the NCAs there are differences in terms of structure, organisation and resources available. The recommendations from this BPG, together with the legal requirements on signal management and the existing guidance (GVP) aim to facilitate current signal management in the EU.

In addition to practical recommendations, SCOPE WP5 also provides recommendations for future research and development (see [Annex 1](#)), aimed at improving signal management within the EU regulatory network.



## 1.4 Context of the Best Practice Guide

The target audience for this BPG is primarily European assessors and signal management staff working at European NCAs involved in any step of the signal management process. The BPG is also useful for other NCA staff, such as policy makers from national agencies or regional pharmacovigilance centres, as applicable. It may also be useful for other stakeholders involved in signal management, such as the EMA or Marketing Authorisation Holders (MAHs).

The BPG does not replace existing guidance, but provides a focus on the practical aspects and challenges of signal management at the level of NCAs. The readers of the BPG should be familiar with all relevant legislation and available guidelines, such as the GVPs Module IX – Signal management (5) and Questions and Answers on signal management (6). A basic understanding of other regulatory procedures, such as Periodic Safety Update Reports (PSURs) and Risk Management Plans (RMPs) assessments and (safety) variations, is also recommended.

The most important aspect to keep in mind in the area of signal detection and signal management is to apply sound scientific and clinical judgment. The BPG aims to help with the legislative context. In the development of this BPG, SCOPE WP5 liaised with other initiative groups including:

- The Signal Management Review Technical Working Group (SMART), which is a collaboration between MSs and the EMA to establish, disseminate and periodically review tools and methodologies to facilitate the implementation of the signal management process
- The Pharmacoepidemiological Research on Outcomes of Therapeutics by a European Consortium (PROTECT) project (9), which aimed to develop new methods and assess existing ones for signal detection from spontaneous reports, electronic health records and clinical trials. The Innovative Medicines Initiative (IMI) PROTECT group has developed a set of recommendations pertaining to good signal detection practices, which were recently published (10)
- The SCOPE General Advisory Board (GAB), which ensured the liaison with the World Health Organization (WHO), the EMA, healthcare professionals and patient organisations.

EU procedures for signal management (including information for MAHs) are provided in the GVP Module IX.

## 1.5 Findings from the survey on signal management

The data used for the development of this BPG were collected through a web-based survey among the MSs on current practices in signal management (with a focus on national activities). The survey was conducted during the period of July 2014 to October 2014. Twenty-five out of thirty-one MSs responded to the questionnaire.

The survey identified several challenges for the MSs, including:

- Ambiguity in terminology and definitions in signal management
- The need for resources and good training

- The need to be aware of the available sources of information and access to data
- The need for tools to support the signal management process.

A summary of the survey findings is provided below, the full text can be found on the SCOPE website: [www.scopejointaction.eu/assets/files/SCOPE-WP5-FULL-report.pdf](http://www.scopejointaction.eu/assets/files/SCOPE-WP5-FULL-report.pdf).

### **Signal detection**

MSs have systems in place to monitor ADRs and perform signal detection in national databases as well as in EudraVigilance. Methods for signal detection in the national databases vary between MSs. The screening of EudraVigilance takes place via the electronic reactions monitoring report (eRMR) tool as provided by the EMA and this was identified as a time-consuming activity.

### **Signal validation**

The majority of MSs have a signal validation step in place. The resources needed for the validation step differ by MS. Challenges identified in relation to signal validation are: limited access to documents, limited information included in ICSRs, lack of resources, lack of expertise of assessors and the definitions in the GVP Module IX.

### **Signal prioritisation**

Prioritisation is a step in signal management and is performed by MSs throughout the whole signal management process. Some MSs have a structured process in place. In the survey, a wish for more guidance on how to prioritise signals was identified.

### **Signal confirmation**

The survey indicated that signal confirmation, as it is described in the GVP Module IX (version 1), creates confusion with regards to the difference between a validated signal and a confirmed signal. The way the process has been divided in the legislation and the GVP creates challenges in interpretation.

### **Signal assessment**

Separating the signal validation and assessment steps is not easy and uncertainty on how to ensure the right focus during the different steps in signal management was identified as a challenge. Compiling all relevant data as well as access to (exposure) data was identified as complex. For the signal assessment, lack of human resources and a need for further training of assessors were also identified as important aspects.

### **Reports of special interest**

With regards to reports of special interest, the survey showed that limited strategies were implemented for signal detection in special populations such as children and elderly and for vaccines, biologicals, medication errors, occupational exposure, medication abuse, etc. A need to improve knowledge and further training of assessors in this field was identified.

## 2. Methodology

This BPG is based on the outcome of the cross-sectional survey. It reflects the situation, knowledge and guidance at that moment in time (October 2014). The data from the survey was analysed and discussed by SCOPE WP5 partners. To identify best practices, the results of the survey and a variety of information sources were used, including feedback from experts, the knowledge within WP5, review of literature and available guidance. A literature review (7) was performed by WP5 to further enrich the BPG.

The draft BPG was reviewed by the SCOPE Work Package Leads (WPL), the SCOPE General Advisory Board (GAB) and the EMA, and comments were received during pilot training from assessors; feedback received was used to optimise the BPG.

Processes within NCAs are organised differently across the EU, taking into account factors such as the size of databases and resources available, and it is therefore expected that signal management processes will differ between MSs. Consequently, not all recommendations will be applicable or relevant to the same extent for every MS.

## 3. Introduction to signal management

### 3.1 General context

The term 'signal' has been used widely in pharmacovigilance and the following three aspects are considered important to better understand the context of the signal management process:

1. **The starting point for signal detection is that all activities take place in the presence of some level of uncertainty and there is always a need to apply sound judgement.** Signals have different degrees of probability according to the completeness and strength of the relevant data assessed. Evidence may be found in different sources, be of differing strengths and can be accumulated or gathered over time. Meyboom et al (11) stated that 'A signal in pharmacovigilance is more than just a statistical association. It consists of a hypothesis, together with data and arguments, arguments in favour and against the hypothesis. These relate to numbers of cases, statistics, clinical medicine, pharmacology (kinetics, actions, previous knowledge) and epidemiology, and may also refer to findings with an experimental character.' This is not, strictly speaking, a definition, but a description. One useful aspect of this description is that it emphasises that signal detection incorporates clinical judgement that goes beyond an automatic process.
2. **The element of 'suggests' in the legal definition of a signal emphasises that a signal is basically a hypothesis and does not necessarily translate in all cases into a definite causal association** (IR, Art 19: 'signal' means information arising from one or multiple sources, including observations and experiments, which suggests a new potentially causal association, or a new aspect of a known association between an intervention and an event or set of related events, either adverse or beneficial, which is judged to be of sufficient likelihood to justify verificatory action).

#### Example

The EMA 2015 Annual Report on EudraVigilance (12) shows that during 2015, the EMA Signal Management Team reviewed in total 2372 potential signals (i.e. drug-event pairs from screening of the EudraVigilance database, medical literature, information from other regulatory authorities with the potential of being a safety issue). Of these, 61 signals validated by the EMA ended up on the PRAC agenda in 2015.



3. **Not all signals represent risks and not all signals will require an additional formal regulatory action** (e.g. update of the Summary of Product Characteristics (SmPC)) after assessment has been performed.

### Example



The EMA 2015 Annual Report on EudraVigilance (12) shows that the PRAC prioritised and assessed 102 signals during 2015. 33% of the signals resulted in a recommendation for an update of the product information (PI), including the distribution of a Direct Healthcare Professional Communication (DHPC) on four occasions to highlight important new safety information to healthcare professionals. Twenty-seven signals (26%) were closed and subject to routine safety monitoring. Four signals resulted in a recommendation to update the RMP; another signal was further assessed through a Post Authorisation Safety Study (PASS), and one signal was evaluated in a referral procedure. The evaluation of 35 signals (35%) was ongoing, including 20 via a follow-up signal procedure and 15 in the next PSUR.

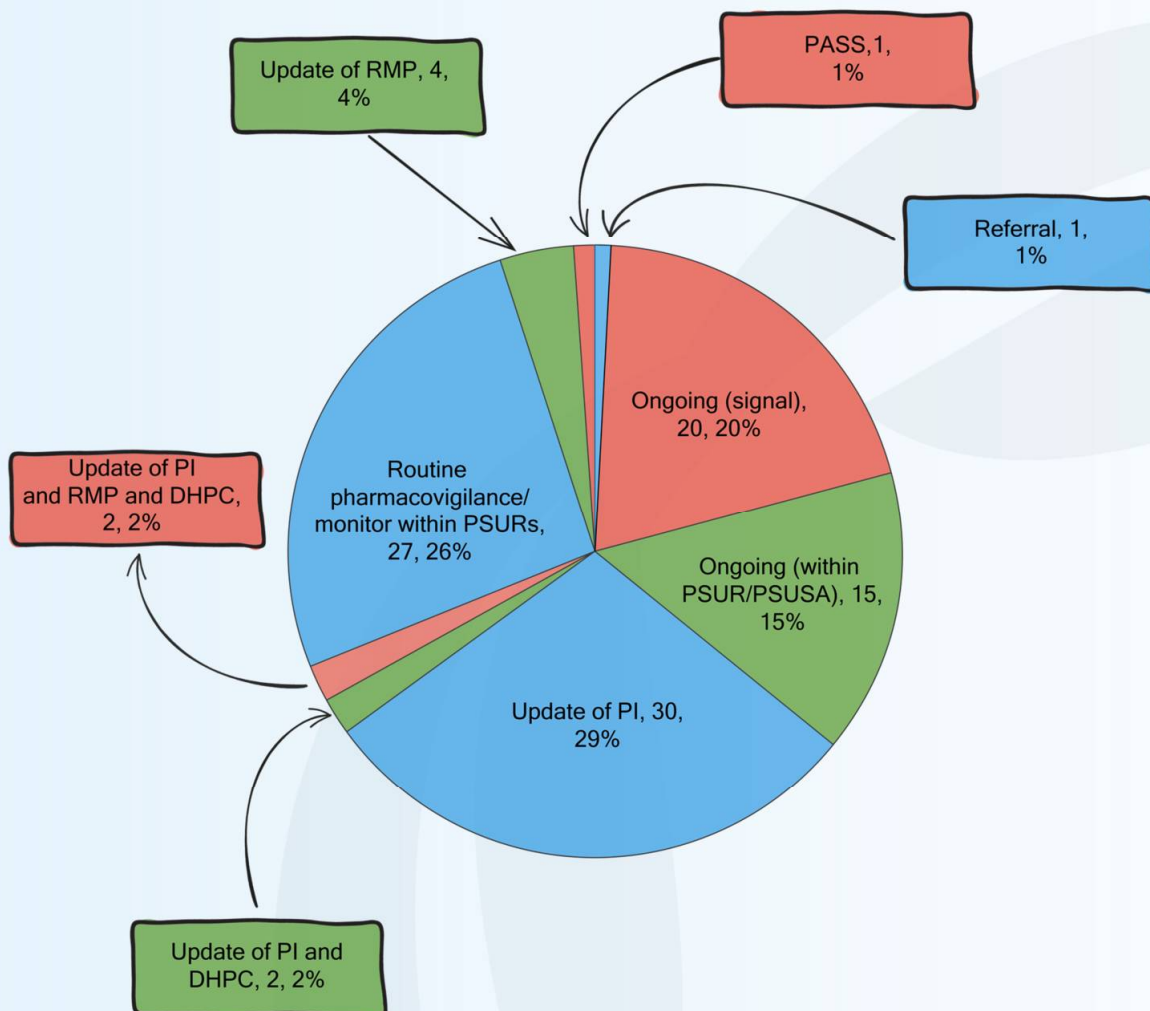


Figure 1. Outcomes of PRAC signal assessments in 2015  
*EMA 2015 Annual Report on EudraVigilance (12)*

## 3.2 Signal management processes at Member State level vs. centralised European level

The 2012 EU legislation introduced legal requirements for (EU) signal management. The most detailed part of the legislation is provided by the Implementing Regulation (IR), which describes activities in detail and assigns responsibilities to different stakeholders (4). As the role and tasks of the PRAC in the EU signal management process are clearly described in GVP Module IX, this BPG focuses on the signal management process within a MS and their interaction with the EU.

The IR also defines that signal management consists of the following activities:

- Signal detection
- Signal validation
- Signal confirmation
- Signal analysis and prioritisation
- Signal assessment
- Recommendation for action.

For some of these activities, the IR provides definitions or explanations, whereas others are explained in the GVP Module IX and/or in the EMA's Questions and Answers document on signal management (6). It should be noted that the terminology used in the EU signal management process is different from the terminology used commonly in scientific literature (8,13). For example, in scientific articles the term 'verification' of a signal is often used and not the term validation. The CIOMS VIII guidance, for example, defines the term 'signal verified' as 'a signal of suspected causality, that has been verified either by its nature or source or by formal verification studies.'

Signal management activities are often described as a linear process (as shown in Figure 2) consisting of different steps to be completed in a sequential order (as is the case in the IR for example), but it is challenging to separate the different steps and not feasible to assign a time sequence or order in which they should be completed. It is acknowledged in GVP Module IX that flexibility may be required during the whole process.

The role of different stakeholders throughout the signal management process as described in the current legislation is shown in the flowchart in Figure 2.

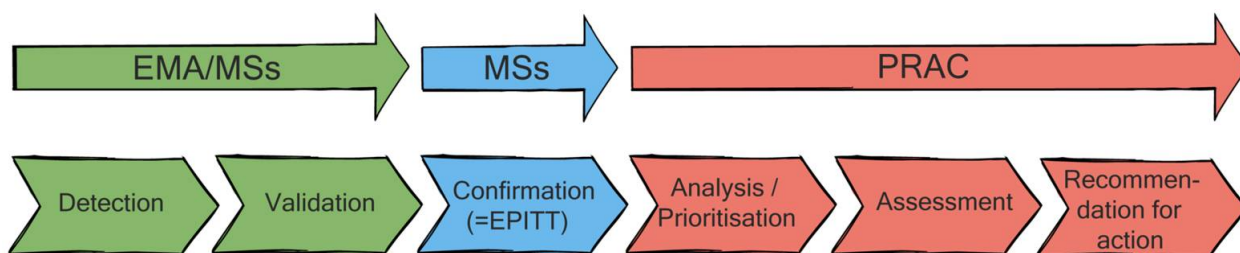


Figure 2. Signal management process/responsibilities and activities for regulators as provided in the legislation

MSs use these concepts in their national signal management process. However, some differences between MSs could be identified based on the MSs' responses to the SCOPE WP5 survey:

1. Some MSs perform the signal detection and validation at national level and then subsequently enter the signal into the European Pharmacovigilance Issues Tracking Tool (EPITT) (as shown in Figure 2).
2. Other MSs add an additional decision-making loop before entering a signal into EPITT (as shown in Figure 3). In this way, a signal may be reviewed in greater depth at national level before the NCA enters the signal in EPITT.

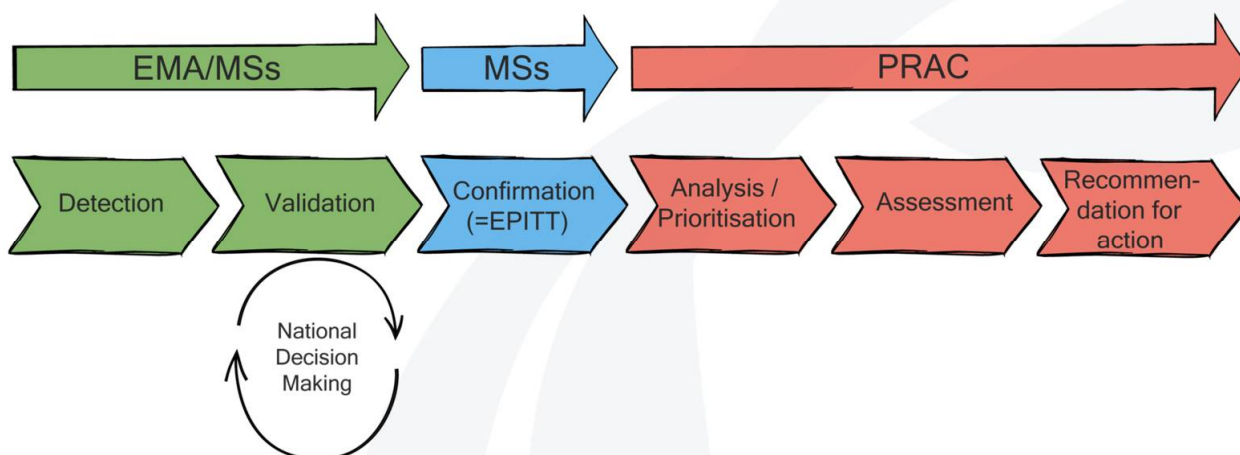
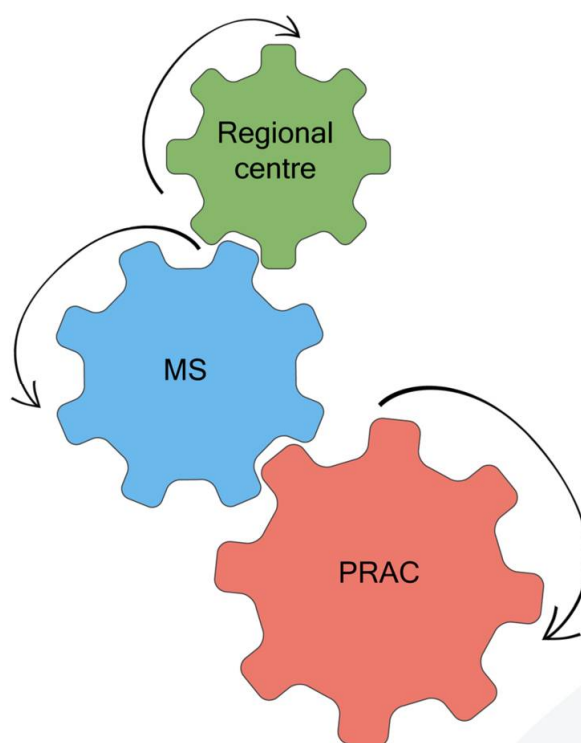


Figure 3. Signal management process as applied at MS level with an additional decision-making loop

In this (optional) additional decision-making loop at national level, differences between MSs in signal validation may originate. Depending on the organisation and the resources in a MS, the validation of the signal might be more extensive at national level. For example, a more elaborate evaluation of data might already have taken place at national level before next steps are taken.

Furthermore, in some MSs, national and/or regional pharmacovigilance centres might be involved in the signal management process and, if that is the case, multiple decision-making loops may be in place (as shown in Figure 4).



**Figure 4. Interaction between national / regional pharmacovigilance centres, MSs and PRAC**

Consequently, the different organisational structures of MSs might lead to different ways of dealing with a signal at the national level and to different timing in entering a signal in EPITT.

The SCOPE WP5 survey identified that MSs may find it challenging to apply signal management concepts/steps defined in the legislation and the GVP (e.g. validation, confirmation, and prioritisation) within their national organisations, especially for those steps that are not included or may have a different understanding in the scientific literature. In some MSs CIOMS VIII guidance and terminology (8) is used in the development of national processes, before the legislation came into force. This might pose challenges, for example in line with the CIOMS VIII guidance, a signal management standard operating procedure (SOP) at the national level might describe ‘how signal prioritisation and evaluation are approached’, whereas in the EU legislation prioritisation is assigned as a responsibility to the PRAC. However, for MSs, prioritisation is a continuous process that is considered at every step of signal management. The EU legislation and GVP guidance describe concepts that apply specifically to procedures at the central EU level, however these might not always be applicable/feasible at national level. Within the EU signal management process, all actions lead to entering a signal into EPITT, but the process that precedes this might differ between MSs as well as between the EMA and MSs. A signal at national level might be reviewed at several different steps (in line with national signal management SOP), before the NCA decides to enter the signal into EPITT.



For their national signal management SOP, MSs, depending on their organisation, can apply signal management definitions and processes or steps that are different from the EU legislation and guidance, as shown in Figure 5. Once a signal is entered into EPITT, definitions provided in the IR and explanations or clarifications provided in GVP Module IX are applicable. However, for the signal management steps that take place at a national level, other working concepts can be more suitable, for example those provided in CIOMS VIII guidance (8).

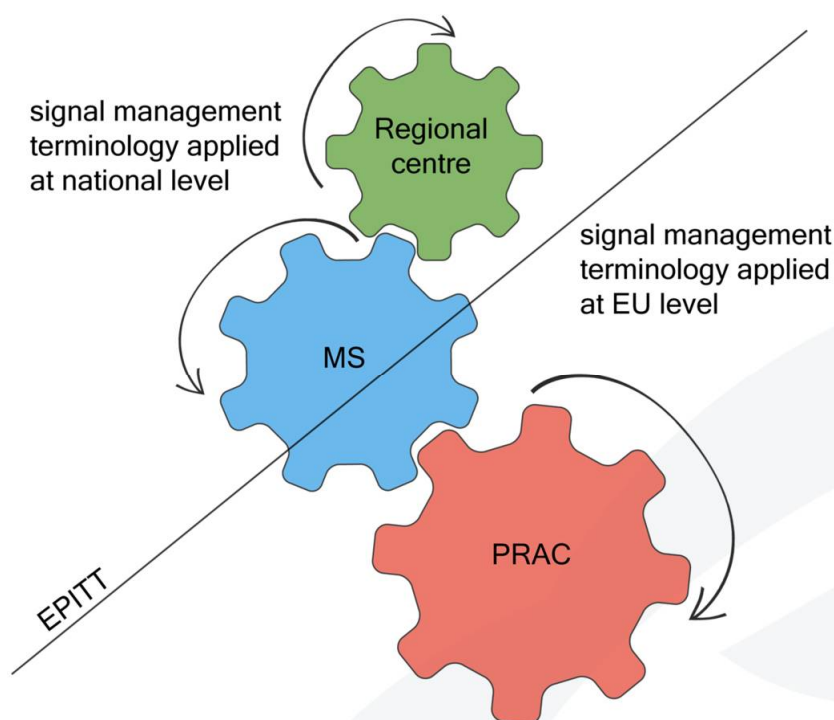


Figure 5. Various stages of signal management process and the various definitions used according to the level where signal management is performed (EU vs national)

### 3.3 Role of PRAC in signal management

As mentioned in the previous section, this BPG focuses on the national signal management processes in the MSs. As both processes, national as well as central EU, are part of the overall signal management process, a brief summary of the process at the EU level is included here; for full information on the central EU level, please refer to GVP Module IX (5) and the Questions and Answers document (6).

The PRAC at the EMA has a central role in scientific assessment and decision-making in relation to signal management.

The PRAC shall regularly review the methodologies used for determining the evidentiary value of a signal and publish recommendations, as appropriate (IR, Art 20(3)). According to the legislation, the evidentiary value of a signal shall be determined by using a recognised methodology taking into account the clinical relevance, quantitative strength of the association, the consistency of the data, the exposure–response relationship, the biological plausibility, experimental findings, possible analogies and the nature and quality of the data (IR Art 20(1)).

The legislation puts specific obligations on MAHs<sup>1</sup>, NCAs and the EMA for the monitoring of the EudraVigilance database, and on NCAs for monitoring data originating in their territory (1-4, see also [section 5.3 Signal Detection](#)). Once the signal identifier – either the NCA or the EMA – has decided that a signal should be entered in EPITT, it can be confirmed or not by the Lead Member State (LMS) or PRAC Rapporteur. If the signal is confirmed, the signal will be discussed during the next plenary PRAC meeting. The PRAC may further amend the scope of the signal management by extending it to other active substances of the same class of medicinal products or to other related adverse reactions. When further assessment is considered needed within the signal management procedure, the PRAC will nominate a Rapporteur and define a timeframe for the assessment. After signal confirmation, PRAC decides on the prioritisation, leads on the assessment of the data and provides recommendations regarding the regulatory actions to be taken. The PRAC ensures that new or changed safety issues are translated into regulatory actions, as appropriate.

After discussion at the plenary meeting, the PRAC recommendation may include any or a combination of the following conclusions (6):

- No need for further evaluation or action at this point in time
- Need for additional information – e.g. via a cumulative review or in the next PSUR
- Need for regulatory action – e.g. update of the SmPC to reflect the findings, RMP update, start of a referral, etc.

Actions recommended by PRAC may be accompanied by additional communication measures, e.g. a Direct Healthcare Professional Communication (DHPC).

If based on the data available, a need for immediate action before the upcoming PRAC meeting is identified, an NCA can act at national level and take temporary measures and trigger at the same time a Rapid Alert (RA) and a review by the Incident Review Network (IRN). This virtual group reviews incidents from a managerial perspective in terms of their impact on public health and the measures needed to address them. This process is explained in the incident management plan (14), which aims to ensure that concerned bodies in the EU take appropriate action whenever incidents (new events or information) arise concerning human medicines. The activities in the plan and of this managerial group focus on managing incidents and do not replace the work of the PRAC, the Committee for Medicinal Products for Human Use (CHMP), or the Coordination Group for Mutual Recognition and Decentralised Procedures – Human (CMD(h)) (14).

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<sup>1</sup> Signals identified by MAHs are outside the scope of this BPG, see GVP IX for more information on MAHs' obligations.

## 4. Recommendations

This section of the BPG presents the SCOPE WP5 recommendations on signal management. An outline of the recommendations is presented in chapter 4, followed by a more thorough best practice guidance in chapter 5 to develop further understanding of the recommendations.

### 4.1 General recommendations

These recommendations refer to general areas in signal management, such as access to data, exchange of information and tracking of signals, which are not related to any specific steps in the signal management process.

- 4.1.1 For signal management activities, access to data is essential and this access should be facilitated.** Access to all relevant documents and data sources is essential to pharmacovigilance assessors involved in signal management to ensure thorough assessment. Some of the documents are publicly available, but not all are easily accessible within all NCAs. Some of the most relevant documents and data sources are clinical trial data, product application dossier, SmPC, patient leaflet, PSURs, RMPs, EPITT, decision-making documents (e.g. from scientific committees or regulatory procedures), scientific literature, data provided by an MAH and data sources outside spontaneous reports, such as registries and databases, etc. MSs should ensure that all relevant information is available for assessors and this includes relevant documents stored within the EMA domain.
- 4.1.2 The EU network would benefit from the possibility of an early exchange of information on signals in order to inform other MSs and prevent duplication of work.** Given there are no tools currently available for this specific purpose, there are a number of ways to facilitate this exchange of information: inform the Lead Member State (LMS) by e-mail, distribute a non-urgent information request (NUI), or enter the signal in EPITT and propose to the LMS to not confirm this signal (meaning that the signal will not be included in the PRAC agenda). In future, this sharing should be facilitated by the creation of a new signal management tool (see [Annex 1](#)).
- 4.1.3 To ease traceability of how signals are detected, validated and assessed, MSs would benefit from a minimum set of variables to be tracked at MS level.** Tracking of signals in a sufficient way at MS level can be a challenge, and various systems and routines are in place across MSs. Based on the information provided in the survey, a minimum set of variables to be tracked at national level was identified.

## 4.2 Recommendations related to signal detection

### 4.2.1 Existing heterogeneity in signal detection methods within the EU network is beneficial.

MSs implement different signal detection methods on different national datasets. The differences in the national databases and the different methods applied can be considered a strength of the system. In signal detection, it is important that the methods applied are appropriate for the respective databases and there is no ‘one size fits all’ solution. Methods that are appropriate for large international datasets would not be appropriate for smaller national datasets. In addition, this diversity in databases and methodologies allows the detection of different signals in the different databases.

### 4.2.2 Disproportionality methods should be applied to databases of appropriate size and background.

Use of disproportionality methods is not appropriate in all situations. Application of disproportionality methods to a dataset that is too small or with a limited set of drugs or events reported might not be relevant and provides no added benefits compared to using qualitative methods and simple quantitative methods. Therefore, it may be more appropriate for small databases to apply qualitative methods or simple rule-based methods (e.g. count of case reports) or a combination of these.

### 4.2.3 The method of disproportionality analysis is less important than the threshold for detection chosen, which should be duly justified.

It is important that any signal threshold applied is appropriate to the size of the database, the products it contains, and the level of sensitivity (how many signals will be identified) and expected precision (positive predictive value, how many identified signals are real signals). This applies when complex disproportionality methods or rule-based approaches (such as reviewing all fatal case reports) are employed. It is important that the chosen approach can be shown to identify signals through a validation/testing process (meaning that the statistical analyses should be robust against spurious associations due to random variability). This process should ensure that the approach can both detect issues that have been identified in the past for the products under review, and also that it is no worse than the previous approach at identifying safety issues of interest for review in a side-by-side comparison. This recommendation is based on findings from the IMI PROTECT group; more detailed recommendations regarding the choice of disproportionality method can be found in the Good Signal Detection Practices: Evidence from IMI PROTECT (10).

### 4.2.4 Focusing signal detection on predefined events is helpful.

Focusing the signal detection efforts on serious events and events that are likely to have a high public health impact (such as Important Medical Event (IME) and Designated Medical Event (DME) lists) is recommended.

**4.2.5 In quantitative signal detection, analysis should be performed at the level of the standard Medical Dictionary for Regulatory Activities (MedDRA) preferred term (PT) level.** Screening at PT level is current practice and there are currently no data to suggest that standard screening at higher aggregation levels (Higher Level Term (HLT), Higher Level Group Term (HLGT) or Standardised MedDRA Query (SMQ)) would detect more signals or deliver signals at an earlier stage in time than when using Preferred Term (PT) level for screening. This recommendation is based on findings from the IMI PROTECT group; more detailed recommendations regarding the choice of level at which screening should be performed can be found in Good Signal Detection Practices: Evidence from IMI PROTECT (10).

### **4.3 Recommendations related to signal prioritisation**

**4.3.1 Prioritisation should be a continuous process performed during the whole signal management process, rather than in a single step.** While prioritisation should be systematically performed during the initial steps of signal management, it does not prevent further prioritisation during the whole process. Signal prioritisation is required to focus the resources available on the most important signals. A standardised approach based on the most important criteria that can be used should be in place, and validated criteria should be employed as much as possible. However, prioritisation could take into account different variables depending on the step of the signal management process.

### **4.4 Recommendations related to validation and assessment**

**4.4.1 A validated signal should be differentiated from a confirmed signal.** Signal confirmation, based on the legal terminology, is a procedural step only relevant when a MS wants to bring a signal to the PRAC agenda. At the EU regulatory level signal confirmation only refers to EPITT. After a signal is entered in EPITT by the signal identifier, the LMS or Rapporteur can decide to either mark the signal as ‘confirmed’ or ‘non-confirmed’ within 30 days. After confirmation, the signal will be discussed at the next PRAC meeting for the initial analysis and prioritisation according to the IR.

**4.4.2 The processes of signal validation and signal assessment could benefit from a consistent approach between different MSs and one way that could help to achieve this is by using a checklist.** The EU network would benefit from a consistent approach to signal validation and assessment, and a tool such as a checklist could be used to achieve this. A basic checklist that summarises the most important activities and relevant sources of information in validation and assessment should be developed to meet this objective. An example of such a signal validation and assessment checklist is provided in [Annex 2](#).

**4.4.3 Multidisciplinary teams with experts from different areas and various levels of expertise can be helpful and increase the quality of signal assessment.** A multidisciplinary team of experts from relevant areas can help provide thorough clinical statistical and pharmaceutical expertise necessary to guarantee the quality of a signal assessment (8). This can be achieved in different ways using both internal and external expertise and will depend on the organisational structure and possibilities in each MS.

## **4.5 Recommendations related to reports of special interest**

**4.5.1 Awareness of methodologies and approaches for analysis of reports of special interest must be raised.** Very few MSs had methodologies in place to help identify signals against all categories of reports of special interest, despite their scientific, public health and political importance.

**4.5.2 Where statistical analysis is applied, subgrouping into specific categories of interest (e.g., paediatric reports, vaccine-related reports) may be a helpful approach for analysis of some reports of special interest.** The IMI PROTECT group identified that subgrouping may improve both the sensitivity and precision of statistical methods (15). Further, such analysis methods may serve to focus assessors' attention on specific areas, leading to higher quality signal detection in these groups. However, use of such approaches should only be considered if the database is of an appropriate size that allows analyses to be statistically valid. This recommendation is based on findings from IMI PROTECT group; more detailed recommendations regarding subgrouping and stratification approaches can be found in Good Signal Detection Practices: Evidence from IMI PROTECT (10)

**4.5.3 Assessors involved in signal management should have knowledge of the guidance in the Product/ Population Specific GVP Modules as they are made available.** GVP P1 – Vaccines for prophylaxis against infectious diseases (16) and GVP P2 – Biological medicinal products (17) and others under development provide helpful strategies for analysis of these product groups.

**4.5.4 Qualitative methods should be used for identification of medication errors.** The survey did not identify dedicated statistical methods proven in identification of such case reports against the background noise in the data. Important case reports may not be highlighted explicitly by reporters or coding personnel using relevant MedDRA terms, and numbers may not be large enough for quantitative analysis.

- 4.5.5 Signal detection activities for medication errors should focus on the identification of harm as opposed to only coded medication error terms.** Whilst the Medication Errors SMQ may assist in identification of some relevant case reports, MSs should not recode reaction terms based on their interpretation by adding medication error terms. Any additional terms thought suitable should be coded in sender diagnosis (E2B(R2) data element B.5.3). Signal detection should focus on harms and understanding whether medication error may have contributed to them.
- 4.5.6 MSs should build relationships between themselves and other national bodies with responsibility for medication errors.** As MSs may not be the primary receiver of medication error data, building relationships between other national bodies will assist in comprehension, detection and communication associated with medication errors.
- 4.5.7 Use of Designated Medical Events (DMEs) or equivalent lists should be considered for analysis of specific reaction terms of interest.** A number of MSs identified this approach as helpful in ensuring a focused review of serious events and those frequently associated with ADRs.

## 5. Best Practice Guidance

In line with the above recommendations, this chapter presents selected topics of interest, where more detail is given on the tasks for each signal management step, with a focus on national processes (at MS level). The last two sub-chapters are more general and refer to the topics of data quality and training.

Each section starts with a brief introduction where current legislation and guidance are presented (if applicable), followed by the best practice.

### 5.1 Tracking of signals

The IR (4) requires NCAs to have an audit trail of their signal management activities in EudraVigilance and for relevant queries and their outcomes, including how signals have been detected, validated, confirmed and assessed. The GVP Module IX (5) has broadened the MS obligations by stating that ‘all validation, prioritisation, assessment, timelines, decisions, actions, plans, reporting as well as all other key steps should be recorded and tracked systematically’.

Once a signal is entered in EPITT, the tracking in line with IR is ensured. Before that step, MSs need to ensure adequate tracking of their signal management activities at the national level.

#### Best practice

Specific requirements for tracking tools at a national level are not described in EU pharmacovigilance legislation or guidance documents. Therefore, it is up to individual MSs to assess their own needs and implement a system that best meets their specific situation and processes.



#### Example

Example of how different tracking systems can be used, depending on the step in the signal management process.

A signal is detected when monitoring EudraVigilance via the eRMR. The ‘signal status’ column and ‘signal comments’ column in the eRMR are used to document the outcome of the validation step. The signal is subsequently discussed at internal meetings; the minutes of these meetings are considered part of the signal management tracking system. Once the validated signal is entered in EPITT, any subsequent steps are tracked from here onwards.



Whereas the tracking tools used may vary widely, based on the survey information MSs were in agreement on the minimum information that should be collected for tracking. As a minimum, the variables mentioned in Annex 3 should be tracked (see [Annex 3](#)).



At the moment, retrieving information about signals followed up in other procedures is challenging, since no systematic tracking (tool) across procedures is in place. According to GVP Module IX (5), tracking systems should also include signals for which the validation process did not suggest a new potentially causal association, or a new aspect of a known association. MSs may use the same systems for tracking both validated and non-validated signals.

It is considered good practice to have processes in place to ensure that non-validated signals are not lost during follow-up. Such examples include:

- Discussion at a dedicated signal detection meeting for information purposes
- Regular review by a National Pharmacovigilance Committee
- Mandatory check of data related to previous non-validated signals during signal detection for the same medicinal product.

The information should be recorded and archived.

## 5.2 Access to relevant information for signal management process

### Best practice

This section presents a general practical review of the most commonly used sources of information for both the initial signal validation and the more exhaustive signal assessment.



The evaluation of data supporting a signal is performed during almost every step of the signal management process, from signal detection to signal assessment. However, it is important to acknowledge that, the importance of each data source, the level of the data review and the aim and focus of the evaluation may vary for each step. For example, during the validation of a signal, the evaluation of the data should be aimed at deciding if further analysis is necessary and the focus should be on determining if the signal reflects new information and if it is at least a reasonable possibility. For signals originating from spontaneous reports, at a minimum, it should be made sure that the signal is not only based on duplicate reports, and that there is plausible time to onset. During signal assessment, the evaluation of the data is aimed at deciding if a regulatory action is needed and the focus should be on reaching a final conclusion on the causal relationship and considering the need for (additional) risk minimisation measures (see Figure 6).

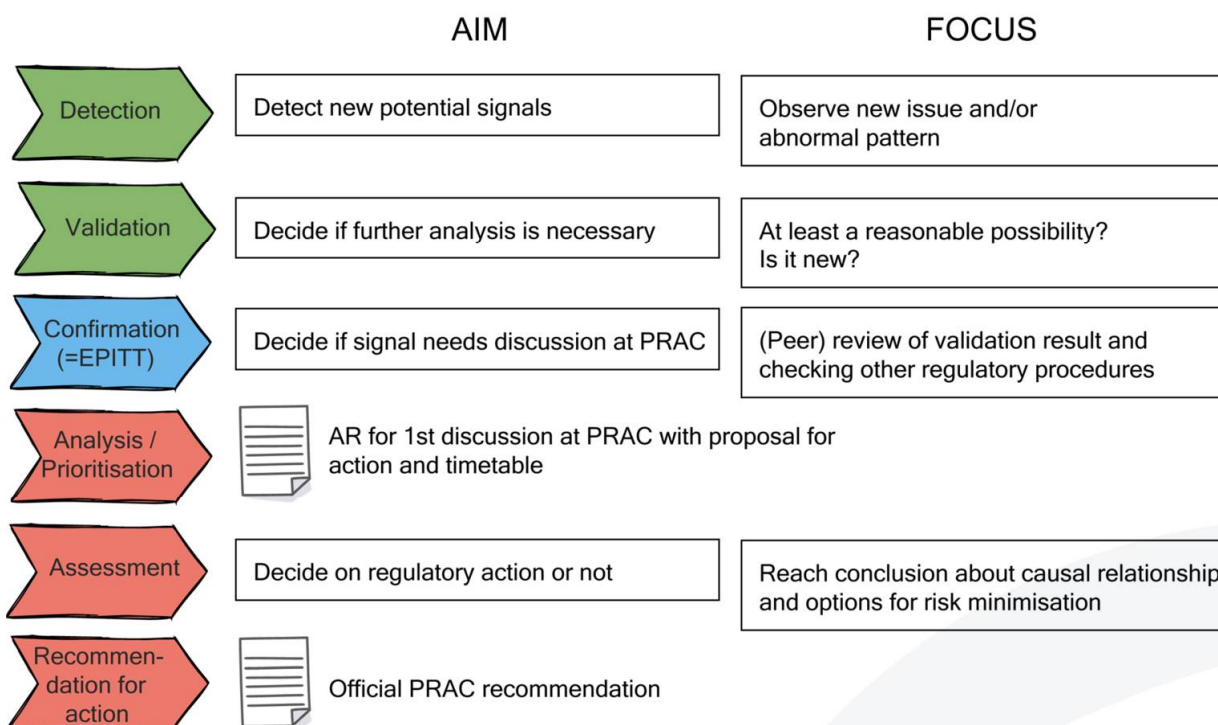


Figure 6. Aims of various signal management steps and how this might influence data evaluation

Furthermore, the data relevant and available at each step may vary, depending on who performs the evaluation (e.g. a different MS) or if additional information has been provided (e.g. by the MAH as a result of a PRAC recommendation).

Signal validation is an important step in the signal management process. In the legislation, validation is discussed as a step in the signal management process that is separate from the assessment of a signal. IR (Art 21) defines signal validation as the process of evaluating the data supporting the detected signal in order to verify that the available documentation contains sufficient evidence demonstrating the existence of a new potentially causal association, or a new aspect of a known association, and therefore justifies further analysis of the signal. Signal validation will determine if a further assessment is warranted or if the signal could be refuted (further assessment is not considered necessary, e.g. validation showed that the signal was based only on duplicate reports).

All activities at every step in signal management take place in the presence of some uncertainty (8) and any decision will need sound judgement.

When analysing the validated signal, NCAs and the EMA may take into account other information available on the medicinal product. There are many useful data sources that assessors can review once a signal is detected. Each data source might have different relevance depending on the step of the signal management process (as shown in Figure 7).

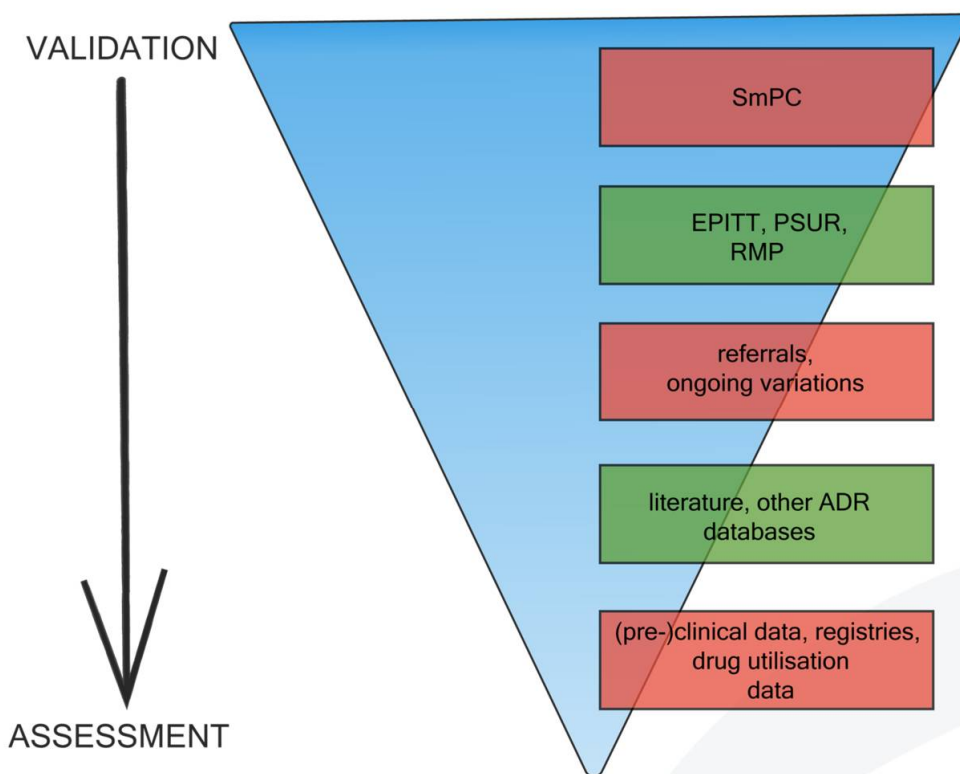


Figure 7. Sources of information and their relevance depending on the signal management step

Practical advice for assessors on how to best use these sources of information in signal management is provided in the next section and it should be highlighted that in every step of the process sound judgement should be applied for each decision taken.

### Summary of Product Characteristics (SmPC)

The SmPC is an important source of information in signal validation to assess whether there is a new potentially causal association, or a new aspect of a known association and, therefore, whether the signal justifies further analysis. In order to evaluate this, the information already included in the SmPC of the active substance should be taken into account. Only signals for which there is no previous awareness and signals that may reflect a new aspect of a known association (such as a change in frequency, temporal persistence, severity or a change in the outcome or reported fatality rate) should be validated.

A signal can relate to an already known safety issue and not reflect new information and therefore not fulfil the definition of a signal. It is important to check if the event is already reflected in the SmPC of the product. However, there are two important points to acknowledge:

- a) **Within a single MS, there may be differences between the SmPCs for a given active substance.** If an assessor notices that an event is mentioned in one SmPC, but not in another (of the same active substance), the event would not fulfil the definition of a signal (it is not new) and can be considered a national harmonisation issue.
- b) **There may be differences between SmPCs from different MSs for the same active substance and it is not practically feasible to check all SmPCs available in the EU.** As a consequence, it can happen that a MS validates and enters a signal into EPITT that appears to be already reflected in the SmPC of another MS. It may occur that a signal discussed at PRAC appears to be reflected in a SmPC somewhere in the EU. This cannot be avoided or solved within SCOPE WP5. If a signal is marked as not-confirmed by a LMS or Rapporteur with the justification that it is already reflected in a local SmPC, this could trigger other MSs to initiate a harmonisation activity at national level.

While access to the currently approved SmPC of a centrally authorised product (CAP) is easy – it is obtained via the EMA website and there is one single SmPC in the whole EU – checking the SmPC of a nationally authorised product (NAP) in different MSs can be very challenging and is not always feasible, particularly in view of language challenges. A SmPC for the same active substance can differ not only across the different MSs, but also within a MS. The IMI PROTECT group developed an SmPC dataset containing the minimum safety information for centrally authorised products (the Adverse Drug Reaction Database) in order to check if a certain event is reflected in the SmPC of a product (9).

### Example

Checking if an event is reflected in the SmPC is not as straightforward as just checking if it is included verbatim in section 4.8 of the SmPC of the active substance. An event can be covered by similar (but different) PTs (e.g. anaphylactic shock by anaphylaxis; vertigo covered by dizziness, swelling tongue covered by angioedema, etc.) or by a HLT. On the other hand, an event might be reflected in the SmPC, but the signal might provide new additional information (e.g. on further anatomical specification, severity or duration) and the event might not be considered to be reflected when this specification is not specified (e.g. rash does cover morbilliform rash, but not Stevens Johnson syndrome; fulminant hepatitis should not be considered to be reflected by liver injury). An event might also be reflected as a class effect, either as a warning or in section 4.8. Expert medical judgement should always be used on a case-by-case basis to determine if the signal reflects information not reflected by the current wording in the SmPC and the need for further action in view of the information already included compared to the information originating from the signal.



In addition to section 4.8 of the SmPC, other relevant sections to check are section 4.3 (for any contraindications), section 4.4 (for any warnings and precautions suggestive of the event), section 4.5 (for any information of a known interaction), and section 4.6 (in case of a signal related to fertility, pregnancy and lactation). It should always be considered that, even when there is information available in these sections, a signal might provide new information that can lead to an update of the SmPC in the same or in a different section.

Regarding drug interactions, it is not always the case that there is reciprocity/mirroring of the information in the SmPCs of both products. Only in the case of drug interactions that lead to a contraindication is reciprocity considered essential. However, full consistency of reciprocal drug-drug interactions information in SmPCs is a challenge and expert judgement should always be used to consider if the signal provides new information on the safety issue.

A signal can also be validated if the available data suggests a change in the frequency of the event reported in the SmPC (e.g. reports can suggest a higher frequency than expected), duration, severity, pattern (e.g. affecting a specific population) or a change in the previously reported outcome (e.g. fatal cases).

### Periodic Safety Update Report (PSUR)

PSURs (when available) are a relevant source of information and can be used if:

1. **There is a PSUR assessment ongoing at the same time of the signal validation/ confirmation.** In this case it is useful to check if the specific topic of the signal is already included in the PSUR.
  - a) If it is already included, the signal could be considered to be addressed in the PSUR assessment procedure and no further assessment might be warranted.
  - b) If the topic is not addressed, it could be considered as to whether to request a discussion in the PSUR (if there is sufficient time for it given the timetable of the assessment); otherwise, if the assessment is already ongoing and there is not sufficient time to address the signal during the current procedure, it could be decided to proceed with addressing the signal via the signal management procedure.
2. **The submission date of the next PSUR is close.** For practical reasons, if the date of submission of the next PSUR for the active substance is close enough, it might be decided to address the signal in the next PSUR assessment.

Furthermore, the most recently available PSUR and its corresponding assessment report can also be useful documents for the signal assessment (also, for example, to check exposure).

The main sections with information on signals are:

- a) Section VII.B.5.15 'Overview of signals: new, ongoing or closed'. This can be checked if the safety issue corresponding to the signal has been addressed.
- b) Section VII.B.5.16 'Signal and risk evaluation'. This section gives information on the risks that are addressed in the RMP of the active substance.

## Risk Management Plan (RMP)

RMPs could also be a useful source of information for the validation or assessment of a signal. Especially interesting in this context are the safety specifications of the product and the pharmacovigilance plan. Within the safety specifications of the product, the important identified risks give information about safety issues for which there is sufficient evidence supporting a causal association and are therefore considered to be already known for the product and also covered in their SmPC.

Checking the important *potential* risks might be informative to assess if during the development of the drug, the risk was identified as potential, and the data leading to the signal might provide additional information on the probability of a possible causal association. For instance, for a signal for which the data supporting a causal association is considered rather weak, the fact that the event is listed as an important potential risk in the RMP of the product might make the signal stronger and help the assessor further in the decision-making process.

It might be helpful for the assessor to have knowledge on the safety profile of the product that was identified during development of the RMP, such as the important identified risks, important potential risks and missing information.

The pharmacovigilance plan in the RMP also provides information on any post-authorisation safety studies that are planned or ongoing for the product and that might aim to further investigate a safety issue. The information provided in this section of the RMP can also be helpful in further managing the signal.

Since March 2014, the EMA has published summaries of risk management plans for centrally authorised medicines on its website to increase transparency and public access to relevant information on medicines. The CMD(h) has also started a programme for publishing RMPs for nationally authorised products when available (18).

## EPITT

EPITT is a web-based system that supports the tracking of pharmacovigilance issues at a European level, including rapid alerts (RA), non-urgent information requests (NUIs) and signals. Signals that have been previously validated by the EMA or MSs are reflected in EPITT, where all relevant information on the safety issue is kept (for non-confirmed signals, a justification for not confirming is provided; for confirmed signals, the signal assessment report and PRAC recommendations are provided). It is therefore a very useful source of information for checking any previous awareness of a specific safety issue and any actions that might have been taken. It would therefore be very beneficial for all assessors involved in signal management to have access to EPITT.

### **Ongoing variations**

When assessing a signal, it is important to know if there is an ongoing variation that addresses the same or a related safety issue. Sometimes a signal may appear at the same time that a variation procedure is addressing the same safety issue at a national level or in another MS. Being aware of this can prevent duplication of work and spending resources on a safety issue that is already addressed.

While this can be relatively easy to check for centrally authorised products or at a national level for nationally authorised products (single national variations), it is usually very difficult to check if a variation is currently ongoing in another MS for a nationally authorised product that addresses the same safety issue. It would be useful for all assessors involved in signal management to have access to data of ongoing safety variations at national level.

### **EMA website for referrals**

The EMA website for referrals provides information on ongoing and completed referral procedures for medicinal products. This information can be of added value if the concerned medicinal product(s) have been assessed through a referral procedure.

The referral assessment report and the recommendations from the EMA can be checked to determine if the new information supporting the signal may change the conclusions made at the time of finalisation of the referral.

### **Scientific literature**

Review of the scientific literature can give useful information to assessors for the review of a signal, especially for signals originating from a national database or EudraVigilance. Checking for any publications regarding similar case reports, pharmacoepidemiological studies or suggestive of a potential mechanism of action, can provide stronger evidence and warrant a further assessment of the signal. Within SCOPE WP8 a document is developed with recommendations on the identification of available data sources outside of spontaneous reporting, which the assessor may find useful.

### **International and national databases**

For signals detected in a spontaneous national database, EudraVigilance and other international databases, such as VigiBase from the WHO, or FAERS (Adverse Event Reporting System) from the Food and Drug Administration (FDA), can be a useful data source to cross-check the data. A further review of the corresponding case narratives may provide further evidence on the potential association.

In the same way, for signals that are detected from other data sources, such as literature, it is useful to check national databases and/or EudraVigilance, in order to see if more case reports can be identified, to assess what further action might be needed.

### **(Pre-) Clinical data**

When available, data from preclinical or clinical studies might provide further evidence for the assessment of a signal. If the clinical trial is large enough and the specific event was investigated, this usually offers very good evidence for or against the signal.

However, it should be noted that even when an event is not observed in a clinical trial, this should not be considered as evidence supporting a lack of association, as clinical trials usually are not able to detect rare adverse events (AEs) or events with a long time to onset.

### **European studies registry**

The European Network of Centres for Pharmacoepidemiology and Pharmacovigilance (ENCePP) is a network of over 170 research centres, existing networks and providers of healthcare data. The network is coordinated by the EMA. Its centres conduct independent studies focusing mainly on the safety of drugs.

The ENCePP database is accessible for free online (19) and can be used to search for ongoing and finalised studies related to a safety issue and an active substance of interest. Summary of protocols are also publicly available, as well as interim and final results for studies registered in the ENCePP database. Therefore, this database can be useful for assessors during the assessment of a signal. It may be useful to check if there is an ongoing study that is relevant for the signal, which provides useful information within an acceptable timeframe, or if it may be beneficial to check with the corresponding investigator.

### **Drug utilisation data**

Drug utilisation data on national exposure and patterns of drug use in different subpopulations can be used to put the case reports into context and for the calculation of reporting rates at national level.

Exposure data at European or national level can usually be obtained from PSURs. However, for more comprehensive drug utilisation data, such as information on the number of prescriptions in a specific country, access to a drug utilisation registry is required. In some MSs such registries already exists as a readily accessible source of information, while for others, access to this kind of information is difficult to get.

A comprehensive overview of drug utilisation databases in Europe is made available by the IMI PROTECT group and is available online (20).

When compiling drug utilisation data from different countries, local legislation, clinical guidelines and clinical practice should be considered, as they influence drug utilisation patterns.



## EMA signal validation table

The EMA circulates monthly to NCAs a signal validation table. The table contains a summary of all signal reviews undertaken by the EMA signal detection team for centrally authorised products and could, for example, provide additional information for evaluation of the data that generated the signal.

## 5.3 Signal detection

According to the IR *'The competent authority of each Member State shall be responsible for monitoring the data originating in the territory of that MS'* (IR Art 18(4)).

MAHs<sup>2</sup>, NCAs and the EMA should continuously monitor the data in the EudraVigilance to determine whether there are new risks or whether risks have changed. For substances found in nationally authorised products, the monitoring of ADR reports is shared between the NCAs as per the 'List of substances and products subject to worksharing for signal management' (21), and the NCAs also monitor all medicines for which no LMS has been appointed. The EMA leads on monitoring EudraVigilance for centrally authorised products.

The legislation does not provide a specific frequency for this monitoring, and states that it should be *'with a frequency proportionate to the identified risks, the potential risks and the need for additional information'*. The IR also states that the EMA shall support the monitoring of the EudraVigilance database by providing NCAs with access to data outputs and statistical reports, customised queries and statistical signal detection methods. In line with the current GVP IX (1), statistical outputs (eRMRs) are produced from ADR reports received in EudraVigilance every two weeks for products subject to additional monitoring, and monthly for all other monitored products.

The IR acknowledges that *'As a general principle, signal detection should follow a recognised methodology'*. However, the methodology may vary depending on the type of medicinal product it is intended to cover'. The detection of a signal shall be based on a multidisciplinary approach (IR Art 19(2)).

### 5.3.1 Signal detection methodology

#### Best practice

Heterogeneous approaches to signal detection are employed across the NCAs. This is a strength of the European signal management system and should be fostered, since this will enable the EU network as a whole to perform high-quality signal detection and allow for different signals being identified (22).



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<sup>2</sup> The enhanced access to EudraVigilance for MAHs, to comply with their monitoring obligations, is expected to come into effect in third quarter 2017.

## Sources of signal detection

Although spontaneous reporting databases are an important focus for signal detection, a signal can arise from a wide variety of sources, such as aggregated data from active surveillance systems or studies, literature information or other data sources.

For example, a signal can arise from a literature finding, and consequently be validated and entered into EPITT. Pontes et al (23) present four examples where a safety signal was detected from a literature report and had an impact on the benefit risk profile of a drug.

## Qualitative and quantitative signal detection

In the scientific community there is agreement that statistical detection methods alone are not sufficient to detect all signals in spontaneous reporting databases (24-26). Therefore, a combination of quantitative and qualitative methods is preferable. In some situations there is no need to implement a quantitative method. If the (MS) ADR database is small, a qualitative review will be complemented by simple metrics, e.g. the number of case reports is equally useful (5).

## Choice of disproportionality methods and selection of adequate detection threshold

Quantitative signal detection relies on statistical disproportionality methods, which are based on comparison of the observed with the expected count of a drug-event association. It is worthwhile to reiterate that a signal of disproportionate reporting (4) does not necessarily constitute a signal of suspect causality. There are currently several quantitative signal detection methods in use, each with so-called “implementation decisions/rules”. For example:

- The selection of specific thresholds for signals of disproportionality to be raised
- Use of additional criteria, such as number of case reports, for signals of disproportionality to be raised
- Deciding on the level of precision at which the data mining is performed.
- Decisions on which case reports to perform the detection on (overall or subgrouping of the database, e.g., vaccines only)
- Deciding whether to look only at suspect drugs or at all drugs regardless of role noted in ICSRs.

MSs use different methods, including qualitative or rule-based methods only (e.g. only number of case reports) with varying implementation decisions. Some studies (24, 25) have compared various disproportionality methods in order to determine which one has the best performance. Existing evidence indicates that there are no significant differences between Bayesian and frequentist approaches as regards to performance, and that it is possible to achieve comparable performance with any method.

The way methods are implemented for a specific database and the associated decisions seem to be more important than the method itself. Recent research from the IMI PROTECT group (26) reinforced this by showing that the choice of signal detection method does not have a substantial impact on the results and should be rather chosen based on convenience and tailored to the database. Since thresholds are database-dependent, universally valid thresholds or other implementation decisions are not possible to recommend. Still, as a guidance, some research showed that when the count of a specific drug-event combination increased from 3 to 5 this leads to a decrease of false positive signals when using the EV database (27).

Any signal threshold used should be tailored to the size of the database, the product it contains, and the level of review that is expected. This applies to complex disproportionality methods, as well as to rule based approaches (such as review of all fatal case reports). Equally, if changes are implemented to an already agreed signal threshold, ideally, the new approach should be tested to ensure that it can both detect safety issues that have been identified in the past for the products under review, and that it is no worse than the previous approach at identifying safety issues of interest for review in a side-by-side comparison.

In conclusion, changes to the threshold should not be made ad-hoc, and should be tested/ justified before implementation. If a MS wants to conduct such a change, Table 1 provides guidance on steps that can be followed.

**Table 1. Steps taken before a change in signal detection method or threshold is implemented**

Steps by step process for a change in signal detection methodology or threshold	
1.	Specify the need/reason for the change (increase in volume of case reports received, new evidence emerged which recommends an updated process)
2.	Develop study plan with relevant experts (e.g. Pharmacoepidemiology Unit, signal detection group, scientifically trained staff). The plan should include the methods that will be tested, timelines and testing methods, and any pre-analysis that is necessary to facilitate the study
3.	Approval of the study plan by relevant persons
4.	Conduct the study. From previous experience, at least 6 weeks of direct comparison of the old and new method/threshold is recommended as well as a retrospective analysis to ensure signals previously identified will not be missed
5.	Discuss the results in a meeting with the relevant experts, including assessors involved in signal management, including positive and negative impacts of making each change (if multiple changes are tested)
6.	If changes are proven successful, next steps would be: <ul style="list-style-type: none"> <li>• Agree a proposal for implementation</li> <li>• Seek feedback from the managers</li> <li>• Implement changes when agreement is attained</li> </ul>

The methods and thresholds used at the moment in various national organisations are presented in [Annex 4](#), with the caveat that no specific method can be recommended in general. Since databases change over time, a regular justification of the method used (as described above), should be performed.

### MedDRA level at which signal detection should be performed

With regards to the level at which signal detection can be performed, higher levels of the hierarchy or Standardised MedDRA Queries (SMQs) do not seem to improve signal detection (28,29) and might even delay signal detection. Nevertheless, SMQs or other aggregation levels may sometimes be useful for further signal assessment once a signal is detected.

### Stratification and subgrouping

The recently finalised Innovative Medicines Initiative (IMI) PROTECT (15) project offered useful insights into the potential utility of stratification and subgrouping when performing routine signal detection. The researchers compared performance of subgroup and stratified (adjusted) analyses to the unadjusted values within five different spontaneous databases of various size and composition. Variables included age, gender, time period, country/region of origin, vaccines/drugs and event seriousness. The conclusions reached were that subgroup analyses consistently performed better than stratified ones, and subgrouping might be good strategy in large, international databases. The variables with the most impact were age and country of origin.

## 5.3.2 Monitoring EudraVigilance with a risk-proportionate approach

### Best practice

The classification in certain risk categories for monitoring products in EudraVigilance is not standardised, but often MSs base their risk-based approach on 1-2 characteristics of the drug, e.g., time on the market, recent media attention or referrals ongoing or other regulatory obligations.



An evaluation of the existing frequency of EudraVigilance monitoring and the experience accumulated so far would be helpful in defining a more risk-proportionate consistent frequency of monitoring to be implemented by MSs.

## 5.4 Signal validation

According to the IR, signal validation is *‘the process of evaluating the data supporting a previously detected signal in order to verify that the available documentation contains sufficient evidence demonstrating the existence of a new potentially causal association or a new aspect of a known association, and therefore justifies further analysis of the signal’* (IR Art 21)).

As already explained (see [section 5.2](#)), during the validation of a signal, the evaluation of the data should be aimed at deciding if further analysis is necessary and the focus should be on determining if the signal reflects new information and if it is at least a reasonable possibility. For signals originating from spontaneous reports, that would include, as a minimum, making sure that the signal is not only based on duplicate reports and that there is a plausible time to onset.

### Best practice

Depending on the organisation and the resources at national level, validation of the signal might differ between MSs. Some MSs have an (optional) additional decision-making loop at national level or other standard operating procedures in place. A more extensive evaluation of data might already take place before next steps are taken.



A relatively detailed guidance on aspects that should be considered when evaluating the evidence supporting a signal, is outlined in GVP Module IX (5).

In order to validate, confirm or assess a signal, the previous awareness of the possible association, the data supporting the signal and the availability of additional data from other relevant sources of information should be taken into account.

For assessors involved in signal management, a practical and hands-on checklist that summarises the most important elements, points to consider and relevant sources of information when evaluating the data supporting a signal would be beneficial.

### Example: signal validation and assessment checklist

An example of a signal validation and assessment checklist has been developed within this BPG and is outlined in [Annex 2](#). The checklist covers elements from signal detection, validation and assessment. Depending on the step in the signal management process, and to what extent the validation of the signal takes place, the checklist can be used with different aims by assessors evaluating the data, to help ensure that all relevant sources of information are considered and the most important actions are performed. This checklist is meant to serve as an extra helping tool for assessors during the validation, confirmation or assessment of signals or ICSRs. It should not be considered mandatory or totally exhaustive, as some other important considerations might have not been included and not all points have to be considered during every step of the signal management process.



### 5.4.1 When to involve Marketing Authorisation Holders in early signal management

The EU signal management process concerns all stakeholders involved in the safety monitoring of medicinal products, including patients, healthcare professionals, MAHs, regulatory authorities, scientific committees and other relevant decision-making bodies. Each one of the stakeholders has specific roles and responsibilities in the signal management process. The MAH mainly has the responsibility to perform the continuous monitoring of the safety of its medicinal products and inform the authorities of any changes that may have an impact on the benefit/risk profile for the medicinal product.

#### Best Practice

For national safety issues, at the first review step, or whenever additional information is needed, MAHs could be contacted by MSs at their own discretion. Equally it may be appropriate for a MS to approach a MAH where they believe they may have identified a safety issue, but do not yet have enough information to validate it as a signal. However, once a signal has been entered into EPITT, the EU signal management process should be followed.



The EMA Questions and Answer document on signal management (6) clarifies how MAHs are informed that a signal will be discussed at the PRAC, and how they are informed of the outcomes of the PRAC signal assessment.

### 5.4.2 Regulatory confirmation of validated signals

Signal confirmation is a formal step in the signal management process according to the IR. Confirmation by the PRAC Rapporteur or the LMS means communicating through EPITT that the signal requires further analysis.

According to the IR, a validated signal that requires further analysis shall be confirmed as soon as possible and no later than 30 days from its receipt (4).

A MS shall confirm or non-confirm signals on active substances for which it has been appointed the LMS or PRAC Rapporteur. For active substances with no signal lead appointed, the MS shall confirm any signals detected and validated in its territory (30).

A validated signal is shared within the EU-network through EPITT for subsequent action. This can either be confirmed (meaning discussion at PRAC for further assessment and decision-making) or not confirmed (no discussion at PRAC). The EU signal lead, the MS itself, or the Rapporteur will decide whether there is reason to confirm or not confirm the signal (IR Art 21(3)). If the signal is marked as confirmed, it is brought to the PRAC agenda for discussion to determine the best course of action. If the signal is marked as non-confirmed, it is not brought to the PRAC agenda. Any signal can be raised again at a later stage if new evidence arises which supports it.

## Best Practice

In the EU signal management process, signal confirmation could be described as a second opinion on the initial results of signal validation at the NCA level and it should be differentiated from signal validation. Signal confirmation is not a full assessment of the signal, and a confirmed signal does not necessarily mean that a causal relationship has been demonstrated. Confirmation in EPITT only means that the signal will be brought to PRAC for discussion at the EU level and further decision-making. The decision, i.e. actions to be taken at the EU level, is up to the PRAC.



It is important to keep in mind that signal confirmation as outlined in IR only relates to a regulatory procedural step in EPITT.

## 5.5 Signal prioritisation

Signals with a potential important public health impact, or which may significantly affect the benefit-risk profile of the medicinal product, require urgent attention and should be prioritised for further management.

### Best practice

Different factors may be taken into account for the prioritisation of signals (IR Art 20(2)) (4), namely whether:



- The association or the active substance/medicinal product is new
- The strength of the association
- The seriousness of the reaction involved
- The documentation of the reports in the EudraVigilance database

Before the IR came into effect, the CIOMS VIII guidance (2) proposed a two-step signal prioritisation process, based on a combination of a first impact analysis and a further signal prioritisation.

Some of the CIOMS VIII criteria are:

- Seriousness
- Rapidly increasing disproportionality score for the impact analysis
- Occurrence during the first few years post launch (newer drugs)

Prioritisation of signals is critical to ensure that acceptable timelines and appropriate resource allocation will meet public health and regulatory obligations (31). A prioritisation tool can help to reduce the subjectivity of the prioritisation process and might increase standardisation.

A novel tool for prioritising pharmacovigilance issues within the MHRA was developed and implemented, called the Regulatory Pharmacovigilance Prioritisation System (RPPS). The RPPS tool (see [Annex 5](#)) provides a systematic approach to prioritise signals according to four categories: health consequences, strength of evidence, regulatory obligations and public perceptions.

Other tools are described in the literature, such as the 2012 FDA (32) publication of a draft guidance for Classifying Significant Post-marketing Drug Safety Issues. Another prioritisation tool was developed and tested in a MAH database by Levitan et al (33).

## 5.6 Signal assessment

According to the GVP Module IX the objective of signal assessment is to further evaluate a validated signal so as to identify the need for additional data collection or for any regulatory action. The preceding signal validation is essential to evaluate whether there is a new potentially causal association, or a new aspect of a known association, that justifies further analysis of the signal. The signal assessment should take into account all available data in order to further increase the strength of the evidence to reach a high-quality decision and signal outcome. Following the PRAC analysis and prioritisation, the signal assessment is performed by the PRAC Rapporteur or LMS and finalised at PRAC.

The aim of the signal assessment step should be to decide whether a regulatory action is necessary, and the focus should be on reaching a final decision on the causal relationship and to consider the need for (additional) risk-minimisation measures.

The data reviewed at this step is usually more extensive. Different sources of information are available to MSs for signal assessment, of which the most frequently used are published literature, expert consultation and additional data provided by MAHs.

### Best practice

The IR (4) gives only high-level instructions on how to perform assessment. All the available pharmacological, non-clinical and clinical data and information from other sources should be reviewed, and the strengths and limitations of each source should be carefully considered.



Sources of information mentioned in GVP Module IX (5) are:

- The application dossier
- Literature articles
- Spontaneous reports
- Expert consultation
- Information held by MAHs and competent authorities



When PRAC recommends further assessment of a signal, PRAC will nominate a Rapporteur for the assessment of the confirmed signal with a timeframe for the assessment. Sometimes a further assessment is not required within the signal management process, if a thorough assessment has been performed in previous steps, or if the safety issue is dealt with in another procedure (e.g. in a PSUR or variation).

While comprehensive scientific literature is already available on signal detection, MSs must mainly rely on overall guidance when it comes to signal assessment. Little guidance can be found in the scientific literature, and the EU network is encouraged to facilitate collaborative research across the network and academia. The outcome of such research and sharing of knowledge could also contribute to better training of signal assessors in the future.

### Example

An example of a signal validation and assessment checklist is outlined in [Annex 2](#). The checklist covers elements from both signal validation and assessment. It can be used by signal assessors to help ensure that relevant sources of information are considered and the most important actions are performed in order to deliver consistent and high-quality assessments.



Signal assessment is a challenging discipline and MSs are expected to deliver high-quality assessment to the EU-network. A thorough and high-quality signal assessment is the base for any regulatory decision in signal management, and any decision should be based on the most comprehensive level of evidence as possible.

Therefore, insight is important into what level of evidence is needed in the assessment, to trigger regulatory actions for drugs and vaccines with different risk profiles. To suggest answers to questions like how many case reports are enough to trigger a signal and when to update the SmPC, there is a need to bring together and share knowledge across the EU-network.

### Example

A paper from 2015 by Segec et al about Strategy in Regulatory Decision-Making for Management of Progressive Multifocal Leukoencephalopathy (34) is a good example of high-level knowledge sharing within the EU network. A tool for regulatory decision management of PML was developed and piloted, and the authors found that the methodology developed for PML was a rational approach to consider available evidence and could improve regulatory decision making. Others are encouraged to use and modify this methodology on other topics.



## 5.7 Reports of special interest

ADR reports frequently relate to areas of special interest, either scientifically, politically, or from a regulatory perspective. They may relate to events occurring in a particular population, for instance paediatrics, geriatrics or use in pregnancy, or could relate to products with unique risks or considerations, such as biologicals or vaccines. Alternatively, reports could highlight concerns about how the product has been used, either by the healthcare professional (medication error, occupational exposure), or by the patient (medication error, misuse, abuse). Such scenarios may warrant additional attention within the signal management process, due to the potential safety risks.

### 5.7.1 Population-based approaches

#### Best practice

Spontaneous ADR reporting systems span across a broad range of populations. This diversity can result in differing safety profiles and should not be ignored. The pharmacodynamics and pharmacokinetics of a medicine may be very different in children compared with adults (35) in relation to the way they metabolise and excrete medicines and can have harmful consequences. The same can be said for geriatric populations (36). In pregnancy, reports need to be considered in context of both the parent and the child. Having additional strategies in place to cover the diversity and potential confounding factors could result in fewer false signals being flagged, fewer missed signals and less masking (37).



Recent research from the IMI PROTECT group (15) recommended when statistical analysis is applied that subgroup analysis may be beneficial in routine first pass signal detection and should be considered and stratified/adjusted analyses are unlikely to provide added value. Subgrouping by population calculates disproportionality statistics within each individual stratum separately, aiding higher quality signal assessment by increasing sensitivity and precision in these groups. As a result of this research, the EMA are implementing the use of subgroups for paediatrics and geriatrics into the eRMRs after a successful pilot phase, which showed them to be beneficial.

As an alternative to the review of this additional data, as part of the routine signal detection process it may be appropriate to define strategies for review of special population groups at a reduced frequency compared to routine evaluation. Dependent on the size of the overall database, and the volume of case reports in the analysis period, this approach may offer the advantage of providing a larger volume of case reports making the regulatory decision-making process easier. However, case reports should not be excluded from routine signal detection to ensure timely identification of the most serious issues. MedDRA have published modifiable paediatric and gender alert term lists that could be used to support pharmacovigilance activities, especially when age/gender information is not available (38).

## 5.7.2 Product/substance based approaches

### Best practice

Vaccine reports were considered a priority for most MSs, however awareness of other product- or substance-based methods was very low.



There is detailed guidance on vaccine signal detection processes in the GVP module on ‘Product or Population Specific Considerations I: Vaccines for prophylaxis against infectious diseases’, which should be followed where appropriate. A signal may also relate to evidence of reduced efficacy or effectiveness, vaccine failures and quality deviations with potential impact on safety, efficacy or effectiveness and could be batch specific. Therefore, signal detection for vaccines should be considered at both brand and batch level.

Evidence from PROTECT found that during statistical analysis ‘subgrouping by vaccines/non vaccines resulted in a decrease in both precision and sensitivity in all spontaneous databases. This was almost exclusively driven by the vaccines subgroup.’ These effects were due to the suppression of known vaccine ADRs as a result of comparing vaccines to each other which although is desirable for certain reactions such as injection site reactions, it is not ideal for more serious reactions (e.g. Guillain–Barré Syndrome). PROTECT therefore recommend that careful consideration should be applied before taking this approach. This emphasises the importance of assessors understanding the rationale underlying selection of statistics and thresholds that have been applied to the data to ensure that the information presented is used appropriately.

One potential way to lessen the effect of known ADR suppression is to apply rule-based criteria to signal detection to identify and always detect certain reaction terms of interest that, under the above circumstances, would be masked. Multiple MSs are using a list of predefined important terms, which flag up reports for assessment. This is explained further in the next section.

There is some research evidence (39) that suggests that, along with new and first in class drugs, more signals are identified for biologicals, highlighting the importance of strengthening analysis of them. Again, full guidance is available in the second product or population-specific consideration GVP module for biological medicinal products (17). However, broadly, the principles described above for vaccine signal detection are common for other biologicals as well.

### 5.7.3 Reaction-based approaches

#### Best practice

When applying reaction-based approaches, most MSs focus on serious medical events and terms frequently associated with ADRs. Various stakeholders have individually developed lists of specific drug-related events; taking into account the seriousness of the event and its likelihood of being drug induced. These event terms are prioritised during signal detection, as they could more likely be true signals or potentially have a larger public health impact. These strategies can help ensure that important reactions terms are highlighted amongst other terms for assessment. Some examples of these lists include:



- Designated Medical Events (DME): those AEs which are rare, serious or which are more likely to be associated with a high drug-attributable risk, for example Stevens-Johnson syndrome (40)
- Targeted Medical Events (TME): other events of special interest associated with particular medicinal products and/or patient populations
- Important Medical Events (IME): a selected group of events that should be considered serious. This list was developed by MedDRA MSSO organisation and coordinated by the EMA (41).

A reaction-based approach can look at these terms regardless of disproportionality or in combination with disproportionality analyses when the numbers of ADR reports are large. They have been implemented into the prioritisation of drug-event combinations in eRMRs to help define the criteria and number of drug-event combination rows to review.

#### Example

Guillain–Barré Syndrome is a serious medical event thought to occur due to effects on the immune system, and occasionally reported after the administration of a vaccine. It is a known event for many vaccines, although causality is difficult to establish, and is commonly reported across all vaccines. As a result, when subgrouping by vaccine/non-vaccine, an extremely large number of case reports would be required for the disproportionality score to be raised. Studies performed in IMI PROTECT (31) indicated that this event was suppressed within a vaccine subgroup. One MS described a reaction-based approach to counteract this problem. They created a list of medical events of interest (including Guillain–Barré Syndrome), which are flagged for signal assessment regardless of the disproportionality score.



MSs should consider using a pre-defined event term list such as the DME list to help prioritise ADRs for review either regardless of disproportionality, to ensure important events are not missed, or in combination with disproportionality, to help focus attention on important terms for selected categories.

#### 5.7.4 Other specified groups of interest

##### Best practice

The definition of ADR in the EU legislation (4) has been expanded to include reports of noxious and unintended effects resulting from medication errors, misuse, abuse and occupational exposure and from uses outside the terms of the marketing authorisation (off-label use). These are often grouped together into a cluster.



It is important these are identified, so that their risk can be minimised, unlike other signals they do not require the establishment of a causal relationship because they are unintended events caused by human error.

No robust statistical methods for automated identification of ADRs from this group are identified, and further research and/or development is recommended in this area to enable efficient identification of these safety issues, which are well understood to have a significant impact on the healthcare system and are often easily preventable. Some of the barriers to analysis of this area are either a lack of data, or an incomplete dataset. Specifically, different national bodies, separate from the NCAs for pharmacovigilance issues, but part of, or linked to, the healthcare system, are often responsible for collection and analysis of such data. Even where data sharing arrangements are in place, these organisations have different goals and purposes, and will not necessarily hold the data in a format easy to analyse alongside NCAs' ICSR data specifically for pharmacovigilance and signal management purposes.

Detection and management of medication errors, misuse and abuse and occupational exposure is unlikely to be the sole responsibility of the NCAs and, as such, it is important to establish or improve relationships between the NCA and relevant areas of the healthcare system. Such relationships should enable sharing of data both to help a MS carry out its pharmacovigilance responsibilities, but also to enable the healthcare network to reduce and learn from incidents that have occurred. Such collaborative networks may also be valuable when sharing other outputs of the signal management system, such as communicating relevant risk-minimisation measures.

### Example



A signal of medication errors potentially leading to inappropriate dose administration was identified by a MS following a communication from their national Organisation for Medication Incidents (42). They reported cases of 8 patients who received a higher dose than intended, including 2 fatalities. This led to a review of their national case reports, which subsequently led to the signal being raised, resulting in preventative measure being put into place. This example highlights the value of NCAs working alongside other areas of the healthcare system.

The working model guidance for exchanging information between different organisations presented in this medication error guidance could also be an example for working with other organisations, for example national poison centres.

There is detailed guidance on the recording, coding, reporting and assessment of medication errors available in the Good practice guidance on recording, coding, reporting and assessment of medication errors (43), which was published by the EMA in 2015. It is important to note that medication error terms should only be recorded against a case when an error has been stated by the original reporter. No assumption should be made by the MS. However, it is worth noting that, in line with Good practice guidance on medication error (43), if a MS (or MAH) thinks a medication error code is warranted, an alternative classification can be provided in the ICH E2B (R2) data element B.5.3 'Sender's diagnosis/syndrome and/or reclassification of reaction/event'. This information could also be used as a means of identifying reports concerning medication errors by creating queries in EudraVigilance to search for relevant MedDRA terms in both the 'Reaction/event' and 'Sender's diagnosis/syndrome and/or reclassification of reaction/event' data elements, resulting in a list of suspected products associated with medication errors.

Because of the nature of the way this data is obtained and coded it may be challenging to analyse using traditional statistical methods used in Pharmacovigilance. The MedDRA MSSO implemented a 27th System Organ Class (SOC) in MedDRA, which contains product quality issues. Some of these areas may provide secondary linkage to medication errors, however, the most valuable asset in identification of these case reports if they have been coded is likely to be the Medication Errors SMQ. IMI PROTECT did not find improved detection performance when comparing SMQs to PTs (29) generally, but this does not exclude their use for specific circumstances, such as medication errors. Should such approaches be adopted it will be important to ensure consistent coding practices to identify relevant case reports, or that routine methods are capable of detection of the most serious safety issues.

Because of the likelihood of missing signals from this group due to the issues described above it is important that MSs signal management system consider the potential for medication errors within routine activities, and that any other approaches should be considered as additional methodologies.

### Example

Leuprorelin is indicated for the treatment of palliative advanced hormone-dependent prostate cancer and works by suppressing testicular steroid genesis. A signal was detected by one MS following a report from a healthcare professional concerning 3 reported cases of increased testosterone levels after treatment with Leuprorelin (44), suggesting a lack of efficacy. It was noted in the reporter's comments section of the report that it could be due to 'a wrong technique in drug administration process'. A further search of the MS's database found 11 similar reports, which suggested either a lack of efficacy and/or a wrong technique being used; however, only 4 of these had an adverse reaction belonging to the medication error HLG. This signal emphasises that the coding of medication errors cannot be relied upon alone and that qualitative analysis is beneficial. Medication errors need to be considered when looking at all signal outputs.



## 5.8 Data quality

### Best practice

Good data quality is relevant for all steps of the signal management process: signal detection, prioritisation, validation and assessment. In addition to incorrect coding, ICSR data quality aspects are to be considered – for example, duplication of reports, absence of information in structured E2B fields, and lack of completeness of ICSR. Recent studies (45) showed that more informative reports (with a minimum of required fields completed) are correlated with true signals. Data quality considerations are addressed on a high level in the EU legislation and more detailed guidance is provided in several of the GVP Modules. In general terms, reference is made to quality management systems, procedures to collect follow-up information and to the relevant standards and terminologies that should be applied by all stakeholders. The EMA has procedures in place to manage duplicate ICSRs and to review the quality of the ICSRs for all organisations reporting to the EudraVigilance database (30).



Consistent and standardised coding of data is important and highlights the importance of appropriate training in the use of MedDRA terminology, especially at the time of data entry, to improve the data quality. With electronic E2B reporting, ICSRs may be automatically loaded to the database without manual intervention. As a result, modern EU spontaneous reporting databases contain data collected by various organisations, all with their own methods of data collection, data processing, coding, etc. As incorrect or inconsistent coding have an impact on data retrieval and analysis processes, SCOPE WP5 reiterates the importance of following the existing guidance on data quality and coding.

Specific skills and knowledge, including clinical knowledge, at the level of the coding staff are required to perform coding (46). Training should be provided to all MS staff involved in ICSR coding in order to achieve the optimum level of coding and to ensure that all the parameters for quality are achieved. The training in MedDRA dictionary of personnel responsible for signal detection activities, is also important. Online training webinars for both coding and information retrieval are available on the MSSO website; for further information on coding of AEs, please refer to the ‘MedDRA Term Selection: Points to Consider’ and ‘MedDRA Data retrieval: Points to Consider’ documents (47,48).

Coding is also highlighted as key challenge for reports of special interest. It is unlikely that, for instance, reporters completing online web forms will select accurate MedDRA PTs related to special situations, when offered the possibility, but rather capture this information in free text. Clearly this creates challenges in the analysis of the data, some of which are described above. The solution to these problems is not considered to be as simple as the addition of extra questions to the reporting systems, and users may have different understandings of terms to those used in the regulatory setting. For example, addition of questions around whether a medication error has occurred have been found to be answered in different ways depending on the stakeholder (based on MHRA implementation experience, unpublished). Patients frequently selected the medication error check box, simply because they had experienced an ADR and therefore considered the medication had been prescribed to them in error (based on MHRA implementation experience, unpublished). Although changing the wording of the question and guidance can improve this information, it is important to consider that the reporter’s perspective may differ depending on their individual circumstances. Guidance from SCOPE WP4 should be used to develop harmonisation in this area across the EU network to aid consistency within signal detection, including reports of special interest.

As a prerequisite for signal management, the importance of data quality is emphasised and all stakeholders should devote appropriate attention to improve it.

## 5.9 Training

Achieving the required quality for the conduct of pharmacovigilance processes and their outcomes by an organisation is intrinsically linked with the availability of a sufficient number of competent and appropriately qualified and trained personnel and having a specific recruitment plan to ensure the competences and skills would be of value (49). As laid down in the legislation, all personnel involved in the performance of pharmacovigilance activities shall receive initial and continued training (IR Art 14(2)).



## Best practice

It is recommended that MSs have a training plan in place to provide staff members involved in signal management with the knowledge, guidance and methods to perform signal management activities in line with their job descriptions. The extent of the specific topics covered should fit the role, experience, knowledge and expertise of the staff member. Such training plan could cover:



- Relevant internal Standard Operating Procedures and Working Instructions
- Guidance regarding signal detection methods: Staff members should be made aware of the signal detection method(s) applied in their organisation and also on how to use the eRMRs from EudraVigilance
- Background documents: Staff members should be made aware of the most relevant guidelines for signal management (e.g. Report of CIOMS Working Group VIII, EMA guideline on the use of statistical signal detection methods, EU SmPC guideline, GVP Module IX on Signal Management and the EMA Questions and Answers document on signal management). The most updated version of the documents should always apply
- EPITT: It is recommended to attend the EPITT webinar training provided by EMA
- MedDRA coding and analysis: The MedDRA MSSO provides a number of different training opportunities, including free face-to-face trainings for regulatory authorities. An online free introductory training curriculum covers MedDRA coding, as well as data analysis (including SMQs)
- EudraVigilance Data Analysis System (EVDAS) training for NCAs organised by the EMA
- Literature search: The staff member should be trained on how to perform literature searches and set up alerts in order to support signal management activities
- Relevant regulatory documents: Staff members should be introduced to the most relevant documents used for signal detection and management, such as SmPCs, PSURs, RMPs, renewals, referrals, variations, as well as the corresponding Assessment Reports. This should also address how to access the documents and information
- External training courses in therapeutic areas and in other topics of interest: In view of the need to maintain and expand the knowledge regarding pertinent topics (therapeutic areas, epidemiology, statistics, pharmacovigilance, etc.), it is encouraged to attend external courses, conferences and congresses in order to build expertise and keep up to date with new developments. The EU network training centre (EUNTC) can be consulted to check relevant training opportunities

This SCOPE WP5 guidance document will be supported by training provided in the context of the SCOPE project. This training will focus on the signal management process and an e-learning module will be made available for use after the SCOPE project has finished.

## 6. Conclusions

The SCOPE WP5 team identified a number of challenges that MSs are experiencing with the interpretation, and some complexities in implementation, of the existing signal management legislation. SCOPE WP5 identified challenging areas and best practice through a questionnaire; of particular importance to the MSs was clarification of requirements regarding the prioritisation, validation and confirmation of signals, as well as the processes for reports of special interest.

In response to these findings, the SCOPE WP5 team created this document of recommendations and BPG to support the legislation and GVP on signal management and make the principles within these documents more widely achievable for all MSs, regardless of the size or structure of the NCAs.

Signal detection methods in individual MSs are not and do not need to be the same, and indeed there is strength in their diversity. Depending on the way the signal management is organised in the different MSs, signals that are brought to PRAC may differ in maturity. Some MSs have additional decision-making loops in place, where some aspects of the signal assessment come into play, whilst others do not. Access to all the necessary documents and data sources is crucial, for thorough assessment of signals and measures should be taken to ensure that they are available to all assessors involved in signal management, where this is not already the case.

In addition to steps that can be adopted at a national level, there are a number of recommendations for the EMA and the EU Regulatory Network to consider as a whole. These cover both processes and IT tools used within signal management and demonstrate the possibility for further efficiencies within the system. Please see [Annex 1](#).

The BPG gives clear and specific advice as to how these recommendations can be achieved, with an aim to improve the quality of signal management throughout Europe. While some can be implemented by individual MSs, others are specific to the EMA or require collaboration across the European Regulatory Network.

## 7. Annexes

### Annex 1. SCOPE WP5 recommendations for future research and development

#### Process-related recommendations

These recommendations impact the processes and activities of signal management, regardless of their implementation within the system.

1. **A risk proportionate approach (as a function of product type or type of safety issue) to EudraVigilance monitoring should be developed.** By taking the conservative approach and monitoring all the substances in the same way, resources are diverted and important signals might be delayed as a consequence. A risk-proportionate approach would allow a better allocation of available pharmacovigilance resources.
2. **The EU network should consider how to facilitate collaborative research in signal assessment methods as a basis for regulatory decision making.** Limited scientific literature is published on signal assessment, and the EU network is encouraged to facilitate collaborative research across the network and academia. The outcomes of such research and sharing of knowledge could also contribute to better training of signal assessors in the future. Both the regulatory and academic circles would benefit from an open scientific dialogue and more research in this area.

#### IT system-related recommendations

These recommendations impact the IT system (software, network resources and services) required for the existence and functioning of a signal management system.

1. **The EU network would benefit from an integrated EU signal management tool combining signal detection and tracking functionalities and replacing the existing Excel based component.** The current eRMR system, although it facilitates the monitoring of EudraVigilance data, would benefit from further improvements in order to allow access to the EudraVigilance data to the level of detail desired by MSs. MSs consider that there would be significant value in a tool that integrates the functionality of the eRMR, EVDAS and EPITT to enable a seamless and linked signal management approach.
2. **The need of a suitable tool to exchange information on preliminary signals within the EU is identified and the EU network would benefit from sharing signals at an early stage.** This tool would facilitate exchange of relevant information at an early stage, to prevent duplication of work.

- 3. Systems which allow cross-procedural tracking of final outcomes of signals is identified as a need (in case the signal is addressed in a different procedure).** The outcomes of signals addressed in other procedures (e.g., PSURS, renewals) are not captured in the current EU signal management tracking systems and this does not facilitate transparency and efficiency, as it might lead to duplication of work and waste of resources.
- 4. A structured SmPC database would be helpful to facilitate validation of signals.** Checking if the ADR is reflected in the SmPC is usually the first step in signal validation. Therefore, the pharmacovigilance system would benefit from an automated tool for this purpose. This tool is already available for centrally authorised products (50), but not for nationally approved products. For nationally approved products, a Core Safety Profile (CSP) approach could be used: a dataset containing the minimum safety information present in the SmPCs from all MSs.

### Recommendations for future research

- 1. There is a trade-off between sensitivity and specificity with all current statistical detection methods, and further research is recommended to optimise these approaches in both EudraVigilance and national systems.** The trade-off between sensitivity and specificity always depends on the subjective value assigned to one true signal lost versus resources spent on one false positive. Traditionally, in pharmacovigilance a higher premium is put on sensitivity. The balance however should be carefully selected and justified.
- 2. Dedicated methodologies for analysis of reports of special interest should be developed.** Limited research was found covering methodologies specific to reports of special interest, despite their scientific and political importance. The EMA and MSs should work together to enable such research to be carried out for the benefit of the network.

### Further detail on suggestions for further development as identified during the project

#### The need for an integrated signal management system at European level

EMA has undertaken significant work in strengthening the statistical methodology included in the eRMR by implementation of IMI PROTECT recommendations. Furthermore, some improvements in the layout of the eRMR have been made, in order to enhance user-friendliness and increase efficiency. However, the fact that the tool remains Excel-based is considered a barrier to further development of the signal management process. Users feel that the lack of true integration/interactivity between the eRMR and the EudraVigilance Data Analysis System poses a limiting factor in improvement of the system. This lack of connection between the different tools reduces efficiency of use of the eRMR and the capacity to assess high volumes of multi-factorial issues fast. The lack of flexibility for an individual assessor to define layout preferences (as might be expected in a web-based interface) was also identified as a barrier.

There would be significant value in a toolset that integrates the functionality of the eRMR, Eudra-Vigilance and EPITT together, to enable an efficient and integrated signal management process across the EU-network. The tools should facilitate users to extract information at whichever point they need, and view it alongside other information in the format they require. A second function and the advantage of having such an integrated system would be to allow an audit trail of the assessment process while simultaneously recording useful information for assessors to consider in future assessments of the issue. The tools should enable information to be shared without the need for additional emails, and consideration should also be given to the ability to collaborate on issues which do not yet meet the legal definition of a signal.

### **The need for an early exchange of information to inform the EU network and prevent duplication of work**

The EU network would benefit from the possibility of an early exchange of information on signals in order to inform other MSs and prevent duplication of work. This would provide transparency of signal detection outputs to other MSs prior to the point that they are confirmed.

Given there are no other tools currently available for this specific purpose, these are the possibilities to facilitate this exchange of information: inform the LMS by email, distribute a NUI, or enter the signal in European Pharmacovigilance Issues Tracking Tool and propose to the LMS to not confirm this signal (to ensure that the signal will not be at the PRAC agenda). In the future, this sharing should be facilitated by the creation of a new signal management tool.

### **A structured SmPC database to facilitate validation of signals**

Checking if the ADR is reflected in the SmPC is usually the first step in signal validation. Therefore, the pharmacovigilance system would benefit from an automated tool for this purpose. This tool is already available for centrally authorised products (50), but not for nationally authorised products. For nationally authorised products, a Core Safety Profile (CSP) approach could be used: a structured database containing the minimum safety information present in the SmPCs of all the MSs could be a helpful tool. The CSP approach has been used in the past at the time of the previous work-sharing where the MAH developed a Core Safety Profile. It would be beneficial for this dataset to include common information from sections 4.3 – 4.9 present in all SmPCs within the EU and any relevant safety information from section 4.2.

### **Systems which allow cross-procedural tracking of final outcomes of signals is identified as a need (in case the signal is addressed in a different procedure)**

The outcomes of signals addressed in other procedures (e.g., PSURS, renewals) are not captured in the current EU signal management tracking systems and this does not facilitate transparency and efficiency, as it might lead to duplication of work and waste of resources. It would be beneficial for enhanced signal management tools to be developed that enable aggregation of safety issues associated with a product, irrespective of the procedure from which they are derived.

### **Tools provided should facilitate a risk-proportionate approach to signal detection**

Whilst we cannot make a recommendation from the data attained from WP5 about the most appropriate signal management strategies for products/substances of differing maturity, it is clear that different approaches may be beneficial. Any enhancement or redevelopment of the signal management toolset should take account of the need for flexibility in strategies. This could include differing review periods for varying maturity, or different thresholds for different groups of product, cases or interest areas. Tools should offer the ability to rapidly adopt new approaches, and to study different methodologies to understand their impact. Whilst different approaches may be adopted it is important that assessors have access to regularly updated disproportionality criteria to enable rapid assessment of a new issue irrespective of the pre-defined review period.

## Annex 2. Signal validation and assessment checklist

### Validation of the signal

*Important sources: SmPC, EPITT, PSUR, RMP, EMA website, other regulatory procedures*

1. Is the event reflected in the SmPC of the active substance?
  - i. For centrally authorised products, check the SmPC available at the EMA website; for nationally authorised products, check the SmPC(s) available in your MS
  - ii. For active substances for which a generic version exists, check first the SmPC of the innovator product (if possible)
    - Check sections 4.3, 4.4, 4.5, 4.6, 4.8, 4.9 of the SmPC for information regarding the event
    - Check if the event might be covered by a similar term or a higher level term in the SmPC
    - Check if the event is reflected in the SmPC of another medicinal product containing the same active substance
    - Check if the event is reflected in the SmPC of a medicinal product from the same class
    - In case of an interaction, you may check if there is information on the interaction in the SmPCs of the other medicinal products concerned
2. Does the event reflect a new aspect of a known association?
  - Increase in frequency of occurrence
  - Change in duration and/or time to onset
  - Change in severity
  - Change in occurrence pattern (e.g. affecting a specific population)
  - Change in previously reported outcome (e.g. new fatal cases)
3. Has the association previously been addressed in a regulatory procedure?
  - Check if there is information in EPITT
  - Check the PSUR of the medicinal product
  - Check the RMP of the medicinal product
  - EMA website of referrals
  - Recently submitted/assessed variations in your MS regarding same/similar safety issue

*Of note: exclude that the signal is only due to duplicates and that there is a plausible time to onset.*

## Assessment of the data (points to consider)

*Important sources: ICSRs, national databases, EudraVigilance, literature*

### 1. Review of the cases supporting the signal

- Number of cases supporting the association (after exclusion of duplicates and cases with no supporting temporal association)
- Number of cases appropriately documented with sufficient information about, e.g., suspect drug, event reported, demographics (age and gender), indication, outcome, concomitant medication
- Consistency of the evidence across cases (e.g. patterns)
- Route(s) of administration and product(s) formulation
- Cluster of reports, e.g., many reports from the same reporter, publication, etc.
- Cases fulfil the diagnostic criteria for the event

### 2. Strengths

- Biological and pharmacological plausibility (possible mechanism)
- Dose relationship
- Number of cases with positive de-challenge
- Number of cases with positive re-challenge
- Low background incidence of the event
- Time to onset

### 3. Clinical relevance

- Seriousness/severity of the event
- Reversibility of the event
- Event affecting special populations (e.g. pregnant women, children, elderly) or patients with pre-existing risk factors
- Events occurring in different patterns of use (e.g. off-label, overdose, misuse, medications errors)
- Association likely to apply to other active substances of the same class
- Potential for prevention



#### 4. Other aspects to be considered

- Possible class effect
- Possible drug-drug interaction
- Possible medication error
- Possible quality issue
- Possible off-label use
- Possible overuse, abuse, misuse

#### 5. Weaknesses

- Poor data quality of case reports
- High number of cases with confounding factors / alternative explanations
- Signs of stimulated reporting e.g. increased media attention
- Abnormal reporting pattern
- Presence of other risk factors for the event: underlying disease, co-morbidities, co-med-ications

### **Additional sources of information**

*Important sources: literature, other ADR databases, clinical trial data, registries, drug utilisation data, studies*

#### 1. Additional data

- National databases (e.g. for signals detected in literature)
- Databases with larger datasets such as EudraVigilance or VigiBase (e.g. for signals detected in national databases, literature or other sources)
- Information on active substances from the same class (e.g. for signals detected in national database or Eudravigilance)
- Literature findings, regarding similar case reports, pharmacoepidemiological studies or studies suggestive of a potential mechanism of action
- Clinical trial data
- Pre-clinical data

2. Information on extent of exposure and characteristics of exposed patients

- Drug utilisation data (national exposure, patterns of use) from national drug utilisation registries or from PSURs
- Healthcare databases

3. Additional information

- RMP of the medicinal product for ongoing or planned studies that might provide evidence on the association
- ENCePP registry for studies for ongoing or finalised studies, which might provide evidence on the association
- Other registries

## Annex 3. Minimum information required for tracking of signals within the MSs

### Variables to be tracked

#### Administrative details

- Drug identification (active substance, Anatomic Therapeutic Chemical Classification (ATC), trademark, drug class)
- ADR description (preferably MedDRA terminology)
- Signal ID: e.g. year, serial number or EPITT number,
- Regional centre involved (if applicable)
- Reference to other associated signals

#### Signal detection

- Source of information based on which the signal was initially detected
- Signal identification date (to be complemented with updates when status is reviewed)
- Number of case reports (if applicable)

#### Signal validation

- Date of signal validation
- Information taken into account for its validation
- Result (output) of the validation process

#### Decision making

- Date of expert/committee advice/opinion
- Expert/committee advice/opinion

## Annex 4. Signal detection methods and thresholds used in various NCAs

Quantitative Method	Number of countries	Applied Thresholds
Proportional Reporting Ratio (PRR)	2	PRR lower bound 95% c.i. $\geq 1$ & $n \geq 3$ cases
	1	PRR lower bound 95% c.i. $\geq 1$
	2	PRR lower bound 95% c.i. $\geq 2$ & $n \geq 3$ cases
	2	PRR lower bound 95% c.i. $\geq 1$ & $n \geq 5$ cases <sup>3</sup> *
	1	PRR $\geq 3$ , PRR lower bound 95% c.i. $\geq 1$ & $n > 2$
Reporting Odds Ratio (ROR)	1	ROR lower bound 95% c.i. $\geq 1$
Information Component (IC)	1	IC lower bound 95% credibility interval $> 0$
Empirical Bayes Geometric Mean (EBGM)	1	EB05 $\geq 1.8$ & $n \geq 3$ & EBGM $\geq 2.5$
	1	EB05 $\geq 1.8$ and $n > 1$ case **

\* Three cases may be used for some drug-PT combinations

\*\* Quantitative method applied only to serious reports ( $n=1$ )

<sup>3</sup> In line with the results from the following publication: Slattery J, Alvarez Y, Hidalgo A. Choosing thresholds for statistical signal detection with the proportional reporting ratio. Drug Saf. 2013 Aug;36(8):687-92.

## Annex 5. Regulatory Pharmacovigilance Prioritisation System

### Strength of evidence

- Disproportionality measure/risk estimate
- Data sources
- Evidence from RCT or meta-analysis
- Biological plausibility

### Public health implications

- Drug/vaccine exposure
- Frequency of ADR
- Health consequences
- Spontaneous case reports

### Agency regulatory obligations

- Recent parliamentary questions
- European obligations
- Ministerial/public health authority concern
- Marketing authorisation holder (MAH) application

### Public perceptions

- Media attention
- Factors likely to cause public anxiety
- Public misperceptions
- Other public concern

## Annex 6. Glossary

Term	Definition
Confirmed signal	A signal that has been entered into EPITT and for which the confirmation step performed either by the signal identifier, the LMS for that active substance or the PRAC Rapporteur, has concluded that the signal should be further discussed at PRAC for further prioritisation, analysis and assessment, according to the IR.
European Regulatory Network	The NCAs from the 31 EEA Member States, together with the EMA and the European Commission (EC) constitute the European Medicines Regulatory Network.
Lead Member State	For nationally authorised products approved in more than one MS, a worksharing has been organised whereby LMSs have been appointed to monitor EudraVigilance data on behalf of the other MSs. The LMS is also responsible for the validation and confirmation of signals in EPITT on behalf of the other MSs for the respective nationally authorised products. LMSs may also be supported in the fulfilment of its tasks by a co-leader. When appointing a LMS, and as appropriate a co-leader, the CMD(h) in collaboration with the PRAC, may take into account whether any MS is acting as reference MS or as a Rapporteur for the assessment of PSURs for the respective product.
Non-confirmed signal	A signal that has been entered into EPITT, but for which, depending on the origin of the signal, either the signal identifier, the LMS for that active substance or the PRAC Rapporteur, has concluded that no discussion at PRAC is warranted and therefore is not set into the PRAC agenda.
Non-validated signal	A signal where the signal validation process of evaluating the data supporting the detected signal has concluded that the available documentation at that point in time does not contain sufficient evidence demonstrating the existence of a new potentially causal association, or a new aspect of a known association, and therefore a further analysis of the signal is not warranted.
Reflected event (in the SmPC of an active substance)	An event for which there is sufficient information already included in the currently approved SmPC of the active substance and therefore it is not considered to be provide new information.

Term	Definition
Signal	Information arising from one or multiple sources, including observations and experiments, which suggests a new potentially causal association, or a new aspect of a known association, between an intervention and an event or set of related events, either adverse or beneficial, that is judged to be of sufficient likelihood to justify verificatory action (IR Art 19(1)). A signal generally involves an active substance regardless of its indication, strength or route of administration and applies to all brand names/medicinal products containing the active substance, including fixed combinations. However, in some instances a signal may be relevant only to a particular indication, strength or route of administration. On the other hand, a signal may encompass all active substances of a therapeutic class.
Signal assessment	The process of assessing all scientific evidence available. This might include pharmacological, non-clinical and clinical data and information from other sources. This review should be as complete as possible regarding the sources of information, including the application dossier, literature articles, spontaneous reports, expert consultation, and information held by MAHs and competent authorities.
Signal confirmation	Procedural step through which a signal that has been entered into EPITT is set for discussion in the PRAC agenda for further prioritisation, analysis and assessment, according to the IR. Depending on the origin of the signal, the confirmation step is performed within 30 days of its receipt by the PRAC Rapporteur (for centrally authorised products), the LMS (if appointed, for nationally authorised products) or by the signal identifier (for nationally authorised products that have not yet been allocated to a LMS).
Signal detection	Process of monitoring post-marketing safety data for information that would suggest a new potentially causal association, or a new aspect of a known association between an intervention and an event or set of related events, either adverse or beneficial, that is judged to be of sufficient likelihood to justify verificatory action. It usually involves a combination of statistical methods and review of individual case safety reports, as well as any relevant source of information (e.g. scientific literature).
Signal identifier	In the context of this BPG, the signal identifier is the regulatory authority (EMA or MS) that detected or first became aware of the signal.
Signal management process	Set of activities performed to determine whether, based on an examination of ICSRs, aggregated data from active surveillance systems or studies, literature information or other data sources, there are new risks causally associated with an active substance or a medicinal product or whether known risks have changed. It includes the following activities: signal detection, signal validation, signal confirmation, signal analysis and prioritisation, signal assessment and recommendation for action (IR Art 21(1)).

Term	Definition
Signal prioritisation	A continuous process performed through the whole signal management process, which aims to identify those signals with a potential important public health impact or which may significantly affect the benefit-risk profile of the medicinal product and thus require urgent attention and management without delay. The prioritisation dictates the timeframe for submission and assessment of data. While signal prioritisation is described in the IR as a process whose responsibility falls on the PRAC after a signal has been confirmed in EPITT, in this BPG signal prioritisation is further explained as a continuous process that should be performed during the whole signal management process, rather than a signal step, and performed also at a national level, by the MSs.
Signal validation	Process of evaluating the data supporting a detected signal in order to verify that the available documentation contains sufficient evidence demonstrating the existence of a new potentially causal association, or a new aspect of a known association, and therefore justifies further analysis of the signal (IR Art 21(1)).
Validated signal	A signal where the signal validation process of evaluating the data supporting the detected signal has verified that the available documentation contains sufficient evidence demonstrating the existence of a new potentially causal association, or a new aspect of a known association, and therefore justifies further analysis of the signal (IR Art 21(1)).



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