# SCOPE Work Package 5
# Survey Report

*Topic: Signal Management*

**Authors:**
Alexandra Pacurariu
Anja van Haren
Anna-Lena Berggren
Birgitta Grundmark
Helle Harder
Mona Vestergaard Laursen
Paul Barrow
Phil Tregunno
Pilar Rayon
Sabine Straus

# 1 Introduction

## 1.1 Document Revision History

| Version | Revision date | Summary of Changes |
|---|---|---|
| 1 | 2nd April 2015 | Creation of initial draft |
| 2 | 17th April 2015 | Major revisions and comments from AH and SS |
| 3 | 19th April 2015 | Major revisions and comments from AH and SS |
| 4 | 28th April 2015 | Minor revisions and comments from AH and SS |
| 5 | 30th April 2015 | Comments from BG, ALB, MVL |
| 6 | 5th June 2015 | Draft circulated again for comments, discussion section reshaped, data is anonymised by moving sensitive information in an Annex. |
| 7 | 17th June 2015 | Final round of comment s |
| 8 | 24th June 2015 | Final |

## 1.2 Definitions and abbreviations

| Terminology | Description |
|---|---|
| ADR | Adverse Drug Reaction |
| AEFI | Adverse Event Following Immunization |
| AEMPS | Agencia Española de Medicamentos y Productos Sanitarios |
| ATC | Anatomic Therapeutic Chemical Classification |
| BPG | Best Practice Guidance |
| CIOMS | Council for International Organizations of Medical Sciences |
| CMDh | Coordination Group for Mutual Recognition and Decentralised Procedures - Human |
| CMS | Concerned Member State |
| CPRD | Clinical Practice Research Datalink |
| DHMA | Danish Health and Medicines Authority |
| DHPC | Direct Healthcare Professional Communication |
| DME | Designated Medical Event |
| EBGM | empirical Bayes geometric mean |
| EHR | Electronic Healthcare Records |
| EMA | European Medicines Agency |
| ENCePP | European Network of Centres for Pharmacoepidemiology and Pharmacovigilance |
| EPAR | European Public Assessment Report |
| EPITT | European Pharmacovigilance Issues Tracking Tool |
| e-RMR | electronic-reaction monitoring report |
| EVDAS | EudraVigilance Data Analysis System |
| FAERS | FDA Adverse Event Reporting System |
| FDA | Food and Drug Administration |

| | |
|---|---|
| GVP | Guideline on good pharmacovigilance practices |
| HPV | Human Papilloma Virus |
| IC | Information Component |
| ICSR | Individual Case Safety Report |
| IME | Important Medical Event |
| IR | Implementing Regulation |
| MAH | Marketing Authorization Holder |
| MEB | Medicines Evaluation Board |
| MedDRA | Medical Dictionary for Regulatory Activities |
| MHRA | Medicines and Healthcare Products Regulatory |
| MPA | Medical Products Agency |
| MS | Member State |
| NCA | National Competent Authority |
| PI | Product Information |
| PIL | Patient Information leaflet |
| PRAC | Pharmacovigilance Risk Assessment Committee |
| PRR | Proportional Reporting Ratio |
| PSUR | Periodic Safety Update Report |
| PT | Preferred Term |
| PROTECT | Pharmacoepidemiological Research on Outcomes of Therapeutics |
| PV | Pharmacovigilance |
| RMP | Risk Management Plan |
| ROR | Reporting Odds Ratio |
| RSI | Reports of Special Interest |
| SCOPE | Strengthening Collaboration for Operating Pharmacovigilance in Europe |
| SmPC | Summary of Product Characteristics |
| SMART | Signal Management Review Technical Working Group |
| SMQ | Standardised MedDRA Query |
| SDR | Signal of disproportionate reporting |
| SOC | System Organ Class |
| WHO | World Health Organization |
| WP | Work Package |

### 1.3 Attachments

| Ref No | Document name | Author(s) |
|---|---|---|
| | | |

### 1.4 Table of contents

### 1.5 Executive summary

The main objective of WP5 Signal management is implementing a common understanding of best practice in signal management across the EU network. A web based questionnaire was considered a relevant and efficient tool to gain information on current practice in signal management among EU MSs. 25 of 31 MSs responded to the questionnaire.

The results of the survey show a picture where there is a lot of heterogeneity in EU with regards to the implementation of the signal management process. Overall, MSs already have good practices in place for monitoring both national and EudraVigilance ADR data, the two main sources of signals, though methods vary between MSs.

The key findings from the survey will turn into best practice guidance, and also challenges were identified, which will need close liaison with EMA and SMART and possibly other stakeholders in addition to the SCOPE project to be addressed. Use of EPITT, e-RMR, GVP module IX update and SmPC alignment were mentioned as important challenges in the signal management process.

In general a difficult signal management terminology is one obstacle mentioned, and MSs find the terminology used in the GVP module IX difficult to separate their national signal management procedure into the steps outlined in this survey. Through the survey the need for training, for increasing awareness regarding available information sources, and updated or new tools to better support the current signal management process were central issues.

As for the validation step, the majority of MSs have a signal validation procedure in place. A specific challenge is managing signals which are not entered in EPITT or those which do not meet GVP module IX definition of a signal. Other challenges in relation to signal validation are: availability of the documents, handling of signals via several products or procedures, limited information and duplicates in EudraVigilance, the lack of resources and expertise of assessors and the difficult implementation of GVP procedures. Prioritization is done differently at level of MSs and at least one MS has a structured and document process in place. Several MSs mentioned they had no or limited experience confirming signals and the survey indicate that signal confirmation generally is a step that many MSs find difficult to implement in the signal management work.

The signal assessment part of the survey leave the impression that while many MSs are well on their way, some are left with no or very little experience in this area. A noticeable variability and knowledge gap is thus identified. MSs have limited strategies in place at the moment for reports of special interest, out of all investigated categories, vaccines and paediatric reports being the ones which receive most attention.

## 1.6 Background

The Strengthening Collaboration for Operating Pharmacovigilance in Europe (SCOPE) Joint Action aims to support EU Member States in operating their pharmacovigilance systems as part of the European Union Network making the best use of experience and practices to support the best use of available national resources. SCOPE is gathering information and expertise knowledge on how Member States run their national pharmacovigilance systems. Using this information, SCOPE will develop and deliver tools, guidance and training to support MSs in their pharmacovigilance activities. Through this approach SCOPE aims to support consistency in Pharmacovigilance approaches across MSs to provide greater knowledge and confidence in MSs' pharmacovigilance work, helping to identify and promote their strengths and expertise while aiding the development in weaker areas thereby increasing the protection of public health. SCOPE aims to deliver sustainable outcomes for member states which last beyond the end of this three year project.

SCOPE is divided into eight separate work packages (WP) and this report concerns Work Package 5 – Signal Management, with Medicines Evaluation Board (MEB), Netherlands as the lead. Work Package 5 seeks to develop an improved understanding of best practice in signal management within the network of National Competent Authorities (NCAs). The basis is formed by the legal requirements, the good vigilance practice guidance and in addition this work package builds on the framework as developed by the CIOMS Working Group on Application of Signal Detection in Pharmacovigilance (CIOMS VIII), European Medicines Agency's (EMA) guidance on medication errors, and liaise with PRAC's working group on signals (SMART), and where applicable will also integrate new information (e.g., from the PROTECT project). Best practice guidelines and toolkits will be developed as appropriate and used for training sessions, aiming to improve signal management in Europe.

The main overarching objective of WP5 is implementing shared understanding of best practice in signal management across the EU network.
Within Work Package 5, there are four topics:
1. Signal detection– lead: MEB (Netherlands)
2. Signal validation/prioritization – lead: AEMPS (Spain)
3. Signal confirmation and assessment – lead: DHMA (Denmark)
4. Reports of special interest – lead: MHRA (United Kingdom)
MPA (Sweden) is in addition an active contributor to WP5.

## 1.7 Context and scope of report:

### *1.7.1 Main goal*

This report provides the review summary and analysis of the responses from the NCAs in the EU Network to the WP5 survey on signal management. A web based questionnaire was considered a relevant and efficient method to easily gain information on tools and methods for signal management used by MSs. This document presents the results of the survey, the description of the current situation in the MSs regarding the practices and resources in place and identifying challenges faced by the MSs. The results will provide the basis for the further work in WP5 in identifying solutions and drafting recommendations for the best practice guidance.

### *1.7.2 Objectives*

The objective of this document is to present the results of the survey for the 4 topics of Work Package 5:

Topic 1 signal detection: identify the sources for signal detection used at member state level, (statistical) methods for signal detection, procedures for tracking, additional monitoring

Topic 2 signal validation and prioritisation: identify validation procedures and processes, use of EPITT, prioritisation procedures and processes

Topic 3 signal confirmation and assessment: identify confirmation and assessment processes and sources of information relevant for signal assessment

Topic 4 reports of special interest: identify procedures in place for signals of special interest, (e.g. special populations, special reactions, and special products).

The survey started with some questions on organisational aspects, and for all topic procedures, challenges encountered and possible solutions were explored.

### *1.7.3 Challenges*

One of the challenges, identified early in the process concerned the definitions as used in the scientific community, based on the CIOMS VIII and the legal definitions as provided in the implementing EU regulation. On one hand the definitions used in the legislation are aligned with the CIOMS VIII definitions, e.g. as to what constitutes a signal; on the other hand the definitions of validation and confirmation included in the implementing regulation differ from the scientific concepts. Therefore we provided explanatory information as an introduction to the survey to ensure a common understanding based on those definitions provided in the legislation.

The numerous initiatives ongoing in EU (e.g., PROTECT and SMART group) with regards to this topic require careful communication and planning in order to avoid unnecessary duplication of work.

The preference for consistency in procedures and at the same time valuing the heterogeneity of the different systems also could be challenging.

## 2 Methodology

### 2.1 Tool and survey method:

The first draft questions for the web-based survey were developed by the 4 topic leads. Further development took place in co-operation with all WP5 participants, mainly through e-mail and teleconferences and in a face-to-face meeting in March 2014. The structure of the survey was divided into 5 sections, starting with general questions, followed by different aspects of signal management processes (as identified by the 4 topics). The survey also contained an introduction on the context of the survey, providing the definitions as laid down in the legislation to put the questions in context. The five sections are the following:

- general questions

- signal detection (topic 1)
- signal validation and prioritization (topic 2)
- signal confirmation and assessment (topic 3)
- reports of special interest (topic 4)

The final version of the WP5 survey on signal management was comprised of 60 questions.

During the development process many constructive suggestions and comments were made by the participants. It was decided providing an answer to any of the questions should not be compulsory, to allow optimal flexibility and get as many responses to the survey as possible.

Validation of the questionnaire was performed: The draft WP5 survey was first piloted with three MSs in May-June 2014, followed by re-drafting and reviewing. Peer review comments from two external experts from the SCOPE Advisory Board were also considered before finalizing of the survey.

Key explanatory information (see below) was included in the beginning of the survey.

**Key explanatory information provided in the beginning of the questionnaire**

The pharmacovigilance legislation reinforces the public health principle of monitoring medicinal products' benefit risk profile throughout the product lifecycle. Part of this surveillance is acquired through the process of signal management, searching for new adverse drug reactions associated with a drug using different sources of information and appropriate tools.
A signal is defined as information that arises from one or multiple sources, 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 (CIOMS, Geneva 2010).
Many different terms are used to describe the signal management process, and this introduction is to ensure that the terms used in this survey are uniformly understood. This survey uses the terms defined in the GVP module IX on signal management, and the management process includes the following steps (see figure). Some of the often used synonyms are mentioned in the text below.

**Signal detection** is the act of looking for and/or identifying signals using event data from any source (CIOMS, Geneva 2010). Quantitative signal detection is the analysis of disproportional reporting often applied during regular periodic monitoring of large databases of spontaneous reports of ADRs. Qualitative signal detection is considered as a manual assessment of single ICSRs or a cumulative review of ICSR case series. Other synonyms often used include signal identification, signal screening and signal monitoring.

**Signal validation** is the process of reviewing the data supporting a detected signal to verify if the available documentation contains sufficient evidence to demonstrate the existence of a new signal or not. This step mainly includes a review of all "known" data sources like the SmPC, PIL, PSUR, RMP, literature, and other relevant data as well as the data that initially triggered the signal. Synonyms: Evaluation, review and analysis.

**Signal confirmation** is the act of confirming or non-confirming a validated signal to decide the most appropriate way to proceed. If a validated signal is confirmed, it will often result in

a further signal assessment. However, if the validation is strong enough or if there is risk of severe impact on the public health, a confirmed signal can directly result in an outcome without further assessment. Signal verification is considered as synonym for signal confirmation, while refuting and dismissal are considered as synonyms for non-confirmation.

**Signal prioritization** is a key element of the signal management process, in order to find the signals with important public health impact or that may significantly affect the benefit-risk profile of the medicinal product and therefore require urgent attention. Prioritization is not an isolated step but rather an integrated part in every step of the signal management process.

**Signal assessment** is the further review of a confirmed signal. This step includes generating "new" data to further increase the evidence for an outcome. This could be a review of a cumulative analysis from the MAH, further examination of the published literature, clinical trial data or documents, expert consultation, and other relevant sources. Synonyms: Signal evaluation, boosting and strengthening.
The last step is the outcome of the signal management process. An outcome can either be that there is no need for further action at this point or there is a need for a further regulatory action. This step could include an update of the SmPC, monitoring of the signal, a new study and other relevant outcome.

An online tool was used for both dissemination of the survey and the analysis. The tool, as provided by the SCOPE lead offered a web-based tool including relatively easy analysis and graphic presentation of responses given.

The final WP5 survey was distributed on 22nd July 2014 with a deadline for completion by 15 September 2014. The timeline was extended to October 1 in order to have as many responses as possible. By the extended deadline of 1 October, 25 of 31Member States answered the survey. One MS replied that they could not complete the survey since they do not have any signal management system implemented yet.

### 2.2 Data analysis (quantitative and qualitative)

The final survey consisted of different types of questions: open questions (requiring free text), multiple choice questions and questions providing a drop down list.

Response rates (%) for the questions were calculated. For all questions where comments could be provided as free text, the answers were analysed and attempts to group the individual answers were made and the results were summarised. Preliminary analyses were presented at the WP5 face-to-face meeting in Copenhagen in November 2014. Final results were discussed in the Madrid meeting (March 2015) where answers, their possible impact, and topics to be part of the best practice guide were further explored. Topics that would require follow up were also identified.

Questions with a drop down list or other predefined answer options were reviewed individually assessing the information provided. Answers were, when suitable/possible, categorised and grouped. For multiple choice questions, the percentage of answers in each category were calculated, based on the number of countries that provided an answer and not on total number of countries (see *Annex 1* for completion rates across questions). Due to

the nature of the questionnaire the analysis of data is mainly descriptive using adequate descriptive statistics measures and graphic representations.

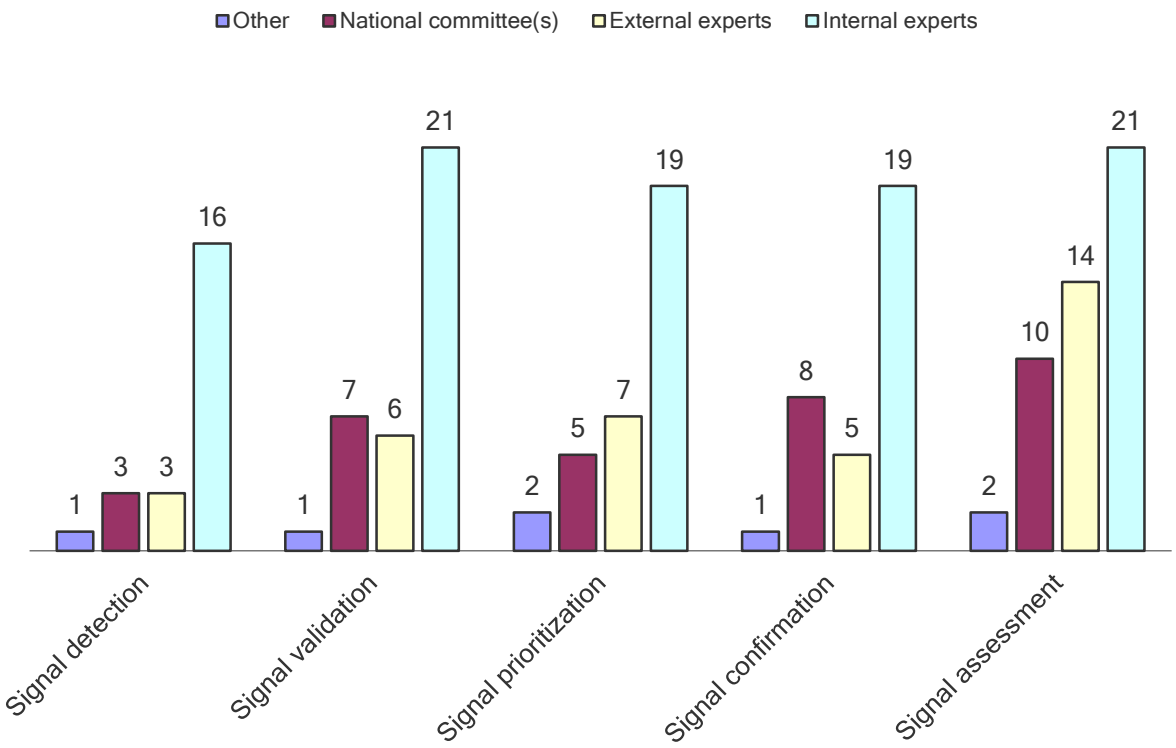
# 3 Findings/Results

## 3.1 General Organization

*Organization*

The majority of MSs indicated that their process of signal detection/signal management is internally organized within the MS. Signal assessment is the step for which external advice is frequently sought (56%) or where national expert committee(s) are consulted (40%). The advice from such committees is not compulsory to follow in all MSs, except one, although the MSs also indicated that the advice is always carefully considered.

**Fig 1**. Expert advice sought during signal management process

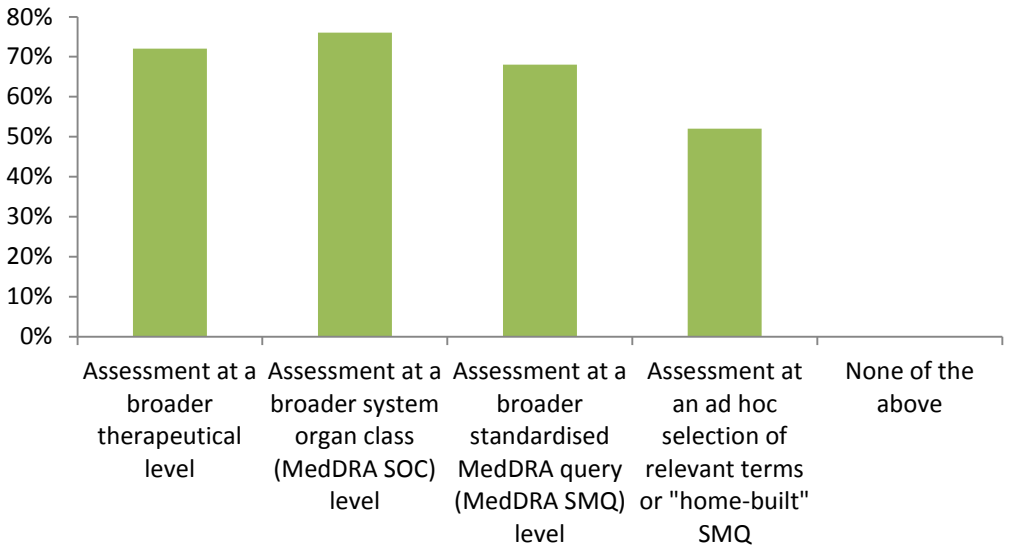



72% of MS indicate that they have a specialized section/group or organization/network which performs signal detection. Answers showed this is mostly internal pharmacovigilance staff, specifically trained, although one MS mentioned 'clinical assessors'. Three MSs mentioned the role of regional/national pharmacovigilance centres in signal detection. In these MSs these are the first recipients of the case reports performing follow up as well. Two countries mentioned external collaborations (with an external expert, or with a national institute for public health). One MS answered that they have different teams for additional monitoring vs ordinary products and another for vaccines vs drugs. Three MSs indicated that different staff is involved in the signal management steps when signals are brought to European level.

*MedDRA*

MS responses show that MedDRA functionalities are widely used, with assessment at SOC level used by 76% and SMQs used by 68%. In addition, half of the MS (52%) use ad hoc selections of terms whereas assessment at broader therapeutic level is used by 72%.

**Fig 2**. What does your signal management procedure include, from the following?

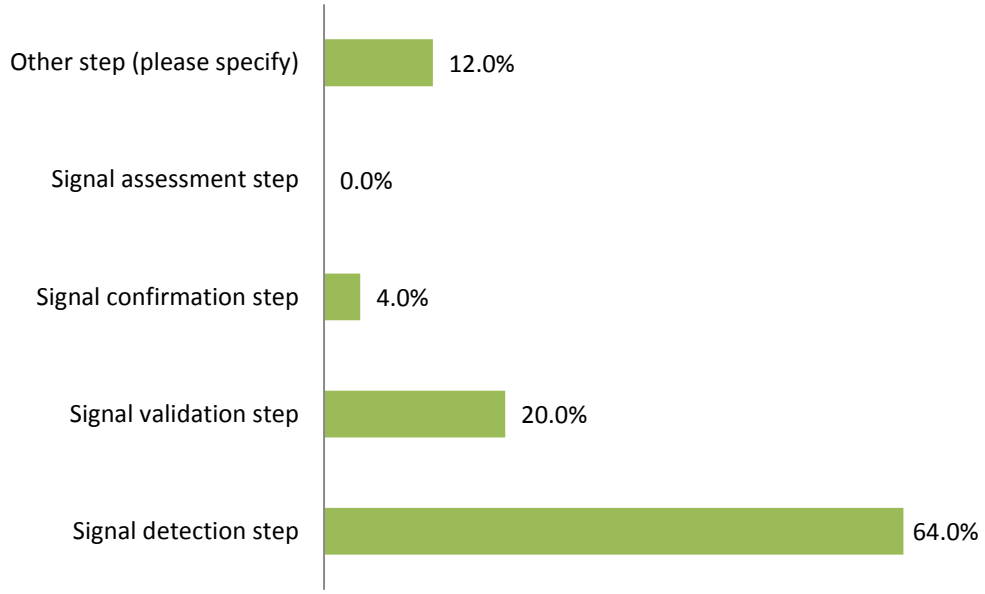



### *Tracking of signals*

The Implementing Regulation requires MSs to have a tracking system of their signal management activities and of the relevant queries and their outcomes, including how signals have been detected, validated, confirmed and assessed. All validation, prioritization, assessment, timelines, decisions, actions, plans, reporting, as well as all other key steps should be recorded and tracked systematically. According to GVP Module IX tracking systems should also include signals, for which the validation process conducted was not suggestive of a new potentially causal association, or a new aspect of a known association.

The majority (64%) of MSs indicated that they record a signal for the first time in their tracking system at the signal detection step, whereas 20% indicated that a signal is recorded for the first time at the signal validation step. One MS noted that for quantitative signal detection method a signal is tracked from the detection step, whereas for qualitative signal detection method, a signal is tracked from the validation step. One MS replied that signals are tracked only via the Minutes of their Drug Safety Committee; one MS did not have a tracking system in place.

**Fig 3**. Starting point of tracking activities for signals




MSs mentioned various tracking tools that are used in signal management and the way the tracking tools are designed varies widely. The same tools are used for tracking both confirmed and non-confirmed signals.

**Table 1.** Tools mentioned to track signals

| Tools |
|---|
| EPITT |
| Microsoft Excel |
| Built within national PV database |
| Dedicated database |
| In house built system |
| Specifically for signals from PV center |
| Vendor IT system (egEmpirica) |
| e-RMR |
| Minutes from meeting(s) |
| Word Document (“validation report form”) |

However for non-confirmed signals some additional approaches were mentioned:
- these are discussed at the Signal Detection meeting for information; or
- these are regularly reviewed by a National Pharmacovigilance Committee; or
- mandatory check of data related to non-confirmed signals during signal detection for the same medicinal product.

Two MSs indicated that they use a built-in tracking system in their national ADR database, whereas also the e-RMR ‘comments column’ and ‘signal status column’ are used by these countries when performing signal detection via that tool. Four MSs answered that they do not yet have a tracking system implemented and some MSs explicitly stated that they will develop a tracking system in the future. When asked what should be recorded as a minimum information into the tracking tool, the answers were quite consistent, with date

and source of information for identification and validation steps, as well as decisions taken perceived as most relevant, see **Table 2**.

**Table 2**. Elements recorded during the tracking process

| What to record in tracking process | % (n=25) |
|---|---|
| Source of information for signal detection | 92% |
| Information taken into account for its validation | 84% |
| Date of signal validation | 80% |
| Expert/committee advice/opinion | 80% |
| Output of the validation process | 80% |
| Date of signal detection | 76% |
| Date of the output | 72,% |
| Date of this opinion (expert/committee advice/opinion) | 60% |

Additional elements for information into the tracking tool were:

- **Drug identification** (active substance, ATC, trademark if relevant)
- **ADR description**
- **Signal status** at the last entry/record:
  - date of status (+start date of signal)
  - number of # reported cases (if applicable)
- **Other signals** associated
- **Signal ID**
  - e.g. year/Regional Centre involved
  - EPITT number (if applicable)
- **If applicable**: PRAC data, agreed Timetable, date of next step

Sixteen MSs answered the question "Please describe any challenges you have encountered in implementing signal tracking and any solutions used to overcome them". Three MSs referred to insufficient staff, little experience and lack of IT tools. Some more specific remarks that have been made by the MS in relation to challenges during signal tracking are presented in Annex 4.

Note: The responses on tracking show that signals are entered into the tracking system(s) early in the process (mostly at detection or validation step).
The tracking systems used within the MSs vary widely. For MSs without their own tracking system, alternative mechanisms are in place to track at least part of the signal management process (e.g. via minutes of meetings). Within a single MS, different tracking systems can be used, depending on the signal detection source, and the next steps in the signal management process. However, the same systems are generally used for tracking confirmed

and non-confirmed signals, whereas some MS have additional processes in place for ensuring that non-confirmed signals are not being lost to follow up. Different views have been expressed on the use of e-RMR for tracking. It was suggested that e-RMR should be developed further for tracking purposes; it was also raised that MSs may wish to incorporate EV data into their own system. The fact that signals can be addressed in different procedures and have different management steps has an impact on the tracking of signals. Procedures for signal tracking can be complex due to national organization of pharmacovigilance (regional/national centres vs centralised organization). Furthermore, signals should be tracked at a national level and also at EU level (via EPITT), with potentially duplication of information and effort. The maturity of signals entered into EPITT varies. The information provided indicated that it is not always clear at what time point in the process a signal should be entered into EPITT.

### 3.2 Signal detection

*Sources of signal*

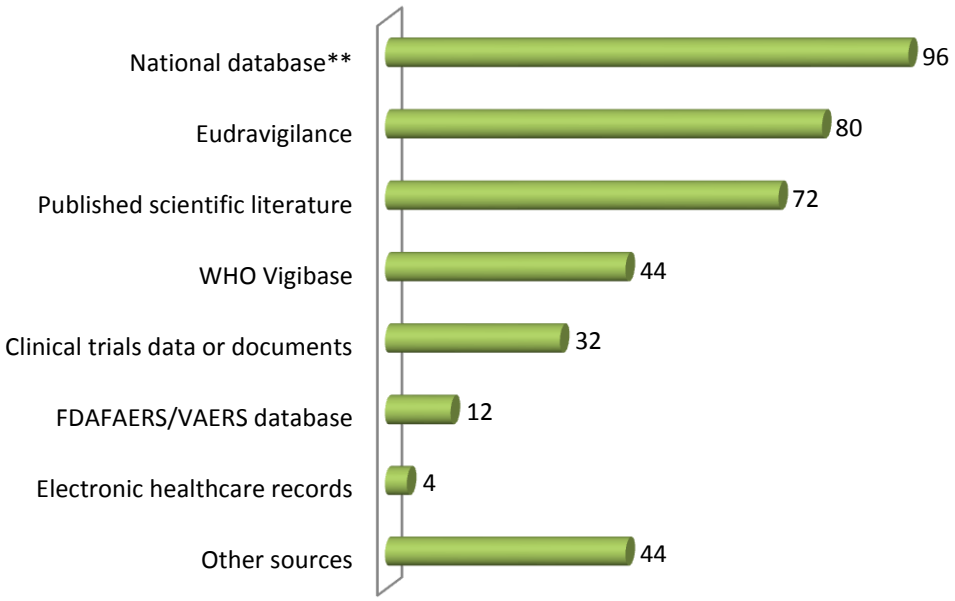
The sources most often screened are national databases (96%), EudraVigilance (80%) and scientific literature (72%) (see Fig 2). Some countries indicated that they also screen other spontaneous report databases: WHO database and FDA database (FAERS) were mentioned in 44% and 12% of the responses respectively.

**Literature:** 72 % countries stated that they search the scientific literature in general. In most MSs the literature search is triggered by a specific safety issue, or it is done for a particular product or screening of selected journals of interest. Two MSs (n=2) mention the use of in house built queries for literature screening and in one member state the screening of the literature takes place at the level of regional centres.
Frequency of reviewing the literature varies from once every month (n=3) to once every 6 months (n=1) and 12% MS mention that they review and search the literature only in case of a potential signal arisen elsewhere. One MS search in the literature for products for which they are lead Member State.
Another MS mentions that "*individual assessors are expected to be aware of literature for specific products*".

Among **other sources**, the following are mentioned:
At national level, in some MS **disease registries** are screened for safety issues. One MS supports disease registries for biological products. From the survey it was also noted that there are two other special programs currently ongoing based on case surveillance approach: one for serious skin reactions and another one for drug-induced liver injury.
Other sources mentioned:

- Signals sent by **MAHs**
- Three countries indicate that they screen media to detect signals
- Two MSs review **queries from healthcare professional or patients** to detect safety issues
- Electronic healthcare records **(EHR)** are screened in one MS
- **Regulatory documents:** PSURs, RMPs, Assessment reports of variations
- **Product information:** SmPC and EPARs
- Assessment reports of national surveys
- Signals identified in other National PV centers and published in PV bulletins or websites

**Fig 4.**Sources of signals screened (%)




** Three countries screen national data by accessing EudraVigilance

Note: Some sources that are mentioned are probably used for further investigating possible signals, signal strengthening and validation. e.g.: SmPC, EPAR, RMP, variation reports. A number of different sources are screened by MSs.

### *Signal detection in EudraVigilance*

According to the implementing regulation, "MSs should continuously monitor the data available in the EudraVigilance database to determine whether there are new risks or whether risks have changed and whether those risks have an impact on the benefit-risk balance". For medicinal products/active substances authorized in more than one EU country, MSs should agree within the CMDh, in collaboration with the PRAC, to appoint a lead

Member State for the monitoring of data in the EudraVigilance database and for validation and confirmation of signals on behalf of the other MSs. EMA prepares monthly or 2-weekly (for products under additional monitoring) data output reports (electronic reaction monitoring reports, e-RMRs) to support monitoring of data by the 'lead Member State'. The 'e-RMR' worksheet' is a formatted Excel file which contains cumulative data on all ICSRs (Individual Case Safety Reports) submitted in EudraVigilance for a given active substance (or combination of active substances) plus the new data corresponding to the period of interest i.e. the latest month or two week period.

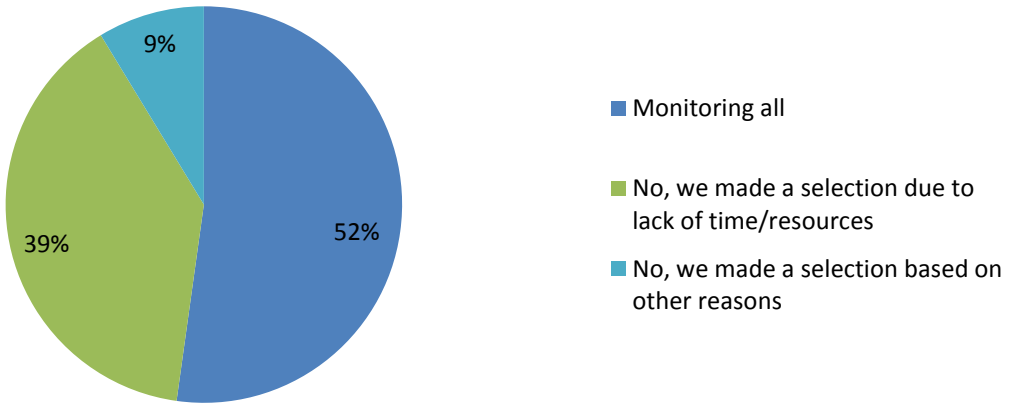
*Number of products monitored*

According to the answers provided the median number of products that a lead MS perform signal detection for is 33 (range: 0-114). Two MSs have volunteered to monitor more than 100 products and three monitor less than 5. One MS declined participation in the work-sharing due to lack of resources and was not assigned any products yet. One MS indicated that the monitoring of the assigned products not started yet. Therefore 92% of countries perform signal detection in EudraVigilance via e-RMR.

More than half of the MSs are monitoring all the assigned products, i.e. all products for which they are lead MS. The remaining 48% indicated that they monitor, only a selection of the products (see Fig.5):

- 39% indicate that they monitor only a selection because of lack of time/resources.
- Two MSs provided information on the way they have selected the products:
    - The trigger to review e-RMRs is represented by evidence found in the national database
    - Assessment of e-RMR is aligned with assessment of PSUR of a particular substance
- 9% made a selection based on other arguments (not further specified)

**Fig 5.** Selection of the products to be monitored as Lead MS



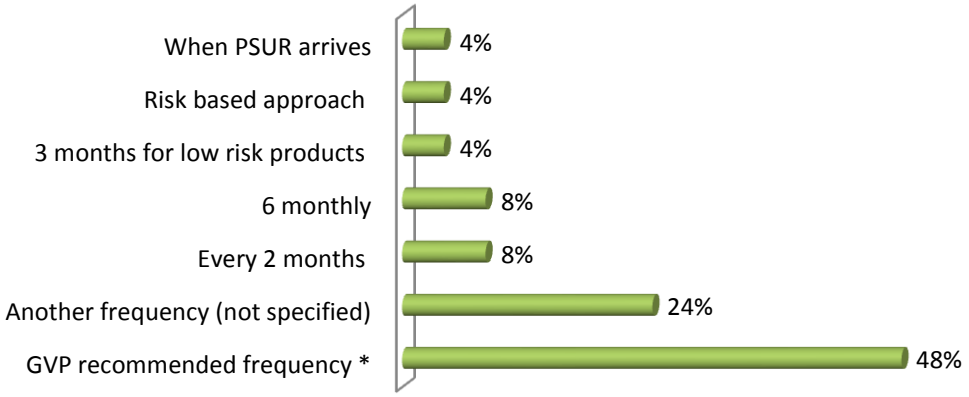

*Frequency of monitoring*

According to the implementing regulation the MSs and the EMA shall ensure the continuous monitoring of the EudraVigilance database with a frequency proportionate to the identified risk, the potential risks and the need for additional information. This is further specified in GVP Module IX, stating that the baseline frequency for reviewing the statistical outputs from

EudraVigilance should be once-monthly. For products subject to additional monitoring the frequency should be every 2 weeks.

Half of the MSs replied that they do not screen e-RMR with the frequency as described in the GVP IX due to lack of time/resources: 52% use a frequency less than stated in the GVP (see Fig. 5). Two respondents indicated that this frequency was decided on a risk based approach.

**Fig. 6** Frequency of signal detection in EudraVigilance (via e-RMR)




*Monthly as a baseline, every 2 weeks for products on additional monitoring list

*Monitoring of the e-RMR*

The e-RMR facilitates the selection of drug-event combinations according to three mutually-exclusive priority levels defined as follows:

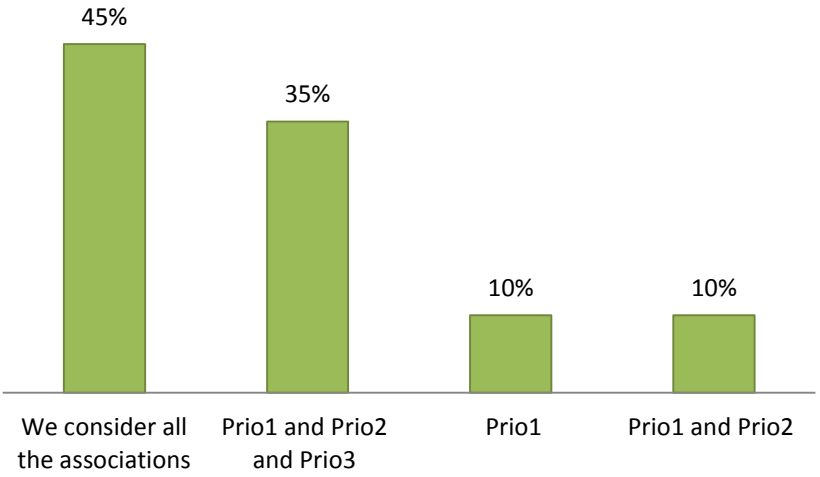
- Priority 1: highest priority. It indicates drug-event combinations received in the reference period classified as DME (Designated Medical Event)
- Priority 2: It indicates drug-event combinations received in the reference period (not included in the priority 1) classified as IME (Important Medical Event) with an SDR (signal of disproportionate reporting);
- Priority 3: It indicates drug-event combinations received in the reference period (not included in the priority 1 and 2) with a fatal outcome, paediatric reports or parent-child reports.

For the remaining drug-event combinations no priority level is assigned. MSs generally use the prioritization system to decide the selection of events to be monitored (see Fig. 6) and, according to this, 55% of the countries indicated that they do not monitor all events.

Additionally, some MSs stated that they monitor additional events:

- Events which were recommended to be monitored by the PRAC or a national committee (n=1 respondent)
- Drug interactions (n=1 respondent)
- Events of special interest for the substance concerned (n=1 respondent)
- Prio 4: that includes PTs with SDR and for which new cases were received (n=1 respondent)

**Fig 7.** Prioritization for monitoring of the events




Overall, MS indicated that they use different approaches to deal with the task of monitoring e-RMRs in view of limited resources:

- Product based prioritization: a selection of products to monitor: either randomly or risk based approach (e.g., based on a trigger from other sources: e-RMRs are reviewed only if a potential signal is identified based on national data).
- Adjust the frequency of monitoring
- Event based prioritization: use the prioritization of the events (either from EMA or supplemented with additional rules) in order to decide which events to monitor in the first place.

Note: Prioritization is used here in the context of the e-RMR and for clarity we will refer to it as risk proportionality. From the analysis of these responses, we observed that a risk-proportionate approach is used, (both product based and/or event based), in view of resources available. Risk proportionality at event level is already built in the e-RMR per product. Many MSs implemented a type of selection, based on product, event and/or frequency.

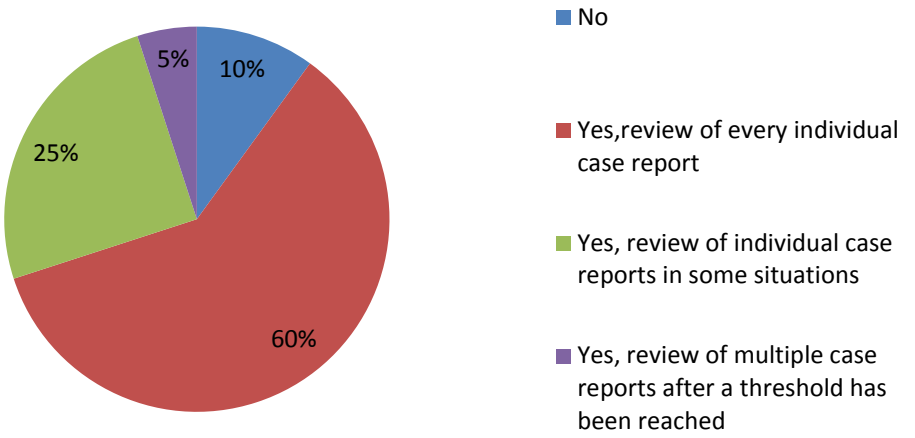
One MS performed a "Retrospective analysis of EV data regarding active substances for which is lead member state to monitor data in EV within work sharing for signal management", the results of which encouraged them to take more products on board for monitoring. Another MS mentioned that they have established a simple flow to help assessors. The flow shows some fundamental issues to consider while screening the e-RMR. (see *Annex 3* for a summary of their findings).

### *Signal detection in national database*

84% of the respondents do screen their national databases for signals. The most used method is the qualitative review (90%), very often on a case by case basis (60%) and applied daily (40%) or weekly (20%).

Q 19: Are you manually reviewing individual cases received (qualitative methods) in order to detect a signal? (n=20)

**Fig 8.** Qualitative review of case reports

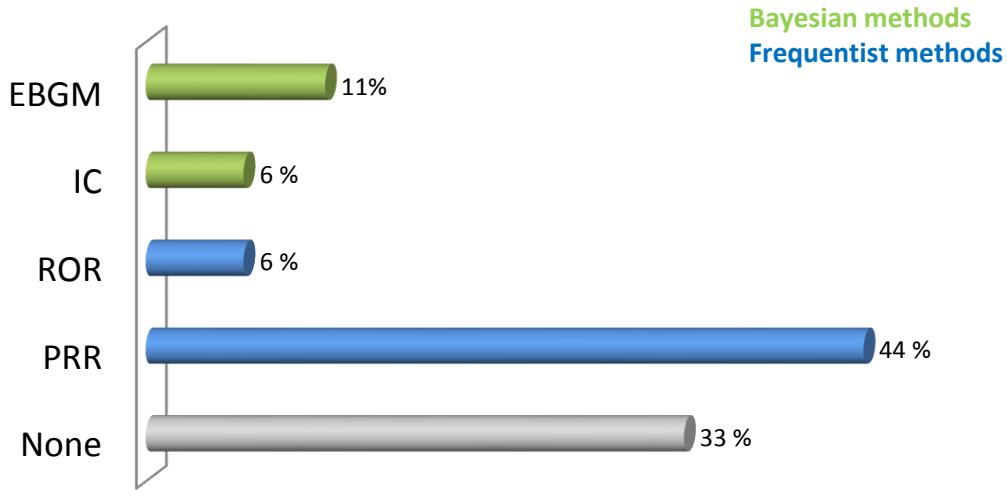



Other additional information on signal detection of national data:

- Signal detection takes place at the level of regional pharmacovigilance centres (n=2)[1]
- *One MS* states that they have weekly signal detection meeting together with medical assessors. The meeting agrees actions and time frames and any validated signals are then entered onto EPITT.

62% of MS screen their national databases with disproportionality methods. PRR is the most used method (44%) and 17% of MS use Bayesian methods (see Fig.9).

**Fig. 9** Disproportionality methods used at MS level (%)




[1] As observed from WP1 survey, in four countries, signal detection takes place at the level of regional centers.

EBGM=Empiric Bayes Geometric Mean, IC=-information component, ROR=reporting odds ratio, PRR=proportional reporting ratio. Two countries use more than one method.

Disproportionality methods are sometimes not applied in view of low number of cases received annually and three MSs mentioned they do not use disproportionality measures but rather they look at absolute number of reports received over time.

The following thresholds are mentioned to be used by MSs:

**Table 3.** Thresholds for disproportionality methods in place at various agencies

| Quantitative Method | Number of countries | Applied Thresholds |
|---|---|---|
| Proportional Reporting Ratio (PRR) | 2 | PRR lower bound 95% c.i. ≥ 1 & n ≥ 3 cases |
| | 1 | PRR lower bound 95% c.i. ≥ 1 |
| | 2 | PRR lower bound 95% c.i. ≥ 2 & n ≥ 3 cases |
| | 2 | PRR lower bound 95% c.i. ≥ 1 & n ≥ 5 cases[2] * |
| | 1 | PRR ≥ 3, PRR lower bound 95% c.i. ≥ 1 & n>2 |
| Reporting Odds Ratio (ROR) | 1 | ROR lower bound 95% c.i. ≥ 1 |
| Information Component (IC) | 1 | IC lower bound 95% confidence interval (c.i.) > 1 |
| Empirical Bayes Geometric Mean (EBGM) | 1 | EB05 ≥ 1.8 & n ≥ 3 & EBGM ≥ 2.5 |
| | 1 | EB05 ≥ 1.8 and n>1 case** |

*3 cases may be used for some drug-PT combinations
**Quantitative method applied only to serious reports (n=1)

In addition, the following is mentioned:

- Lower threshold for: fatal cases (n=2), parent-child and child cases (n=2 countries), as well as for alert terms (predefined important terms) (n=1)
- For non-national cases a stricter threshold is applied such that not only new PTs are assessed (n=1)
- Different thresholds for products under additional monitoring (n=1)

Note: The majority (84%) of MSs screen their national data using different methods. Some MSs do not use disproportionality methods for detection in their national database, and in

[2] 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.

some cases the added value is probably limited (e.g. in small databases) and only use the qualitative review complemented by observed counts of cases.
Retrospective evaluation of the methods and continuous adjustment of thresholds and other implementation decisions based on real time are being used in some of the MSs.

40% of the countries use specific software for signal detection, e.g.: Empirica (n=2, 8%), Vigilyze/VigiMine (n=1, 4%) and house built systems (n=7, 28%).

- **Empirica** is a commercial software developed by Oracle. It uses Bayesian methods and thresholds are reviewed regularly and can be adjusted following validation studies.
- **VigiMine** provides statistical data regarding the case reports in VigiBase. It is currently available to the members of the WHO Programme for International Drug Monitoring and Uppsala Monitoring Centre staff. It allows filtering of the results on a number of statistical criteria, as well as stratification by age, sex, country, and year of reporting.
- **Vigisegn** (one specific house built system from one MS) is based on PRR method and allows subgroup analysis. No other details are given.
- One MS is in course of implementing a specific software which will consist of a Bayesian method (a variant of GPS method). The program is publicly available at: (see Annex 4 for details).

Three other countries mention they do quantitative detection within EudraVigilance only.

Three countries validated the quantitative methods used in their national databases. One of them is performing regular validation to adjust the thresholds and based on a validation study they decided to change from PRR to EBGM method. One MS intend to perform the validation in the near future.

The frequency of signal detection in national databases with quantitative methods differs between MS as seen from Table 4, the most used frequency being every 6 months.

**Table 4.** Frequency of signal detection

| **Quantitative methods** | | | | **Qualitative methods** | | | |
|---|---|---|---|---|---|---|---|
| At each incoming case | | 5% | | **Daily** | | **40%** | |
| **3.2.1** | Weekly | 3.2.2 | 11% | 3.2.3 | At each incoming case | 3.2.4 | 10% |
| 3.2.5 | Every two weeks | 3.2.6 | 5% | 3.2.7 | Weekly | 3.2.8 | 20% |
| 3.2.9 | Monthly | 3.2.10 | 16% | 3.2.11 | Monthly | 3.2.12 | 15% |
| **3.2.13** | **Every 6 months** | **3.2.14** | **21%** | 3.2.15 | "As needed" basis | 3.2.16 | 5% |
| 3.2.17 | "As needed" basis | 3.2.18 | 11% | | | | |

Q25: Does your Member state follow different signal detection methods for drugs under additional monitoring compared to other drugs?
With regards to the drugs from additional monitoring list, 15% of respondents stated they follow different signal detection methods compared to other drugs:

- Different thresholds for products under additional monitoring: a broader range of drug-event combination is assessed if the product is under additional monitoring compared to normal products (n=1)
- Looking for new reports associated with all the reactions on medicines under additional monitoring (n=1)
- Subject to prioritization only (n=1).

### *Challenges and areas of improvement for signal detection*

Some of the remarks that have been made by MSs in relation to challenges are mentioned in Annex 4 and summarized and classified in the table below:

| Challenges | N | % |
|---|---|---|
| Lack of resources/experience | | |
| Too many potential signals/false positives | 5 | 28% |
| Lack of expertise/training for SD | 4 | 22% |
| Lack of resources | 7 | 39% |
| Lack of adequate software | 2 | 11% |
| Quality of the ICSR data | | |
| Missing data in ADRs | 2 | 11% |
| Underreporting | 1 | 6% |
| Duplicates | 1 | 6% |
| Wrong coding | 1 | 6% |
| Data formatting | 2 | 11% |
| Other issues | | |
| Alignment of various national SmPCs | 1 | 6% |
| Masking effect | 1 | 6% |
| Media influence | 1 | 6% |
| Checking the SmPC is time consuming | 2 | 11% |

They also offered suggestions for improvement, as:

- The importance of regional centres which have a closer relationship with healthcare professionals and this might facilitate communication and reporting.
- Reporting rate values (number of reports in relation to drug use) could be useful to put the incidence of the reaction in the context.
- "Intra-class" PRR might be an useful tool which might improve detection.
- More risk proportionality would be helpful: Looking at DME or new substances should be a priority. Other prioritization tools were mentioned:
    - Impact Analysis – a prioritization tool which takes into consideration the strength of the data and the seriousness of the ADR help focusing on the most important events[3]

[3] Emma Heeley, Patrick Waller and Jane Moseley. Testing and Implementing Signal Impact Analysis in a Regulatory Setting Results of a Pilot Study Drug Safety 2005; 28 (10): 901-906

- Regulatory Pharmacovigilance Prioritisation System (RPPS) - Statistical tool used to assign the signal a timeframe, takes into consideration public health implications and agency obligations[4]

- Consultation with the National PhV Committee and ad-hoc expert groups is considered helpful in the process of decision making.
- When/if number of ADR cases in relation to (experienced) staff allows it, manual signal detection should always be used alongside quantitative methods.
- Staff should include individuals with clinical experience.

One MS started a project to build a database of the adverse reactions described in the national SmPCs in order to make the process of checking the information in the SmPC faster.

### 3.3 Signal validation and prioritization

*Signal validation*
*General procedure and sources of information*

Q39: *Once the signal has been detected by your national pharmacovigilance team, have you implemented a formal documented process in order to validate it? (Y/N)*

Nearly 80% of MS responded affirmative. The five countries that answered no have provided the following comments:

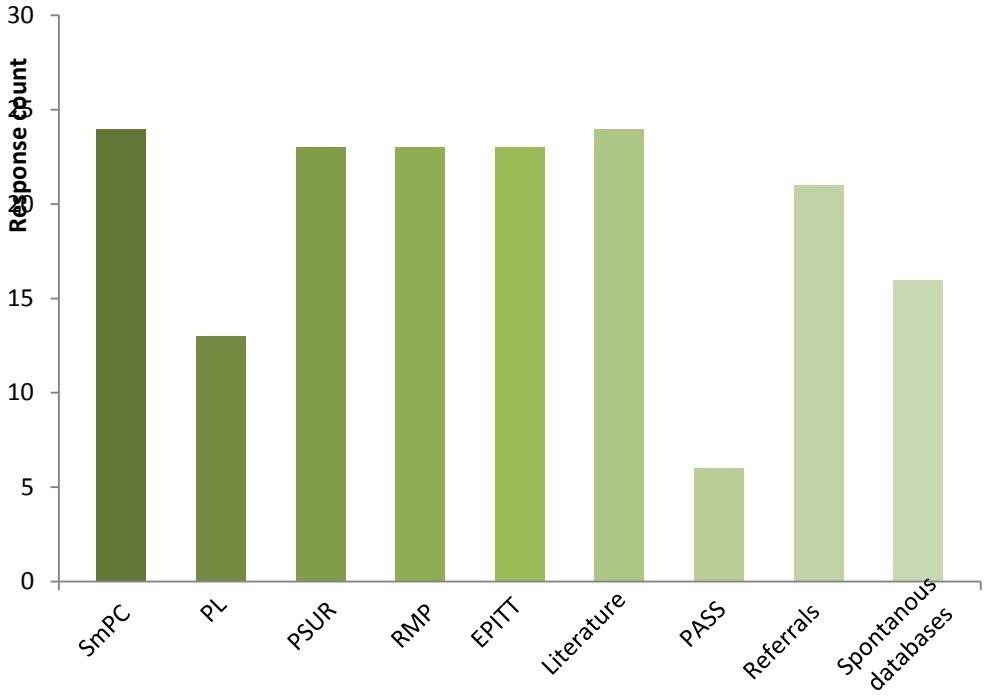
- Not yet - in process of authorization of SOP
- Still no procedure in place but follow the recommendations in the GVP module IX Signal management
- Signal detection meetings, Word document
- Implementation of a quality system for signal detection is in progress, it will likely to be finalized in Q1 2015.
- A system is being set up.

Q 40: *Please indicate which sources of information are used for signal validation*

For sources of information for signal validation, all respondents indicated that their MSs used Summary of Product Characteristics (SmPC) and scientific literature, and most of them (n=23) use Periodic Safety Update Reports (PSURs), Risk Management Plans (RMPs), or EPITT. Many countries also used EMA website of referrals, other spontaneous databases, and patient leaflets. Some respondents (n=6) responded that they used a PASS registry such as through ENCePP.

[4]Seabroke S, Wise L, Waller P. Development of a novel regulatory pharmacovigilance prioritisation system: an evaluation of its performance at the UK Medicines and Healthcare products Regulatory Agency. Drug Saf. 2013Oct; 36(10): 1025-32

**Fig 10.** Sources of information used for validation phase




Thirteen countries specify other sources of information:

- Other Agencies website (sometimes PI of the drug/class) (n=3 respondent)
- National databases (i.e. drug interactions, birth defect registries, database on signals reported monthly by the national safety centres) (n=3 respondents)
- WHO database (n=3 respondents)
- FDA list of signals (n=3 respondents)
- Micromedex (n=2 respondents)
- Drug usage data (n=1 respondent)
- Consultation with external experts if needed (n=1 respondent)
- EudraVigilance (n=1 respondent)
- Assessment reports (n=1 respondent)

Six (26%) countries specified other sources of information that they would like to use for signal validation and one respondent would like advice in this regard. The responses given are summarized below:

- Quarterly WHO Signal reports (n=2 respondents)
- Electronic Health Records (n=2 respondents)
- Large-linked databases like EU-ADR or GPRD (n=1 respondent)

- Drug utilisation data (n=1 respondent)

### *Signals not entered in EPITT*

*Q42: Do you have validated signals which were not entered in European Pharmacovigilance Issues Tracking Tool (EPITT)?(Y/N)*

Nine (37.5%) countries have validated signals finally not entered into EPITT. The following provides a summary of comments received:

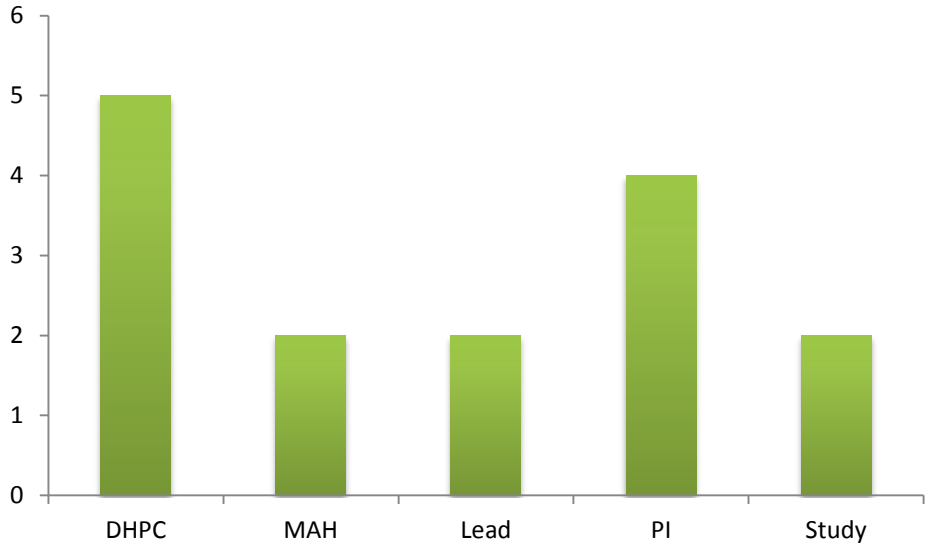
- Local issues, which sometimes are directly discussed with the MAH following another procedures- 3 MS
- Consideration to consult the lead MS previously, who should later confirm the signal- 2 MS (one of the MSs express concerns about the existence of two parallel procedures with two levels in EPITT)
- Related to medicinal products not authorized in other EU countries or that correspond to illegal/borderline products- 1 MS
- Purely national products- 1 MS
- Under monitoring in the PSUR- 1 MS
- Not a relevant issue: question of harmonization of product information, only monitoring needed (signal validated but not confirmed as to enter it in EPITT)- 1 MS

Notes: Also national issues might need communication at an EU level in order to prevent possible duplication of work and to inform other MSs of issues that might also be relevant for them. At the moment a NUI request (or Rapid Alert if this is the case) seems to be the only tool available to communicate this within the EU network without having to add it to the PRAC agenda.
Some other countries raised the point that legislation is not clear enough on defining different steps, in this case differences between signal validation/confirmation and assessment.

*Q43: If you have validated signals that are not entered in EPITT, then please explain what outcomes are decided at national level (e.g. communication with health care professionals, monitoring, start study, other)(free text)*

Usually they end up in a DHPC or other ways to inform prescribers, requesting the MAH for more information, or informing the lead MS just in case action at EU level is required. However, sometimes an update of the PI is deemed necessary or even a study is performed.

**Fig 11.** Outcome of validated signals not entered in EPITT




DHPC=Direct Healthcare Professional Communication; MAH=action requested from Marketing authorisation holder; PI=update of product information; Study=a specific PASS was requested to investigate the issue.

As part of follow up, the WP5 considered that it would be interesting to have an estimate of how many signals which are validated are not brought to PRAC, see *Annex 3* for more details.

### *Safety Issues which do not meet GVP definition*

*Q44: Do you have safety issues identified within your signal management process that do not meet the GVP definition of a signal? (Y/N)*

Nine (37.5%) countries have identified safety issues that do not meet the GVP definition of a signal:

- Issues occurred with borderline products: illegal or food supplements (2 countries)
- Quality defects or device failures (2 countries),
- SmPC harmonization issues (i.e. not considered new information but may not be adequately reflected in national SmPC -3 countries),
- Further additional monitoring in the PSUR is considered (1 MS)
- Issues mainly related to local (national) prescribing practices (1 MS).

One MS raises the point that it is not clear in GVP what to do in cases where there is non harmonization of product information compared to literature or other countries. Another situation not clear in GVP is when the MAH has been asked to present a cumulative review but they submit directly a variation, or both things, which were accepted by EMA.

### *Additional tools/methods*

*Q45: Please describe any additional tools or methods that you use for signal validation and you think are helpful to share (free text)*

Key messages:

- One MS specifies that the validation step is undertaken by a Committee, before entering the validated signal in EPITT (or to other Offices or Departments in case of illegal/borderline products)
- Other MS comment that the validation step benefits from Internal and external expert meetings, even they have quarterly meetings with Health Care Professionals (see Annex 3 for more details)
- One MS indicates it has been resulted very useful a database for reference of what is already included in the SmPC
- In another MS, when a (very) rare event is detected in relation to a certain drug in EV they sometimes do the top ten list of: "For which drugs has this been most often reported", or to seek if it is reported for just this drug or for a class of drugs or a disease/ indication related event
- In other countries it is possible and useful to perform a Drug Utilization Study in their prescription database (more details are gathered by scope WP8 )
- Another MS mentioned the existence of a database for reference of what is already included in the SmPC of the products. At follow up the concerned MS confirmed that the database is not an automated tool, rather a repository of the approved version of PI as pdf versions however the utility of an automated database similar to the one developed by PROTECT for centralized products was acknowledged.

### *Challenges*

*Q46: Please describe which problems have you encountered or experienced during this process. Do you have any solutions? (free text)*

One of the most recurrent problems is related with the availability of the documents. One MS launches the idea of having all sources of documentation needed for signal validation available in an accessible tool, at least EMA documents.

The signals most difficult to handle pointed out by the MSs are non-serious ones, signals concerning several products with different lead MSs, when the cases in EV has less quality information, or in other languages, or when there are duplicate cases (sometimes sent by MAHs as well other reports that are not truly ICSRs).

Some countries recognize that some safety issues already known have not been fully implemented in their SmPCs, making false suspicions of a signal. In this regard, one MS reminds that the signal detection process should not constitute a SmPC harmonisation.

Finally, two additional difficulties are pointed out: the lack of resources and expertise of assessors and the difficult interpretation and implementation of GVP.

### *Signal prioritization*

### *General procedure*

*Q47: Have you implemented a formal process in order to prioritise a signal ?(Y/N)*

Out of the 22 countries that responded to this question, 9 (41%) respondents stated that they have implemented a formal process for signal prioritization. Most countries that have

developed a formal process for signal prioritization usually have a SOP. In one case the criteria have been published[5].
One MS states that the priority is sometimes given in the e-RMR.

However, 13 countries have not implemented a formal process to prioritize signals, although it could be implied/present informally in every step of signal management or in process of considering its development. Some countries answered that they follow GVP, that the prioritization is given by PRAC, or that this is done on case by case basis.Consequently, although in some cases is not a formal step, a total of 20 countries perform a kind of prioritization as it can be seen from the answers to Q48.

Q48: At which step during signal management do you prioritise?

| Answer Options | Response Percent | Response Count |
|---|---|---|
| An ongoing prioritisation after each step in the signal management procedure | 52 % | 12 |
| Prioritisation only after signal detection | 13 % | 3 |
| Prioritisation only after signal validation | 17 % | 4 |
| Prioritisation only after signal assessment | 4 % | 1 |
| We do not prioritise the detected signals | 13 % | 3 |

### *Criteria consideration*

*Q49: To determine Public Health Impact which specific criteria are considered?Please indicate the level of importance within your MS processes for each criteria*

*Q50: To determine Public Perception of the risk, which specific criteria are considered? Please indicate the level of importance within your MS processes for each criteria*

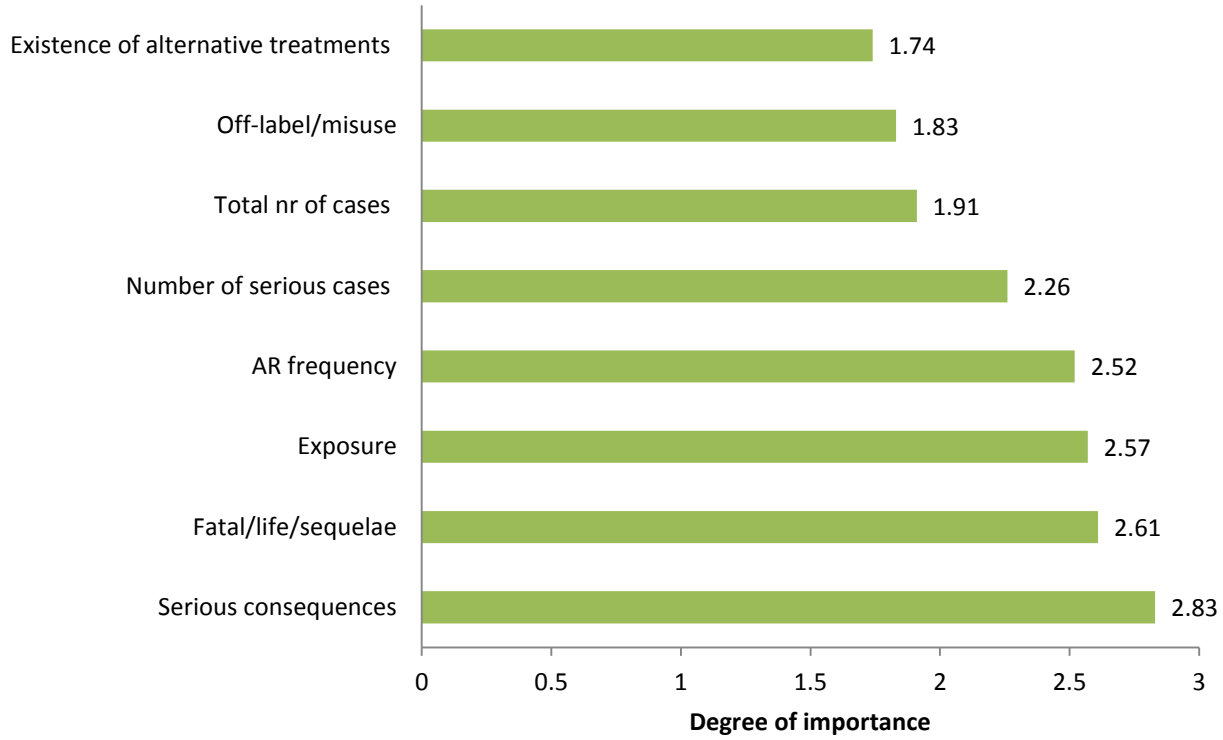
Criteria related to **Public Health Impact:**

The MS were asked to choose and rate between the following criteria:

- High exposure of patients or prevalence of use
- Frequency of ADR in treated population
- If the ADR has serious consequences
- Total number of fatal, life-threatening or permanent sequelae cases
- Total number of serious cases
- Total number of cases
- The issue is associated with off-label or misuse
- Availability of alternative treatments

[5]Seabroke S, Wise L, Waller P. Development of a novel regulatory pharmacovigilance prioritisation system: an evaluation of its performance at the UK Medicines and Healthcare products Regulatory Agency. Drug Saf. 2013Oct;36(10):1025-32

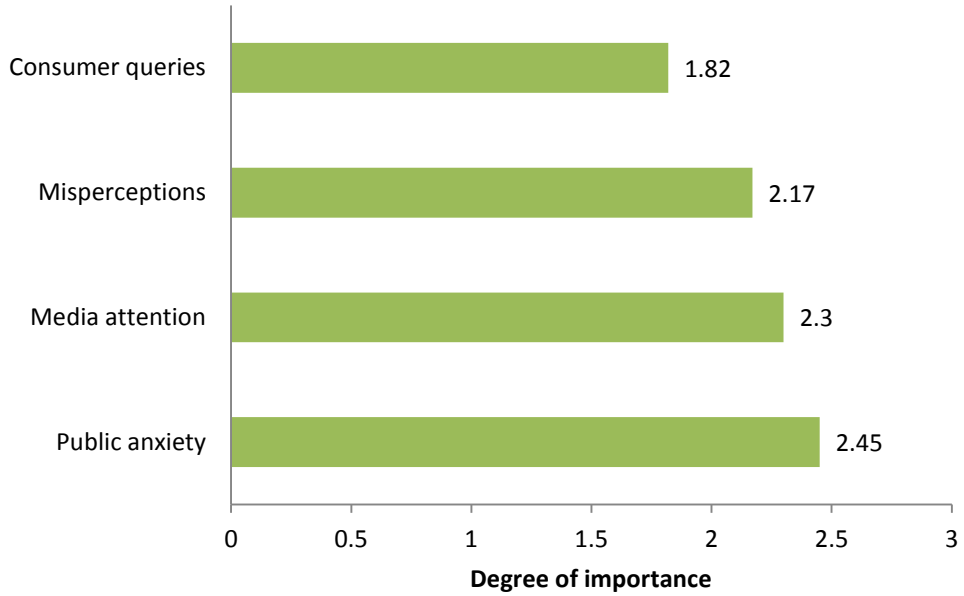
**Fig 12.** Public Health impact criteria and degree of importance (as measured by MSs)




The rating method (range: 1 to 3) for the presented criteria was: the "Not considered" scores 0, "Not important" scores 1, "Important" scores 2, and "Very important" scores 3 points.. The mean between the total score and the number of answers obtained is the final rate.

The most important criteria considered is if the ADR has serious consequences (rating 2.83), followed by the total number of fatal, life-threatening or permanent sequelae cases (2.61) and high exposure of patients or prevalence of use (2.57). Eleven countries have provided additional comments to this question. Out of them, nine indicate that when any criteria with total number of cases is considered, they also took into consideration the reporting rate, to provide context for the data. The remaining two countries provide other important criteria to consider for Public Health Impact: preventability, reversibility, embryotoxicity/congenital anomalies, pediatric and geriatric reports.

**Fig. 13** Public perception of the risk criteria and degree of importance (as measured by MSs)




The rating method (range 1 to 3) for the presented criteria was: the "Not considered" scores 0, "Not important" scores 1, "Important" scores 2, and "Very important" scores 3 points. The mean between the total score and the number of answers obtained is the final rate

Within the public perception of risk, the most important criteria considered by the MSs is the presence of factors likely to cause public anxiety (2.5), followed by recent media attention (2.3), public misperceptions (2.1), and if there are queries from consumers (1.8).One additional comment was received stating that these criteria should be considered more in relation to how best to communicate (which is the focus of WP8 Risk Communication package).

### *Relevant challenges and experiences to share*

15 MSs (62.5%) offer additional information to share. Most valuable options are the following:

- One MS is testing a new method by scoring the signal strength (value of the cases + disproportionality in databases + literature) and the health impact (seriousness + type of drug + type and no of patients affected) (see Annex 3 for more information regarding this tool).

- One MS states that validation and assessment are very similar for them. In this case, many other terms are screened, as well as the strength of the signal (contributing factors, concomitant medications, medical background, time to onset, de-challenge and re-challenge, biological plausibility as evidence in studies, PSUR and RMP information) before discussing the signal in an internal meeting where the decision to enter it in EPITT is taken. Very similarly, another MS look into the type and strength of evidence (spontaneous only, or literature(studies), biological plausibility, the nature of the ADR (seriousness, reversibility, preventability), the substance

(target population, indication, conditions of use), current or potential risk minimization measures, broader impact on public health)

- Another MS states the importance of drug utilization data
- One MS more indicates that they look into seriousness and the impact in public health, despite of not having much experience yet
- One MS raises an additional point recognizing that as different standards exist for different drug classes, they also sadly sometimes take into account what is likely going to be accepted as a signal politically in-house and within the PRAC
- One additional MS shares the idea of the fast track procedure for urgent signals, involving other relevant departments and the drug safety committee at an early stage in the signal management process

The following challenges are mentioned to have been encountered by MSs:

- Harmonization is needed as this is not an objective criteria, and we should be consistent among different countries, therefore sometimes it could be useful to have more discussion between MSs before the signal is presented at the PRAC.
- The level of evidence needed for old products and vaccines is difficult to establish.
- Now that MAHs should start to send signals to all MSs as well as EMA, duplication of work is envisaged.
- Drug utilization data in other EU countries would be helpful.
- Lack of experience.

### 3.4 Signal confirmation and assessment

#### *Signal confirmation*

Signal confirmation is the act of confirming or non-confirming a validated signal to decide the most appropriate way to proceed. If a validated signal is confirmed, it will often result in a further signal assessment. However, if the validation is strong enough or if there is risk of severe impact on the public health, a confirmed signal can directly results in an outcome without further assessment.

#### *Confirming signals detected at national level*

*Q53: Describe how you confirm a signal after validation and how you continue to assessment or outcome for a signal detected at national level (free text)*

*Key messages:*

- 5 MSs (20%) had no experience with confirming signals, and 3 (12%)of them stated they had no existing procedure in place for this.
- 17 MSs (68%) have described a process for confirming signals that is similar to the GVP IX outline, and it appears that these MSs recognise the difference between validation and assessment.
- 10 MSs (40%) discuss signals with teams of experts e.g. in national safety committees, safety boards, signal management teams or other expert groups.
- 3 MSs (12%) consider a validated signal the same as a confirmed signal.

- 2 MSs (8%) involve the MAH(s) in this stage of the signal management process. They describe how they (if applicable) send questions to MAH and ask for more data as part of the signal validation.

### *Confirming validated signals received from EMA or other member states*

*Q54: Describe your procedure for confirming validated signals received from EMA or other Member States (free text)*

*Key messages:*

- 10 MSs (40%) follow more or less the same procedure for confirming signal detected at national level and validated signals received from EMA or other Member States.
- 2MSs (8%) have different procedures.
- 3 MSs (12%) mention specifically involvement of PRAC members as part of confirming validated signals received from EMA or other Member States.
- 6 MSs (24%) state they have no experience in this or never received a validated signal from EMA or other Member States.

## *Signal assessment*

Signal assessment is the further review of a confirmed signal. This step includes generating "new" data to further increase the evidence for an outcome. This could be a review of a cumulative analysis from the MAH, further examination of the published literature, clinical trial data or documents, expert consultation, and other relevant sources.

### *Sources of information used to assess a confirmed signal*

*Q55: Which sources of information do you use in order to assess a confirmed signal?*

23 MSs (92%) provided response, 2 MS (8%) skipped this question, and 1 MS (4%) had no experience with signal assessment.

The GVP outlines different sources of information that could be used during signal assessment, and 8 main categories were presented in this question.

*Key messages:*

- 22 MSs (88%) use published literature during the assessment
- 20 MSs (80%) indicate that expert consultation and data provided by MAH are used in the assessment.
- Clinical trial data/documents and the product application dossier are also used by many MSs. Half of the countries have access to claims, healthcare insurance databases, drug utilisation registries or other health registries and use these as part of the assessment.
- In addition to the predefined options, 4 MSs (16%) also mention EudraVigilance, EPAR, SmPC and Vigilyze as other sources of information, although these sources relate to signal validation according to the GVP Module IX.

| Answer Choices | Responses | Respondent |
|---|---|---|
| Published literature | 96% | 22 |
| Clinical trial data or documents | 65% | 15 |

| | | |
|---|---|---|
| Product application dossier | 57% | 13 |
| Expert consultation | 87% | 20 |
| Data provided by MAH | 87% | 20 |
| Claims databases/Healthcare insurance db. | 17% | 4 |
| Drug utilization registries | 43% | 10 |
| Other health registries | 35% | 8 |
| Other (please specify) | 35% | 8 |

The importance of choosing the information that better fits the purpose is illustrated by the quotes from 3 MSs (see Annex 4).

### *Additional activities to further increase the evidence*

*Q56: Are there any additional activities you apply to further increase the evidence concerning the signal? (free text)*

*Key message:*

- 8 MSs (32%) have previously started a project or performed a registry study to analyse a signal more thoroughly, and 7 MSs (28%) do both.

| Answer Choices | Responses | Respondents |
|---|---|---|
| Registry study | **64%** | 7 |
| Clinical study | **18%** | 2 |
| Start a project to analyze the signal more thoroughly | **64%** | 7 |
| Other activities (please specify) | **55%** | 6 |

### *Assessment procedures*

*Q57: Does your assessment procedure for validated signals received from EMA or other MSs differ from the assessment procedure of your own (national) signals? (Yes/No)*

| Answer Choices | Responses | Respondent |
|---|---|---|
| Yes | **19%** | 4 |
| No | **81%** | 17 |

*Key message:*

- The majority of MSs have the same assessment procedure for validated signals received from EMA/other MSs and signals detected at national level.

### *Skipping signal assessment*

*Q58: Have you had any confirmed signals, which were proceeded directly to the step "recommendation for action" without further assessment step? (Yes/No)*

| Answer Choices | Responses | Respondent |
|---|---|---|
| Yes | **29%** | 6 |
| No | **72%** | 15 |

*Key message:*

- Only 6 MSs (24%) have at least once skipped the assessment step, because either the evidence after signal validation was strong enough, or because it was an urgent signal.

### *Additional tools or methods for signal assessment*

Three MSs (12%) benefit from bringing different people and assessors together to discuss signals in dedicated meetings. A fourthMSs gave details on how they use national health registries in the signal assessment. Relevant quotes from different MSs can be found in Annex 4.

### *Relevant problems or experiences to share*

*Q60: Please describe which problems have you encountered or experienced during signal assessment. Do you have any solutions? (free text)*

*Key messages:*

- Compiling all relevant data can be difficult. Sometimes MAH does not deliver what is expected/asked for.
- Exposure data is not always available.
- Availability of quick-to-use epidemiological data sources.
- Methodology issues like dealing with masking, inability to stratify sufficiently by sub-population and indication, dealing with confounding by indication and drug-drug interactions.
- Mixing up the signal validation and assessment steps and uncertainty how to place the right amount of work in the different steps.
- The under-usage of EPITT causes unnecessary doubling of signal management efforts throughout Europe. Lowering the threshold for entering signals in EPITT.
- Lack of resources

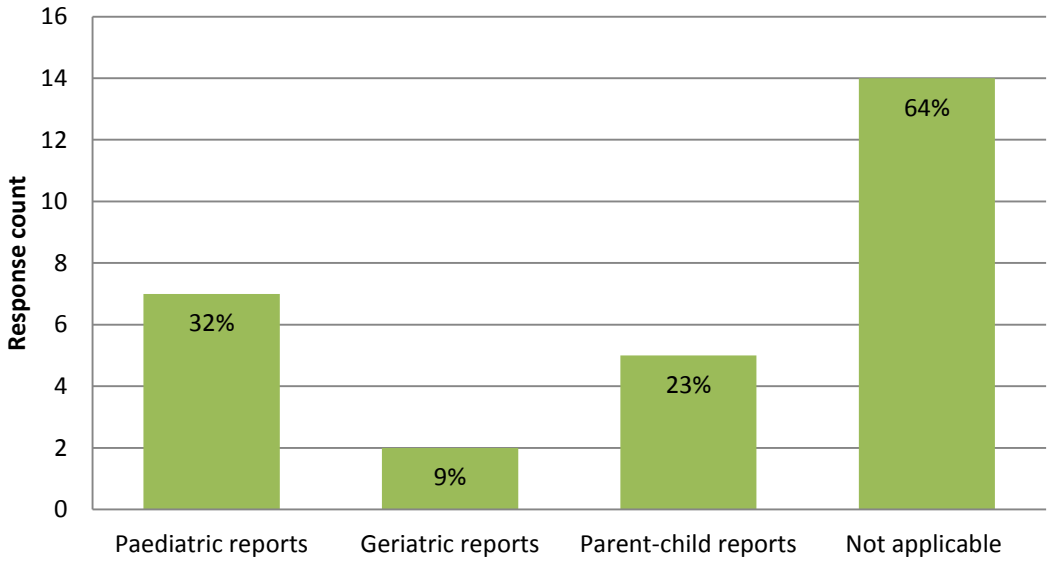
## 3.5 Reports of special interest (RSI)

### *The existence of additional strategies and processes for signal detection in reports of special interest*

Questions Q28 to Q31 investigated for which categories of reports of special interest do MS have additional strategies in place. The RSI were classified in: population based approaches, product/substance based approaches, reaction-based approaches and approaches based on other RSI.

For population-based approaches, two thirds of countries do not have any additional strategies in place for this category. The most common strategy concerned paediatric reports for which one third of countries have a special strategy, see **Fig 14**.

**Fig 14**. Population based approaches

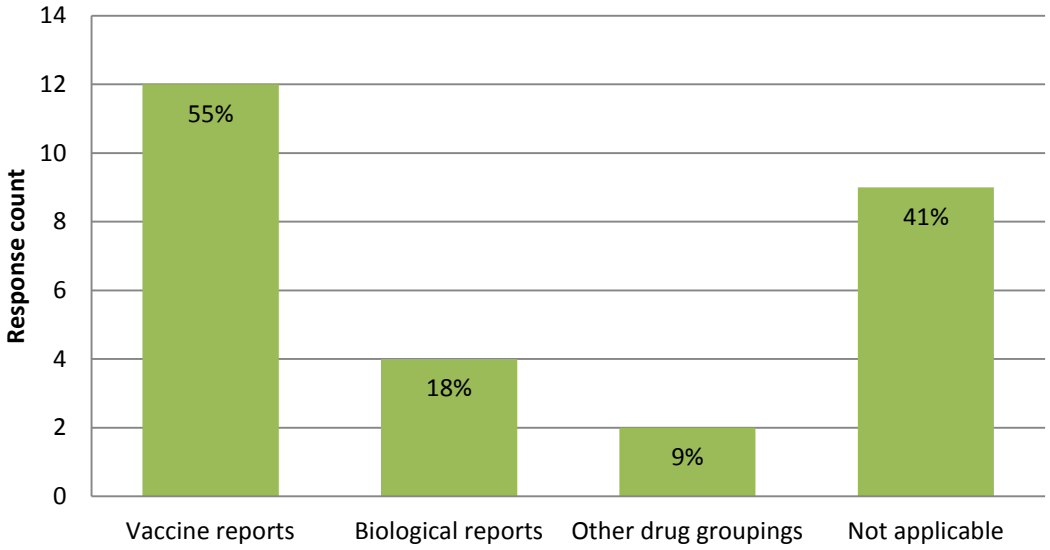



MSs that have additional strategies in place for paediatric reports were more likely to also have strategies in place for other population-based reports. The correlation between different strategies in different countries is presented in the table below.

| Q29: Correlation between positive options selected | | | |
|---|---|---|---|
| Respondent A | Paediatric reports | | |
| Respondent B | Paediatric reports | Geriatrics reports | Parent-child reports |
| Respondent C | Paediatric reports | | Parent-child reports |
| Respondent D | Paediatric reports | | Parent-child reports |
| Respondent E | Paediatric reports | Geriatrics reports | |
| Respondent F | Paediatric reports | | |
| Respondent G | Paediatric reports | | Parent-child reports |
| Respondent H | | | Parent-child reports |

For product/substance-based approaches, most respondents indicated that their MS had additional strategies in place for vaccines. Out of the four questions (Q29-Q32), this was the only question for which Not Applicable was *not* the most common response, see **Fig 15**.

**Fig 15** Product/substance based approaches




When the data for vaccine reports is compared with the other answers from the same questions, some patterns emerge, see below:

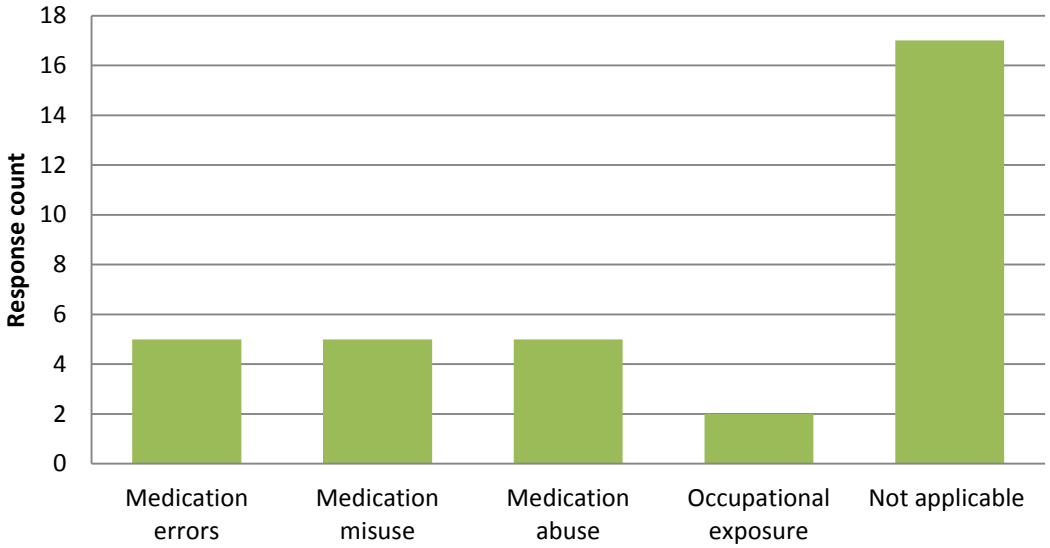
| Q30: Correlation between positive options selected | | | |
|---|---|---|---|
| Respondent A | Biological reports | | Vaccine reports |
| Respondent B | Biological reports | | Vaccine reports |
| Respondent C | Biological reports | | Vaccine reports |
| Respondent D | Biological reports | | |
| Respondent E | | Other drugs | Vaccine reports |
| Respondent F | | Other drugs | Vaccine reports |

All seven respondents who had selected paediatric reports also selected vaccine reports, suggesting that almost one third of MSs have additional strategies in place for both paediatric population and vaccines. These results suggest that having additional strategies in place for signal detection in vaccine reports is a priority for most MSs.

For reaction-based approaches, half of the 22 respondents indicated that their MS had additional strategies in place for designated medical events and/or important medical events. Designated medical events was selected ten times, while important medical events was selected seven times. Six respondents indicated that their MS had additional strategies in place for both designated and important medical events.

Other groups of interest approaches showed the fewest signs of existing additional strategies for signal detection. Almost 80% of respondents selected Not Applicable for this question, the highest proportion for any of the four questions. (This may be due to the fact that this question categorised miscellaneous options together). Occupational exposure was the least selected option, with only two respondents choosing it.

**Fig 16.** Approaches based on other groups of interest




A total of five respondents out of the 22 who answered the question indicated that their MS had additional strategies in place for signal detection in these other groups of interest. Of the five who did, two indicated that there were additional strategies in place for all four options, and the remaining three indicated that there were additional strategies in place for medication errors, medication misuse, and medication abuse. As all five responses for medication errors, misuse, and abuse came from the same five respondents, we can deduce that MSs often deal with this cluster of three types of reports together.

| **Q32: Correlation between positive options selected** | | | | |
|---|---|---|---|---|
| **Respondent A** | Medication errors | Medication misuse | Medication abuse | Occupational exposure |
| **Respondent B** | Medication errors | Medication misuse | Medication abuse | Occupational exposure |
| **Respondent C** | Medication errors | Medication misuse | Medication abuse | |
| **Respondent D** | Medication errors | Medication misuse | Medication abuse | |
| **Respondent E** | Medication errors | Medication misuse | Medication abuse | |

A quarter of respondents have no additional strategies in place for signal detection in reports of special interest. Across the four questions, and after Not Applicable, vaccines was the second most common option chosen, and occupational exposure and other drug groupings the two least frequent.

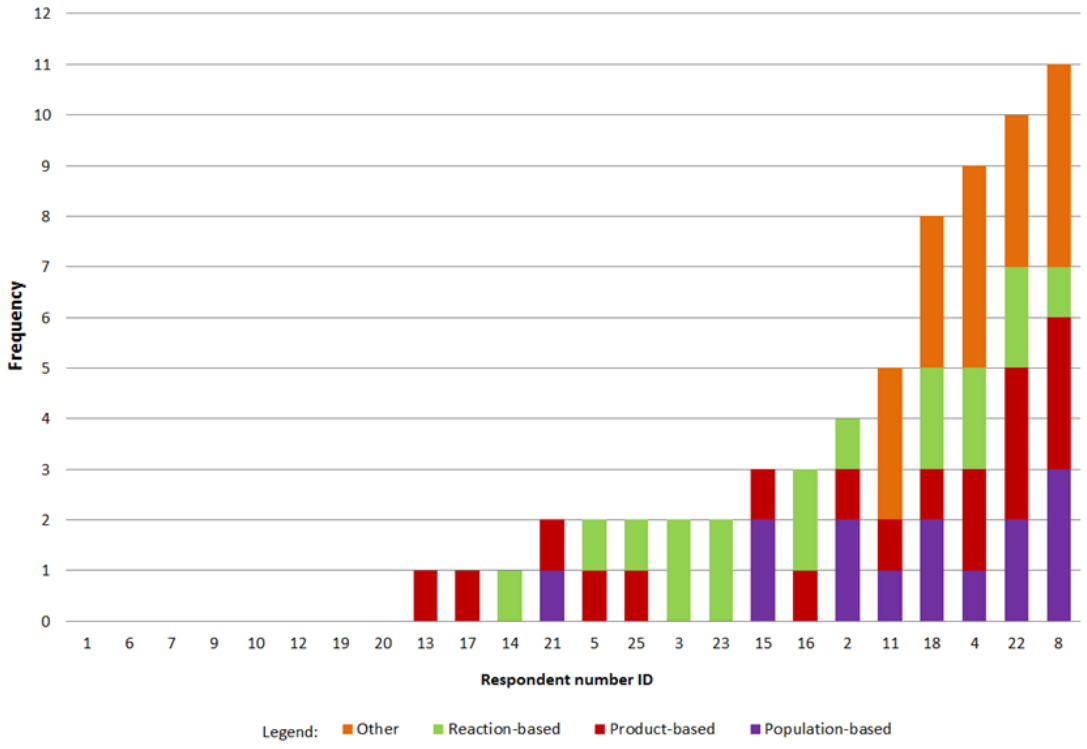
| **Type of special interest report** | **Frequency** |
|---|---|

| | |
|---|---|
| Vaccine reports | 12 |
| Designated medical events | 10 |
| Important medical events | 7 |
| Paediatric reports | 7 |
| Parent-child reports | 5 |
| Medication errors | 5 |
| Medication misuse | 5 |
| Medication abuse | 5 |
| Biological reports | 4 |
| Geriatrics reports | 2 |
| Other drug groupings | 2 |
| Occupational exposure | 2 |

Distribution and variance of data:

Three quarters of respondents indicated that their MS had strategies in place for less than 4 types of RSIs.

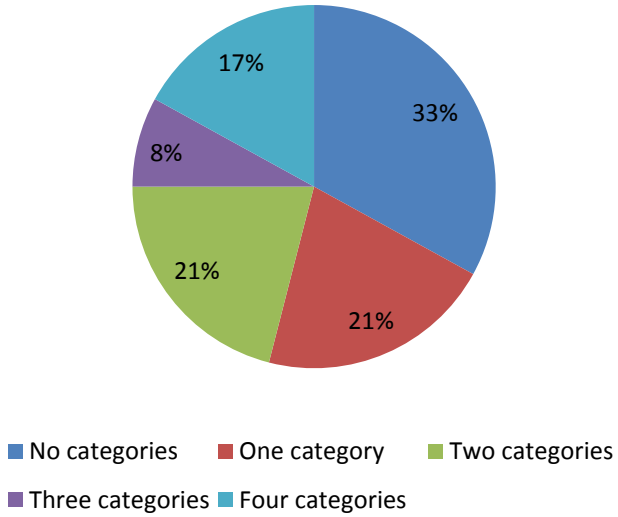
**Fig 17** Distribution of data per respondent and per category, in ascending order



*N.b. The x axis in the above graphs refers to an unique number ID for each respondent. This ID number can be used for tracking respondents' responses to other parts of the survey. For example, one can check how Respondent 6, who indicated no strategies in place for RSI reports, answered other parts of the WP5 survey.*

Looking at the survey data across the four questions, responses suggest that most MSs do not have additional strategies in place for most types of reports of special interest. Four respondents indicated that their MS had additional strategies in place across all four main categories – population-based, product-based, reaction-based, and other groups of interest approaches – but the spread of their data varied. Considering that six respondents indicated that there were no additional strategies in place for *any* of the four categories, the survey data suggests that there is great variance between MSs in how many or how few types of reports of special interest receive additional strategies for signal detection.

**Fig 18** Number of respondents which indicated the existence of additional strategies for one/two/three or four categories of RSI




### *Description of methodological approaches used to identify signals in reports of special interest*

Respondents were given a chance to provide further detail on their answers to Q29-Q32 using free text: For each of the categories of special interest selected above where additional signal management strategies are in place, please describe the methodological approach used to identify signals

All 11 categories listed received at least two descriptive responses, while three respondents provided further information under 'Other'.

While there was a variety of approaches described by respondents as a whole, many respondents, when looked at individually, described the same approach for several different categories of reports. Uniformity of approach was present in individual responses across the categories, but not within different categories across the respondents. For example, the 12 responses for vaccine reports are summarized in Annex 4.

All seven of the respondents who provided descriptions for at least three of the 11 categories listed in Q33 described the same – or a very similar – approach for most, if not all, categories. Across all categories and respondents, some key recurring approaches indicated include:

- Liaison/collaboration with relevant national bodies and/or experts in assessing
- Use of alert terms (predefined important ADRs), which flag up reports for assessment
- Calculation and review of disproportionality values
- Granting of priority status in manual screening of the national ADR database
- Listing all drug-event combinations for reports of special interest on the weekly signal list, regardless of the disproportionality value

### *Signal detection process for special interest reports vs signal detection process for general reports*

Q34: Is the signal detection process for special interest reports different to the signal process followed for other general reports?

All 24 respondents answered this question, with four (17%) answering yes, and 20 answering no. The four respondents who answered positively each gave very similar responses to their responses for Q33. Two respondents gave almost identical answers, suggesting that some respondents interpreted Q34 as a repetition of Q33. The answers can be found in Annex 4. Considering the apparent variability in respondents' interpretation of Q34, it is not possible to assess with certainty, the reliability or significance of the data for it.

### *Differences in how drug and vaccine safety issues are treated compared to other products*

Q35: *Are there differences in how you detect, evaluate, record and track drug and vaccine safety issues in comparison to other kinds of products*

Out of 24 respondents, five (21%) selected Yes.All five respondents further elaborated in the free text part. Answers tended to focus more on signal detection, rather than on safety issues in general. Some answers were, again, very similar to those given to Q33. The five responses can be paraphrased as follows:

i. A different working group for signal detection for vaccines, which uses the same software tools, but calculates the disproportionality values only within drugs and vaccines.

ii. A particular focus, for monitoring of vaccine safety, on denominator data (target populations), immunisation recommendations, and consideration of quality issues and medication errors.

iii. Sub-grouping disproportionality values by vaccine and drug, meaning that vaccines given to a healthy population are compared with a similar group only. Carrying out

observed versus expected analysis using a national electronic healthcare record database.

iv. For vaccine reports, working in partnership with the national Ministry of Health. Using the NCAs assessment, which is consulted by national experts.

v. Assessing reports involving vaccines by staff with specialist knowledge on vaccines.

### *Additional sources and tools used*

Q 37: Additional sources and tools for the detection or management of signals of special interest

Key messages:

- Use of Micromedex, EBSCO (Medline), Martindale, BNF, FDA website, PubMed, Cochrane.
- No additional sources yet, but developing a smartphone app for ADR reporting to enhance consumer and HCP reporting.
- Review of literature performed to detect signals.
- Some categories of special interest undergo an annual selective internal statistical descriptive analysis. These analyses sometimes reveal issues of concern.
- Respondent reiterated the sources used for signal detection in general, namely: EudraVigilance; National database; Published scientific literature; Electronic healthcare records; Clinical trials data or documents and Other.
- Contacting the national organisation responsible for collecting patient safety incidents for medication errors.

One respondent focused on sharing and exchanging important information across the EU, another one focused on identification of key products or issues. Relevant verbatim answers can be found in Annex 3.

The MS who answered the question about additional tools and methods had, in earlier questions, demonstrated that their respective MSs had in place additional strategies for detecting signals across a wide spectrum of special interest reports. Both had selected at least one option in each category of approach, One had indicated the existence of additional strategies for a total of 11 different approaches, while the other had indicated the same for eight of them. The spectrum of responses may be more interesting than reporting about the "best in class" or "most active".

As Q37 asked respondents to describe additional tools/methods used *which they think would be helpful to share*, responses may not be indicative of the tools and methods actually used by respondents. Respondents may have been put off by answering this question if they did not believe their tools or methods were sufficiently significant or helpful for others.

### *Challenges*

Q38: Relevant problems or experiences to share

Two of the responses focused on the lack of expertise and training, while a further two responses mentioned the problem of coding policies. One respondent complained about the

large amount of data that ends up on the weekly signals list. The five responses can be summarised as follows:

i. Availability of experts/assessors

ii. The approach for paediatric case reports results in too many weekly signals.

iii. Limitations of national databases and the lack of an international coding system which is consistent for all member states. States have to manually re-code suspected products in order to do any analysis. Suggestion: products case reports should be transmitted with at least one international code, and mismatching codes should be rejected. Cases in EudraVigilance are recoded, making analysis in EVDAS accessible, but analysis in internal databases are compromised unless cases have already been recoded. Suggestion: All queries in EVDAS could be made by selecting the cases of specific countries only.

iv. Insufficient specialist education and training on signal detection of vaccines.

v. Reports of special interest are sometimes difficult to recognize due to coding policies (MedDRA). Suggestion: Guidance on coding of these cases.

## 4 Discussion of the results

This survey was performed to support WP5 that examines signal management at the level of the Member States. The results showed that the way legal requirements and definitions provided in the implementing regulation and the Directive are interpreted varies between them. There are several factors that might explain these differences e.g.: differences in national databases and the methodologies used specifically tailored for the particular databases, variability in resources and experience, differences in pharmacovigilance organizations, etc. At the start of the survey we provided explanatory information to create common understanding of the way the terms and definitions should be interpreted. The answers indicated that there was no common understanding. From this we concluded that there is a need for detailed guidance and explanation of the terms used in the legislation, in order to acquire this common understanding.

Lack of resources is a well-recognised and recurrent theme across all respondents and will be addressed in detail SCOPE detail in WP7 Quality Management Systems has one topic examining how member states manage their (limited) resources – under 'Resource management'. The lack of expertise can be addressed through training and better communication among MS in order to share the available expertise. Besides interpretation of terms and definitions and lack of resources/experience, there are other recurrent themes which occur across several topics: use of EPITT and the need for a signal management tool.

### *Signal detection*

The results of the survey show that member states have implemented the mandatory monitoring of the EudraVigilance database and review the output as provided by the EMA in line with the obligations laid down in the implementing regulation. However due to limited resources, some MS chose to limit the number of products monitored or to decrease the frequency of monitoring.

According to the Implementing regulation EudraVigilance should be monitored with a frequency proportionate to the risk, and this is further detailed in GVP Module IX. The

results showed that there was a preference for a more risk proportionate approach than currently described. This could for example be based on maturity of products, their overall risk profile, the exposure and/or the time in the life cycle.

The e-RMR is the tool provided by EMA based on the legal obligations. In the survey several challenges were identified concerning its utilization and user friendliness. The fact that the e-RMR is driven by product rather than signal means the tool requires more resources Updates to the e-RMR aimed to reduce the workload should be encouraged.

The majority of the member states also perform signal detection on their national data, using a mix of qualitative and quantitative approaches. As identified in WP 4 and also from WP 5 survey, national databases vary greatly in size and content and are different from the European database. These differences have an impact on what methodologies could and should used for signal detection and on the way that the different databases will contribute to the European network. Various studies (including recent findings from PROTECT) have shown that the database background may have an impact on the results of signal detection. In addition to national databases differences, the different strategies and methods used influence the number and type of signals detected. This heterogeneity in databases and methods used for signal detection at the European level should be fostered, since this will enable to EU system as a whole to better perform signal detection

Some member states use also additional sources e.g. electronic healthcare records (EHR) or registry data to further complement their signal detection activities.

Reported challenges in signal detection mainly refer to lack of resources and experience or low quality of ICSR data. Regarding the low quality of ICSR data which is sometimes due to incorrect/inaccurate coding, it is important to raise awareness for MedDRA training options on coding and on available guidance documents. Other challenges mentioned are: media influence, difficulty of checking of inclusion in the SmPC process, alignment of various national SmPCs and masking effect.

In the legislation requirement for tracking are laid down, and according to our results this has been implemented in different ways across MSs. Based on the results, the minimum criteria for tracking could be identified. A challenge for tracking is represented by signals addressed in different procedures. As an additional challenge answers showed that some Member States have two levels of tracking: tracking at national level (with own national procedures) and tracking at EU level (via EPITT). This may lead to duplication of information/effort. More guidance on how best to track all signals well as on the minimum information to be tracked would be beneficial and would ensure a common approach in signal tracking among the EU network

### *Signal validation and prioritization*

The MSs commented on different challenges in signal validation, and most often the availability of documents was mentioned. In addition, handling of signals via several products or procedures, limited case information and duplicates in EudraVigilance, the amount of evidence needed for old products, lack of resources and expertise of assessors and difficult implementation of GVP were also mentioned. Furthermore, interaction with MAHs and a clear understanding of their role and obligations within signal management was highlighted as another issue sometimes difficult to handle for MSs. More guidance and consensus on when to involve the MAH would be valuable.

If the signal lead MS would also be responsible for the assessment of PSUR and RMP, access to relevant document would probably be easier. But since this is not always the case, it would be helpful, if pharmacovigilance staff was ensured access to all relevant information such as PSUR, RMP, variations, EPITT, national and international registries, drug utilization data etc.

Signals that MSs find particularly challenging to validate are non-serious signals, signals for several products (e.g. a class) with different signal lead MSs and signals with poor quality case data. In addition, unaligned nationals SmPCs result in a situation where known ADRs are sometimes signaled by some MSs, but not by others. The primary step in signal validation is to check if a particular ADR is listed in the SmPC, and MSs indicate that this is time consuming and challenging, since it needs to be performed manually by the assesor. Having a complete overview of all ADRs listed in the SmPCs would be an important move to facilitate the work in signal management. This work was partly done within the PROTECT project but will need to be updated and extended to all products, if it is to be widely and routinely used by MSs.

From the results it was clear that the time spent by MSs in further evaluating a signal before entering it in EPITT varies: some MSs felt that each signal identified should be entered into EPITT whilst others preferred to only enter the signal into EPITT after a further evaluation at national level. This difference in approach might lead to different levels of maturity of the signals entered in EPITT and the EU-system might benefit here from a more common approach. This could be achieved by either having clear guidance on agreed criteria and when to enter a signal in EPITT. The signal management system should be adapted to the purpose of sharing information in an earlier stage, without creating undue burden on the system. Ideally, the system would provide a signal management tool that allows adequate tracking of signals and early sharing of information in the EU-network throughout the signal management process. At minimum three levels of signal communication are identified: 1) Signals brought to PRAC for discussion at EU level (current practice), 2) Communicating national signals that could be of interest for other MSs and 3) Signals that are still preliminary (e.g. under monitoring) might be communicated earlier to prevent duplication of work in other MSs.

Most countries have a process for signal prioritization, although sometimes it is not a formal or documented step. Ongoing prioritization through all steps in the signal management procedure is most widely performed. However, in the GVP module IX prioritization is mentioned as a separate step after validation, and thus the “real world” prioritization method in a majority of the MSs is not in line with the GVP. MSs have different approaches to prioritization of signals, and although some guidance is available in the GVP module IX, MSs expressed need for more guidance with regards to how to prioritize. A more homogeneous approach through a structured framework and guidance for prioritization would be beneficial. One MS has developed and published such criteria, which could be used as a basis for a prioritization tool to facilitate decision-making process and provide more transparency of this process among all MSs

### *Signal confirmation and assessment*

Several MSs mentioned they had no or limited experience confirming signals, and the survey indicate that signal confirmation generally is a step that many MSs find difficult to implement in the daily signal management work. Considering signal confirmation as an

isolated step as outlined in survey introduction does not appear to adequately, reflect a day to day practise in all MSs. For many MSs the confirmation is mainly considered in relation to validated signals received via the EU channel (EMA or other MSs) as described in the GVP Module IX. Guidance on scientific confirmation (intermediate step between validation to assessment) versus regulatory confirmation (pushing signals through EPITT to PRAC) is important.

Difficult signal management terminology is one obstacle mentioned, and MSs find the terminology used in the GVP module IX difficult to separate their national signal management procedure into the steps outlined in this survey. Separating signal validation and signal assessment was difficult for many MSs. Thorough guidance regarding how to place the right amount of work in the different steps, to ensure that signals are shared between MSs at the right time and with an adequate level of information, will be beneficial for all MSs.

The signal assessment part of the survey leave the impression that while many MSs are well on their way, some are left with no or very little experience in this area. A noticeable variability and knowledge gap is thus identified. Guidance in signal assessment aimed at both experienced and less experienced MSs will be valuable. To help MSs deal with the signal management procedure outlined in the GVP module IX, checklists and high-level guidance on possible outcomes of validation and assessment will be of use. Other concerns such as access to additional sources of information for signal assessment including national health registries and drug utilization data and methodological issues relating to signal assessment are mentioned and will be referenced.

The use of EPITT is mentioned as a cause of unnecessary doubling of signal management efforts throughout Europe with suboptimal use of EU resources as a consequence. Not all reasons for this are clear from the survey however, it should be further explored. Though, it is evident that currently there is no mechanism to share signals across EU other than through EPITT. The need of a suitable signal management tool to exchange information on preliminary signals in EU was identified (see also validation topic above), and the EU network will benefit from an informal opportunity to share signals in early stages of their management.

### *Reports of special interest (RSI)*

Twelve types of reports of special interest (RSIs), grouped into four main categories, were the focus in this survey section. The data suggest that only a minority of MSs represented in the survey responses use additional strategies for signal detection for most types of RSIs. Out of the 12 types of RSIs, two thirds of respondents indicated that their MS had additional strategies in place for two or fewer types of RSIs. Vaccines, stand out as an exception, with half of the 24 respondents stating some sort of existing additional strategy for signal detection.

There is great variance between the different MSs in how many kinds of RSIs receive additional strategies, as well as in the strategies themselves. Most MSs use the similar additional strategies for dealing with different types of RSIs. When asked to describe any problems encountered during the RSI signal detection process, responses focused on the lack of specialist training and experts, and on problems in coding policies. Reports of special interest is a topic which would benefit from further guidance and discussion in order to

reach a more consistent approach through EU. WP 5 aims to raise awareness regarding the topics of special interest and the actual possibilities to monitor them.

## 5 Conclusions

The aim of WP5 package was to implement shared understanding of best practice in signal management across the EU network. The results of the survey describe a picture where MSs already have good practices in place for monitoring both national and EudraVigilance data. MS have limited strategies in place at the moment for reports of special interest.
There is a lot of heterogeneity in Europe with regards to the implementation of the signal management process. Such heterogeneity may in our opinion in itself bring added value, especially with regards to the signal detection step. Different working methods in signal management may increase the chance of detecting signals and differences may also be necessary for different national working situations (e.g. regarding resourcing, size and experience). An overall one-size-fits-all perspective will not in our opinion be a goal which would improve signal management within the EU. This said the WP5 is aiming to provide recommendations for those signal management steps which could benefit from a more consistent approach. Also, there is a need to clarify the terms and definitions.

In the EU perspective we find there is a need for training in the signal management field. Such training would include increasing awareness regarding available information sources, and improving tools to better support the processes. Close liaison between MSs, EMA (e.g., through SMART) will be required when developing best practices regarding resources such as the use of EPITT, e-RMR and potential updates of GVP module IX.

## 6 Recommendations

The key findings from the survey will turn into best practice guidance. Challenges have beenidentified, which will need close liaison with EMA and SMART and possibly other stakeholders in addition to the SCOPE project to be fully addressed. The use of EPITT, e-RMRs, updating GVP module IX and SmPC alignments were mentioned as important challenges in the signal management process, which will require collaboration across the EU network to improve.

The Best Practice Guide will address a number of areas highlighted in the survey as requiring improvement, as well as areas where best practice is currently lacking. Some of the key themes are addressed below.

It is proposed that an effort is made to clarify the definitions and terminologies used for the different steps in the signal management process. Furthermore, it is proposed to analyse the use of a ‘signal worksheet’ or template (or ‘signal checklist’, especially for the validation and assessment steps), to make clear what is expected at each step. Recommendations will be made for the minimum information regarding individual signals to be tracked at each step.

The clarity of the degree of transparency in Signal Management within the EU network could be improved by providing guidance on when to enter a signal in EPITT (for discussion at the level of the PRAC), or to share national signals that can be of interest to other MS, or to share ‘early’ signals in order to prevent duplication of work. A future integrated EU signal management tool that would combine the goals of the e-RMR and EPITT is suggested.

As regards the monitoring of EudraVigilance via the e-RMR, a risk proportionate approach (different form the approach taken in GVP IX) will be explored and also suggestions for better use of the e-RMR will be developed.

This report has highlighted that limited strategies are available for managing reports of special interest. Recommendations will focus on practical steps that can be taken to meet the pharmacovigilance legislative requirements, using case studies and/or practical examples.

Where suitable, the recommendations will make reference information that is already available and training materials to help MSs to make best use of the tools that are currently available.

## 7 References


1. CIOMS Working Group. Practical aspects of signal detection in pharmacovigilance. Geneva; 2010
2. EMA. Guideline on good pharmacovigilance practices, Module IX – Signal management. 2012.
3. Commission Implementing Regulation (EU) No 520/2012. 2012;
4. Almenoff JS, Pattishall EN, Gibbs TG, DuMouchel W, Evans SJW, Yuen N. Novel Statistical Tools for Monitoring the Safety of Marketed Drugs. Clinical Pharmacology & Therapeutics. 2007 May 30;82(2):157–66.
5. Hauben M, Madigan D, Gerrits CM, Walsh L, Van Puijenbroek EP. The role of data mining in pharmacovigilance. Expert Opin Drug Saf. 2005;4:929–48.
6. Candore G, Juhlin K, Manlik K, Thakrar B, Quarcoo N, Seabroke S, et al. Comparison of Statistical Signal Detection Methods Within and Across Spontaneous Reporting Databases. Drug Saf. 2015;1–11.
7. Seabroke S, Wise L, Waller P. Development of a novel regulatory pharmacovigilance prioritisation system: an evaluation of its performance at the UK Medicines and Healthcare products Regulatory Agency. Drug Saf. 2013Oct; 36(10): 1025-32
8. Pizzoglio V, Ahmed I, Auriche P, Tuber-Bitter P, Haramburu F, Kreft-Jaïs C, Miremont-SalaméG;Implementation of an automated signal detection method in the French pharmacovigilance database : a feasibility study, Eur J ClinPharmacol. 2012 May;
9. WP1 Survey: Introductory Survey of EU National Competent Authorities,

# 8 Annexes

Annex 1 Completion rate across questions

**Annex 1 link**

Annex 2 Synonyms used in SCOPE WP5 s

**Annex 2 link**

Annex 3 Summary of information received t

**Annex 3 link**

Annex 4 Selection of verbatim responses.d

**Annex 4 link**

Annex 5- Survey final version.pdf

**Annex 5 link**