Signal and Risk Management
Best Practices

Katharina Hartmann
What is a signal?

A signal is:
Information .....that suggests a new potentially causal association or new aspect of a known association...... judged to be of sufficient likelihood to justify verificatory action. (Signal Definition – CIOMS Working Group Report VIII (2010))

NOTE: The term “signal” does not indicate a safety concern. As long as the signal is under “validation” or “evaluation” it is merely an “observation under assessment” After evaluation it may be refuted (“unsubstantiated”) or classified as “potential or identified risk”
Types of signals

Easy to identify:
Single cases of rare events, e.g. thrombocytopenia, severe skin reactions etc.

Moderately hard to identify:
Frequency imbalances, disproportionality

Difficult to identify:
Disproportionality only in subsets, interaction with other risk factors

Early / potential signals
- Pre-clinical data:
  - Safety surveillance in pre-clinical studies
  - Look for anticipated risks
  - Expected for new vaccine

Single case signals ("striking cases")
- Single important serious cases from any source
  - Focused medical evaluation

Multiple statistical signals
- From case series, PSURs / PBRERs etc.
- From registries and databases (VAERS, Vigibase, national / company database, etc.)

Information from other sources
- Scientific literature
- Reports from regulatory authorities
- Media / internet
- Databases
- Competitive intelligence, etc.
Examples of signals

An AEFI occurring more commonly in a treatment group as compared to an alternative / placebo treatment group

A clustering of events common to a medical condition or syndrome occurring more commonly in a treatment group as compared to an alternative / placebo treatment group

A known AEFI for a specific vaccine not previously seen with the new vaccine, now newly reported

Cases of a designated medical event – e.g. vaccine-specific events, immune-mediated events, etc.

Occurrence of a rare AEFI with a near zero background incidence rate
## Signal Management

### Principles

<table>
<thead>
<tr>
<th>Principle</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>Proactive collection of information about vaccines to understand balance of benefit and risk to protect public health</td>
<td></td>
</tr>
<tr>
<td>Fundamental part of routine pharmacovigilance</td>
<td></td>
</tr>
<tr>
<td>Decisions and communication must be appropriately prompt and take into account public health impact</td>
<td></td>
</tr>
<tr>
<td>Effective monitoring of the process</td>
<td></td>
</tr>
<tr>
<td>Documentation of decision making and communication</td>
<td></td>
</tr>
</tbody>
</table>
Signal Management Guidelines


- EU Guidelines on Signal Management:
  - GVP Module IX Rev 1 2017
  - Addendum 1
  - GVP PI

- FDA Guidance for Industry:
  - Good Pharmacovigilance Practices and Pharmacoepidemiologic Assessment
Signal Management Principles for Industry

1. Early detection of safety signals
2. Validate and evaluate any safety signals
3. Communicate safety issues appropriately
4. Manage new safety risks in a timely manner
5. Ensure effective tracking of actions in response to a new safety signal
6. Continually monitor the safety profile throughout the product lifecycle
Signal in the field of vaccines may also relate to:
- Evidence of reduced efficacy or effectiveness
- Vaccine failures
- Quality deviation with potential impact on safety, efficacy or effectiveness (e.g., batch related issues).

Standard case definitions to be used (i.e., Brighton case definitions).

Single report of serious events only to be processed as a signal in case of a causal association to the vaccine.

Specificities of signal detection in mass vaccination programmes, incl. observed to expected analyses.

Special considerations in vaccine signal detection when performing statistical disproportionality analyses.
Tools to reliably identify signals

- Standardized nomenclature to describe event: MedDRA
- Application of the nomenclature in a consistent manner: Coding convention rules
- Standardized grouping of medically similar terms: Synonym list / Coding thesaurus
- Standardized methodology for case identification: Brighton Case Definitions, Standardized MedDRA Queries, SMQs
Signal detection

Qualitative (Descriptive) Analysis

Case-by-case analysis:
- Early potential signals from pre-clinical studies
- Signals from individual case safety reports (ICSRs), e.g.,
  - the striking case
  - a priori suspect case
  - newly arisen suspicion
- Signals from case series
- Signals from aggregate data sets (e.g., DSURs, CSRs, PSURs / PBRERs, RMPs)
- Signals from other sources, e.g.,
  - literature, health authorities, media, internet, social media, competitors

Quantitative (Disproportionality) Analysis

Data mining in databases:
- Identification of statistically prominent disproportionate reporting of pairs of vaccines and adverse events:
  - Signals of disproportionate reporting (statistical signals)
- Data mining results (i.e., statistical signals) must be evaluated in the clinical context
- Data mining results are highly situation dependent, e.g.:
  - reporting sources / collection methods,
  - type of medicinal products in the database, medicinal terminology / coding
  - date of creation of database
# Data Mining for Signal Detection

Data mining for the detection of Signals of Disproportionate Reporting (SDR)

<table>
<thead>
<tr>
<th></th>
<th>Event of interest</th>
<th>All other events</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>Vaccine of interest</td>
<td>A</td>
<td>B</td>
<td>A+B</td>
</tr>
<tr>
<td>All other vaccines</td>
<td>C</td>
<td>D</td>
<td>C+D</td>
</tr>
<tr>
<td>Total</td>
<td>A+C</td>
<td>B+D</td>
<td>A+B+C+D</td>
</tr>
</tbody>
</table>

2 x 2 Contingency Table:

Proportional Reporting Rate (PRR) = \[
\frac{A}{A + B}\] / \[
\frac{C}{C + D}\]

Reporting Ratio (RR) : \[
\frac{A}{(A + B)}\] / \[
\frac{(A+C)/(A+B+C+D)}\]

Reporting Odds Ratio (ROR): \[
\frac{A}{C}\] / \[
\frac{B}{D}\]

Proportional Reporting Rate (PRR) = \[
\frac{A}{A + B}\] / \[
\frac{C}{C + D}\]

Reporting Ratio (RR) : \[
\frac{A}{(A + B)}\] / \[
\frac{(A+C)/(A+B+C+D)}\]

Reporting Odds Ratio (ROR): \[
\frac{A}{C}\] / \[
\frac{B}{D}\]
Frequentist signal detection methods support the analysis of AEFI reporting rates, but may not be appropriate in all situations.

Quantitative methods highly support traditional signal detection methods, but they cannot replace the medical and scientific signal evaluation.

Data mining results generate hypotheses, these must be analyzed within the context of relevant clinical data.

New EU PV legislation requires signal detection - GVP Module IX Signal Management provides Guidance and Requirements on structures.

None of the data mining methods are validated, there is no gold standard, and such methods may not be appropriate in smaller data sets.
Signal Detection Systems
Safety databases

WHO: Vigibase – uses the WHO Bayesian confidence propagation neural network (BCPNN) for quantitative signal detection (mathematical modeling)

EU: EudraVigilance – uses the Signal of disproportionate reporting (SDR) for quantitative signal detection

FDA: VAERS - Screening algorithms, uses the Multi-Item Gamma Poisson Shrinker (MGPS) program for quantitative signal detection

National Authority database
- little or no competitor data
- more cases on specific vaccines
- smaller overall data set size
- link to sales data and look at reporting rates
- comparison to background of an international database (with caveats)

Company databases
Signal management process

Generic process aligned with CIOMS VIII and GVP Module IX
Signal management process

**Detection**
Apply signal detection methods & thresholds to screen for unexpected findings.

**Triage**
Application of clinical context & medical judgment through medical review to determine whether the Safety Observation merits further verificatory action.

**Validation**
Preliminary data analysis supporting the unvalidated signal, to verify that the available documentation is strong enough to suggest a new potentially causal association, or a new aspect of a known association, & therefore to justify further assessment of the signal.

**Evaluation**
In-depth analysis of a validated signal which may entail the collection of additional data & analyses of additional data sources.

**Final assessment**
The outcome of Signal Evaluation is a final assessment determining whether a signal represents an Adverse Reaction (e.g., the drug is causally associated with the event).
Signal evaluation strategy / 1
Strength of evidence in the clinical context

Data gathering:
- Generate case series, literature reviews, clinical and pre-clinical data review
- Additional sources of information

Methodology:
- Define search strategy
- Use qualitative methods
- Use quantitative methods

Data analysis:
- SMQs used?
- Case series analysis (descriptive narratives of the cases):
  - are all relevant facts present
  - other risk factors present
  - Clinical relevance
- Conclusion regarding signal confirmation / ad hoc report
Signal evaluation strategy /2
Strength of evidence in the clinical context

SNIP Criteria:

**Strength**
- Strength of association / strength of signal

**New**
- «newness» of event
- Whether or not the issue or some aspects of it is new

**Importance**
- Clinical importance of the event, as judged by seriousness and severity

**Prevention**
- Potential for preventive measures
Final assessment
Signal evaluation outcome

• Completion of the signal evaluation within defined timeline
• Safety meeting with different functions within the company to determine overall outcome:
  • Determination if evaluated signal constitutes a risk
  • Determination if identified or potential risk is important (i.e., of public health significance or likely to adversely alter benefit-risk profile)
  • Recommendation on potential actions

**Identified risk**
- Vaccine reaction supported by sufficient evidence

**Potential risk**
- Inconclusive / lacking information
- Map to indeterminate signal

**Unsubstantiated risk**
- No risk attributable to vaccine / other etiologies
- Map to refuted signal*

---

*CIOMS VIII Chapter II.c Definition and taxonomy of drug safety signals
## Signal Tracking Workflow

### Example from Industry

<table>
<thead>
<tr>
<th>DETECTION</th>
<th>TRIAGE</th>
<th>VALIDATION</th>
<th>EVALUATION</th>
<th>FINAL ASSESSMENT</th>
</tr>
</thead>
<tbody>
<tr>
<td>Apply signal detection methods &amp; thresholds to screen for unexpected findings</td>
<td>SIGNAL TRIAGE: Application of clinical context &amp; medical judgment through medical review to determine whether the Safety Observation merits further verificatory action</td>
<td>A preliminary analysis of the data supporting the unvalidated Safety Signal with the goal of verify that the available documentation is strong enough to suggest a new potentially causal association, or a new aspect of a known association, &amp; therefore to justify further assessment of the signal</td>
<td>An in-depth analysis of a validated Safety Signal, which may entail the collection of additional data &amp; analyses of additional data sources.</td>
<td>The outcome of Signal Evaluation is a final assessment determining whether a signal represents an Adverse Reaction (e.g., the drug is causally associated with the event)</td>
</tr>
</tbody>
</table>

![Signal Tracking Workflow Diagram](chart.png)

**DETECTION**
- Safety data

**TRIAGE**
- Safety Observation
- Signal Triage

**VALIDATION**
- Validation
- Validated Signal

**EVALUATION**
- Evaluation of Signal

**FINAL ASSESSMENT**
- Positive
- Negative
- Insufficient Information
- Ongoing Monitor
- Closed: Safety Issue
- Closed: not Supported Safety Issue
Signal prioritization and timelines

**High**
- Signal with important impact on public health / patient health for serious events
- Highest level of urgency - immediate attention
- **1 month** – to evaluation & endorsement

**Medium**
- Potentially important impact on public health
- Medium level of urgency – attention in short term
- **3 months** – to evaluation & endorsement

**Low**
- Moderate/low impact on public health
- **6 months** – to evaluation & endorsement
# Signal Detection Toolkit

## Example

### Local AEFIs

<table>
<thead>
<tr>
<th>Reviewed for</th>
<th>Frequency</th>
<th>Severity</th>
<th>Prolonged duration</th>
<th>Unusual pattern or trends</th>
</tr>
</thead>
</table>

### Systemic AEFIs

<table>
<thead>
<tr>
<th>Reviewed for</th>
<th>Frequency</th>
<th>Severity</th>
<th>Prolonged duration</th>
<th>Unusual pattern or trends</th>
<th>Events relevant in context of vaccine safety (see list of designated medical events DME)</th>
</tr>
</thead>
</table>

### SAEs

<table>
<thead>
<tr>
<th>Reviewed for</th>
<th>Events relevant in context of vaccine safety (see list of DMEs)</th>
<th>Risk factors / interactions</th>
<th>Biological plausibility</th>
</tr>
</thead>
</table>

### Pregnancy

<table>
<thead>
<tr>
<th>Reviewed for</th>
<th>Adverse outcome in mother</th>
<th>Adverse outcome in offspring</th>
</tr>
</thead>
</table>

### Known and potential risks with vaccines

<table>
<thead>
<tr>
<th>Reviewed for</th>
<th>Anaphylaxis</th>
<th>Anxiety related responses incl. syncope</th>
<th>Evidence of transmission of infectious agents</th>
<th>Live attenuated vaccines: symptoms resembling wild-type disease</th>
<th>Vaccination errors</th>
<th>Vaccination failure (lack of efficacy)</th>
<th>Lot-related AEFIs</th>
</tr>
</thead>
</table>

### Designated Medical Events (Brighton case definitions)

<table>
<thead>
<tr>
<th>Reviewed for</th>
<th>Abscess</th>
<th>Anaphylaxis</th>
<th>Cellulitis at Injection Site</th>
<th>Chronic fatigue</th>
<th>Convulsion / seizures</th>
<th>Diarrhea</th>
<th>Encephalitis / Myelitis / ADEM</th>
<th>Guillain Barré syndrome/ Fisher syndrome</th>
<th>Hypotonic hypersensitive episodes (HHE)</th>
<th>Intussusception</th>
<th>Meningitis, aseptic</th>
<th>Narcolepsy</th>
<th>Thrombocytopenia / ITP / evidence of bleeding</th>
<th>Immune mediated disorders</th>
</tr>
</thead>
</table>

21
# Signal detection checklist

**DATA SOURCE(S)**

<table>
<thead>
<tr>
<th>Product:</th>
<th>□ AAAA</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>□ BBBB</td>
</tr>
<tr>
<td>Data source:</td>
<td>□ Clinical Trial Database:</td>
</tr>
<tr>
<td></td>
<td>□ Global Safety Database</td>
</tr>
<tr>
<td></td>
<td>□ Other - please specify:</td>
</tr>
<tr>
<td>Cut-off date:</td>
<td>________________________</td>
</tr>
</tbody>
</table>

**ITEMS REVIEWED**

<table>
<thead>
<tr>
<th>Safety Observation?</th>
<th>Yes (see below)</th>
<th>No</th>
<th>N/A</th>
<th>Not reviewed</th>
</tr>
</thead>
<tbody>
<tr>
<td>Solicited AEFIs</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Unsolicited AEFIs</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>SAEs</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pregnancies</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>AESI / DMEs</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Other (specify)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

**SAFETY OBSERVATION(S)**

Description:

**ACTIONS/SIGNATURE**

- □ No safety observation (no action required)
- □ Safety Observation: SMT Chair notified
- □ Emergent Safety Issue: Head Vaccine PV notified

<table>
<thead>
<tr>
<th>Date</th>
<th>Signature</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
</tr>
</tbody>
</table>
Workflow Signal Management
Example

Data from all sources
Risk Management

• Risk management is necessary to enhance the benefit risk balance in real life.
• Risk minimization should be proportionate to the risks.
• Risk management is a cornerstone for sustainable market availability.
• Risk management protects patients, can avoid crisis and enhance knowledge about the vaccine.
• Quality management systems are an integral part of risk evaluation and management.

Main focus of RMP:
• Pre-and post-marketing benefit-risk management and planning
• Risk minimization plan
• Post-authorization safety studies: Data collection
• Risk minimization measures
• Ensuring effectiveness of measures
Risk Management

Guidelines

• ICH E2E: Pharmacovigilance Planning

• EU Risk Management Systems
  • GVP Module V
  • GVP PI

• FDA Guidance for Industry:
  • Good Pharmacovigilance Practices and Pharmacoepidemiologic Assessment
**Risk Management**

**Purpose**

- The objective of a risk management strategy is to ensure a positive benefit risk balance over time in real world setting.
- To propose a structure for a pharmacovigilance plan and safety specification that summarizes the identified and potential risk of a medicinal product.

**Principles**

- Planning of pharmacovigilance activities throughout the product life-cycle.
- Science-based approach to risk documentation.
- Effective collaboration between regulators and industry.
- Applicability of the Pharmacovigilance Plan across the ICH regions.
Risk Management

- Risk Management is a complex process which needs governance structure.
- Safety Management Teams (SMTs) / Vaccine Safety Teams (VSTs) are an operating model to ensure vaccine safety and to document continuous and permanent safety evaluation of a vaccine product.
Types of risks

Identified risk
- Adequate evidence of an association and the risk occurrence between the medicinal product

Potential risk
- There is some basis for suspicion of an association between the medicinal product and the risk occurrence, but it is not confirmed

Missing information
- There is insufficient or no data
- Additional data / evidence must be collected using a risk management plan
Identified / Potential risks

Negative impact on the benefit – risk balance

Implications for public health

Depend on several factors:

- Impact on the individual patient
- Seriousness of the risk
- Frequency of occurrence
- Preventability of the risk
What is an important risk?

An important risk?

Clearly an important risk!

In general, an important risk is any risk that is likely to be included in the contraindications/warnings and precaution section of the product information.

Most discrepancies in understanding important risks are related to disability and life-threatening conditions or medical significance. These assessments require medical judgement.
Risk Management – new concept
From Risk Management to Benefit / Risk Management GVP Module V

Risk Management Cycle

- Identify and analyze
  - risk quantification and benefit assessment
- Evaluate
  - benefit risk balance and opportunities to increase and/or characterize
- Select and plan
  - risk characterization / minimization and benefit maximization techniques
- Implement
  - risk minimization / characterization and benefit maximization

Data collection

monitor effectiveness and collect new data from:
- clinical trials
- spontaneous reports
- literature
- epidemiological studies
- registries
Risk Management System (RMS)
Definition GVP Module V

Definition

‘a set of pharmacovigilance activities and interventions designed to identify, characterize, prevent or minimize risks relating to a medicinal product, including the assessment of the effectiveness of those activities and interventions’.

• Overall aim:
  • to ensure that the benefits exceed the risks by the greatest achievable margin for the individual patient and for the target population as a whole

• Multiple risk evaluation:
  • Characterization of the safety profile including missing information
  • PV activities to further monitor the safety profile and adapt characterization
  • Risk minimizing measures and assessment of their effectiveness
Risk management process

Risk management is the process of measuring or assessing and developing strategies to manage the risk. Risk management is based on 3 pillars:

- **Safety profiles**
  - All identified or potential risks compiled, along with a record of what is missing in terms of safety information
  - Part II Safety Specification of EU RMP

- **Risk assessment / PV planning**
  - Plan for further identifying, characterizing, and assessing risks
  - Planning contains both routine and additional pharmacovigilance activities
  - Part III Pharmacovigilance Plan of EU RMP

- **Risk Management Plan (RMP)**
  - Plan for minimizing the risk
  - Integral part of the risk management plan
  - Contains routine and additional risk minimization activities
  - Part V Risk Minimization Measures of EU RMP
## Risk Management Plan (RMP) Principles

A detailed description of the risk management system
Risks need to be understood in the context of benefit

<table>
<thead>
<tr>
<th>Identification and Characterization</th>
<th>Indicate how to characterize further the safety profile</th>
</tr>
</thead>
<tbody>
<tr>
<td>Identify or characterize the safety profile of the medicinal product(s) concerned</td>
<td>Indicate how to characterize further the safety profile</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Document measures to prevent or minimise the risks associated</th>
<th>Describe what is known about the safety profile</th>
</tr>
</thead>
<tbody>
<tr>
<td>Document post-authorization obligations that have been imposed as a condition of marketing authorization</td>
<td>Indicate level of certainty that efficacy shown in clinical trials is seen in everyday practice</td>
</tr>
<tr>
<td>Implicit requirements:</td>
<td>Include how effectiveness of risk minimisation measures will be assessed</td>
</tr>
</tbody>
</table>

- Document measures to prevent or minimise the risks associated, including assessment of effectiveness of the interventions.
Structure of an EU Risk Management Plan for Vaccines

- **Part I:** Product Overview
- **Part II:** Safety Specification (8 modules)
- **Part III:** Pharmacovigilance Plan: Routine PV activities, Additional PV activities
- **Part IV:** Plans for post-authorisation efficacy studies
- **Part V:** Risk minimisation measures
- **Part VI:** Summary of activities in the risk management plan by medicinal product
- **Part VII:** Annexes to the risk management plan
Preparation of the RMP

- The preparation is a highly collaborative exercise
- Project lead is within PV with roles and responsibilities of the different contributors / stakeholders clearly defined
- RMP preparation should be coordinated with preparation of other submissions
- The modular structure facilitates preparation
  - Tailored modules per product and marketing authorization application type
  - Updates per module
  - Core RMPs and additional regional RMPs
  - Exchangeable modules with PSUR
Preparation of RMP
Regulatory guidance and structure

Core RMP follows EU requirements
- GVP (Good Pharmacovigilance Practice) Module V
- GVP PI: Product- or Population-Specific Considerations I: Vaccines

Product overview
Safety specification
Pharmacovigilance plan incl. post-authorization safety studies
Plans for post-authorization efficacy studies
Risk minimization measures and evaluation of their efficacy
RMP: Part Pharmacovigilance Plan

The pharmacovigilance plan should be based on the safety concerns summarized in the RMP module VIII of the safety specification.

A safety concern is defined as:
- an important identified risk
- an important potential risk
- missing information

- Identification of new safety concerns
- Further characterization of known safety concerns including elucidation of risk factors
- Investigation of whether a potential safety concern is real or not
RMP: Part Pharmacovigilance Plan
Pharmacovigilance activities

**Routine pharmacovigilance**

- Pharmacovigilance activities required to fulfil legal requirements as described for the Pharmacovigilance System (e.g., in the Pharmacovigilance System Master File)
- Routine pharmacovigilance relies mainly on passive surveillance

**Additional pharmacovigilance**

- May include non-clinical studies, clinical trials or non-interventional observational studies (e.g., active surveillance)
- A safety concern may have no, or a number of additional pharmacovigilance activities associated, depending on the nature of the concern, the degree to which the concern is already characterized and the feasibility of respective trials or studies
Risk Management Plans
Industry Experience

Increasing trend to request EU specific RMP as global document
- e.g., wish to see specific reference to SPC sections vs generic statements relating to the CCSI

Strong emphasis on paediatric use
- May require a paediatric RMP

Additional requests for:
(examples)
- Studies in individual countries based on theoretical concerns
- Country specific PV activities / local RMPs where an EU RMP has been agreed
- Country specific utilization studies
- Variable interpretation of what constitutes an important risk
Risk Minimization Plan

When is a specific Risk Minimization Plan needed?
Not invariably but requires justification (in the EU in approx. 18% of RMPs)

Additional measures to mitigate known risks need to be:
- Appropriate to the level of risk
- Feasible in practice
- Effectively communicated
- According to local regulations and medical culture

Current toolkit is limited
- Provide example(s) of proposed tools
- Propose how effectiveness of risk minimization will be monitored (impact on spontaneous reporting unlikely to be acceptable)
Risk Minimisation Measures (RMM) Methods

Information:

**Routine risk minimization activities:**
- Product information for healthcare professionals (in the EU the SmPC)
- Package leaflet (Patient Information Leaflet PIL)
- Labelling on outer packaging

**Additional risk minimization activities, e.g.:**
- Training
- Checklists
- Educational material
- Direct healthcare professional communication (DHPC)
- Pregnancy prevention program

Prescribing restrictions (legal status)

**Additional risk minimization activities, e.g.:**
- In-patient use only
- Specialised physicians only
- Special administration
- Controlled distribution systems
Risk minimization tools  GVP Module XVI

- Black box warning
- Direct Healthcare Professional Communication (DHPC) letter (“Dear Doctor Letters”)
- Change of product labeling
- Publications
- Training
- Seminars
Other GVP references related to Risk Management Planning

**Module VII Periodic Safety Update Report:** The PSUR provides a benefit-risk evaluation during a reporting interval; it is linked to the RMP and includes some common sections. Completing a PSUR may result in a need to update the RMP.

**Module VIII Post-Authorization Safety Studies:** PASSs are considered additional PV activities that may be interventional or non-interventional.

**Module IX Signal Management:** A new risk or a change to a known risk occurring in a signal workup may be classified as a safety concern that triggers an RMP update; thus potentially needing additional PV activities for further characterization and additional risk minimization activities.

**Module XII: Continuous Pharmacovigilance:** ongoing benefit-risk evaluation, regulatory action and planning of public communication: Risk management is an ongoing process throughout the product life-cycle and should respond to any changes in the benefit-risk profile. Effective communication about a safety concern is an important form of risk mitigation.

**Module XV Safety Communication:** Provides principles for communicating significant new emerging safety information about a medicinal product, primarily to HCPs and patients. It covers DHCPs, which may be an additional risk minimization measure within an RMP.

**Module XVI: Risk minimization measures:** Selection of tools and effectiveness indicators: Provides the principles for developing and implementing additional risk minimization measures (such as educational or controlled access programs) and for evaluating their effectiveness using process and outcomes indicators.
Signal and Risk management Summary

Signal detection
- Event rate imbalance
- Disproportionate reporting
- Striking / important case

Signal evaluation
- Confounders
- Alternative causes
- Verification that new information is strong enough for further confirmatory actions

Signal confirmation
- Evidence of causal association
- Priority assessment

Risk assessment
- Outcome of the signal management process
- Extent of risk
- Impact of risk

Risk mitigation
- Risk mitigation strategy
- Risk minimization plan
- Risk minimization measures

B / R assessment
- In a structured manner clear explanation of the methodology and reasoning used
- Clear assumptions, considerations and judgement or weighting supporting the B / R conclusions