Vaccine Safety Monitoring and Pharmacovigilance Tools
Advanced Pharmacovigilance Mini E-Workshop
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dcvmn
Developing Countries Vaccine Manufacturers Network

Signal and Risk Management Best Practices

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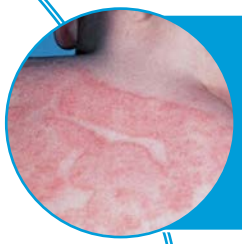
What is a signal?

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)

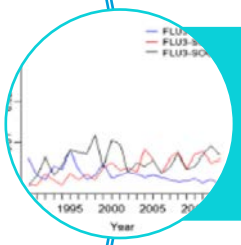
NOTE: The term "**signal**" does not indicate a safety concern. As long as the signal is under "validation" or "evaluation" it is merely an "**observation** under assessment"
After evaluation it may be refuted ("unsubstantiated") or classified as "potential or identified **risk**"

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

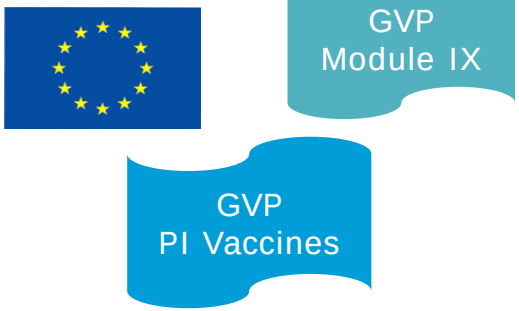
Signal Management

Principles
Proactive collection of information about vaccines to understand balance of benefit and risk to protect public health
Fundamental part of routine pharmacovigilance
Decisions and communication must be appropriately prompt and take into account public health impact
Effective monitoring of the process
Documentation of decision making and communication

Signal Management Guidelines

- CIOMS Working Group Report VIII (2010)

- 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

4. Manage new safety risks in a timely manner

1. Early detection of safety signals

2. Validate and evaluate any safety signals

3. Communicate safety issues appropriately

5. Ensure effective tracking of actions in response to a new safety signal

6. Continually monitor the safety profile throughout the product lifecycle

Vaccine Signal Management

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).

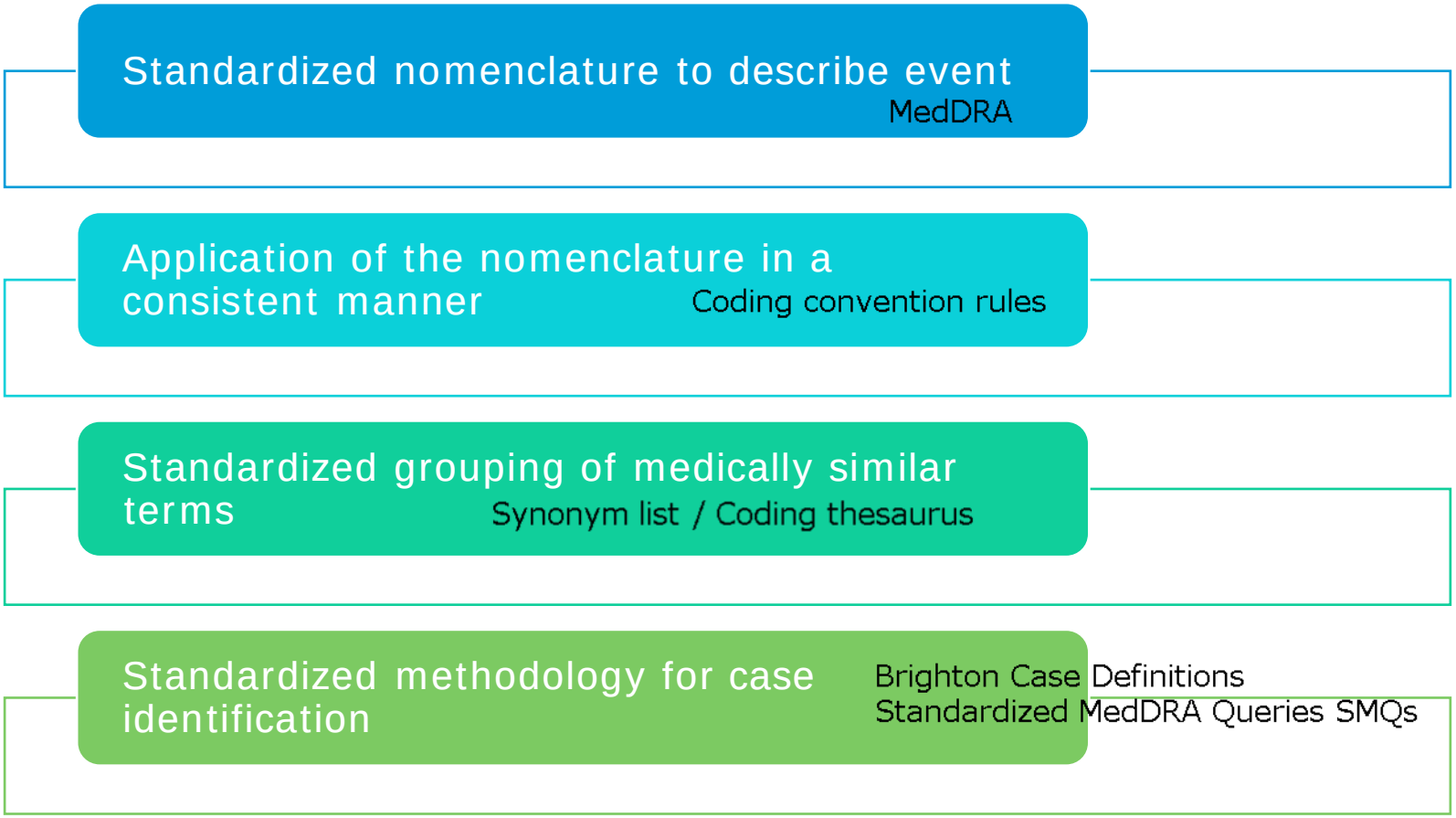
Standard case definitions to be used (i.e., Brighton case definitions).

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



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)

	Event of interest	All other events	Total
Vaccine of interest	A	B	A+B
All other vaccines	C	D	C+D
Total	A+C	B+D	A+B+C+D

2 x 2 Contingency Table:

Proportional Reporting Rate (PRR) = [A/(A + B)]/[C/(C + D)]

Reporting Ratio (RR) : [A/(A + B)] / [(A+C)/(A+B+C+D)]

Reporting Odds Ratio (ROR): (A/C) / (B/D)

Strengths and limitations of Quantitative Signal Detection

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

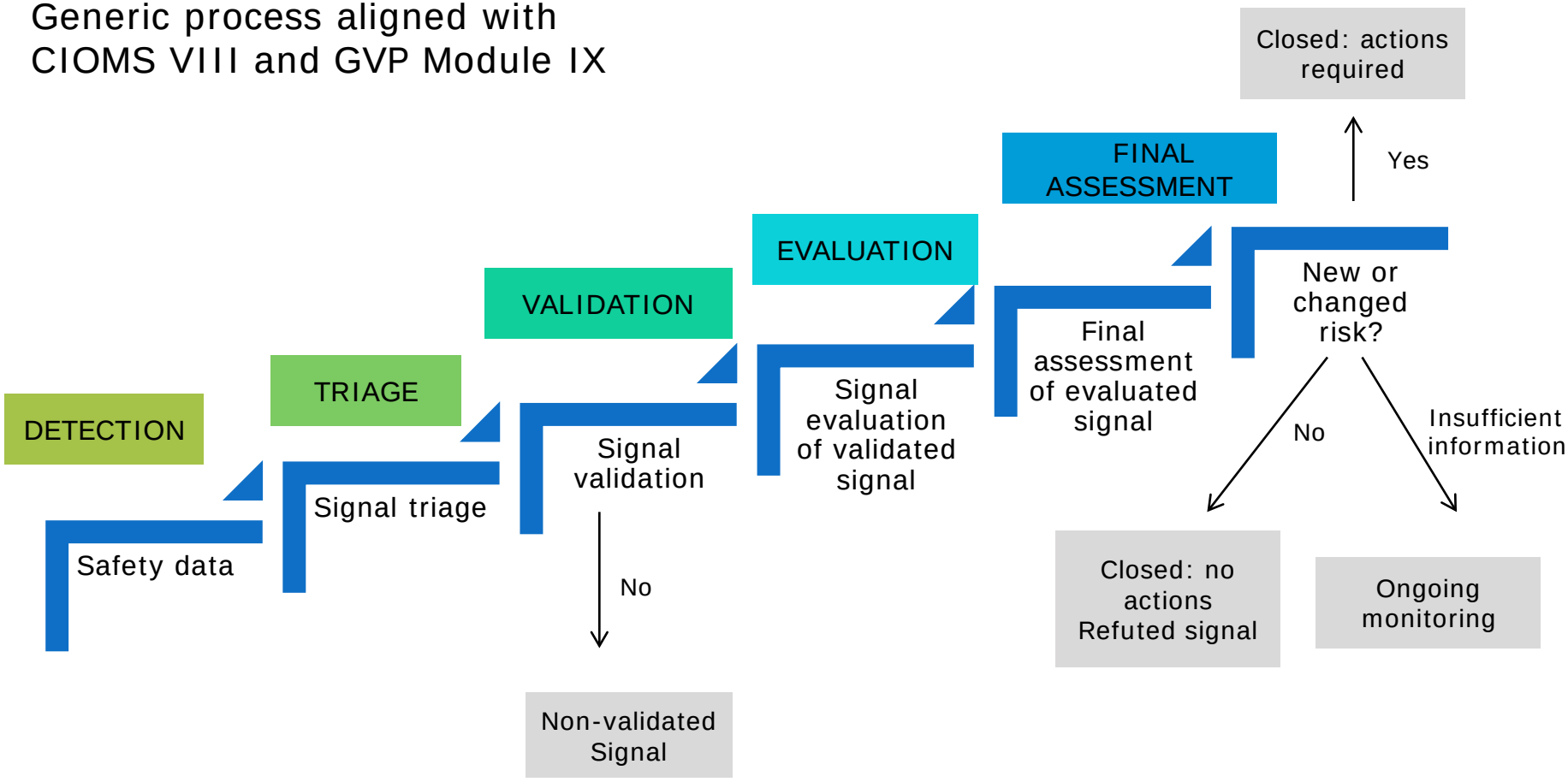
National Authority database

Company databases

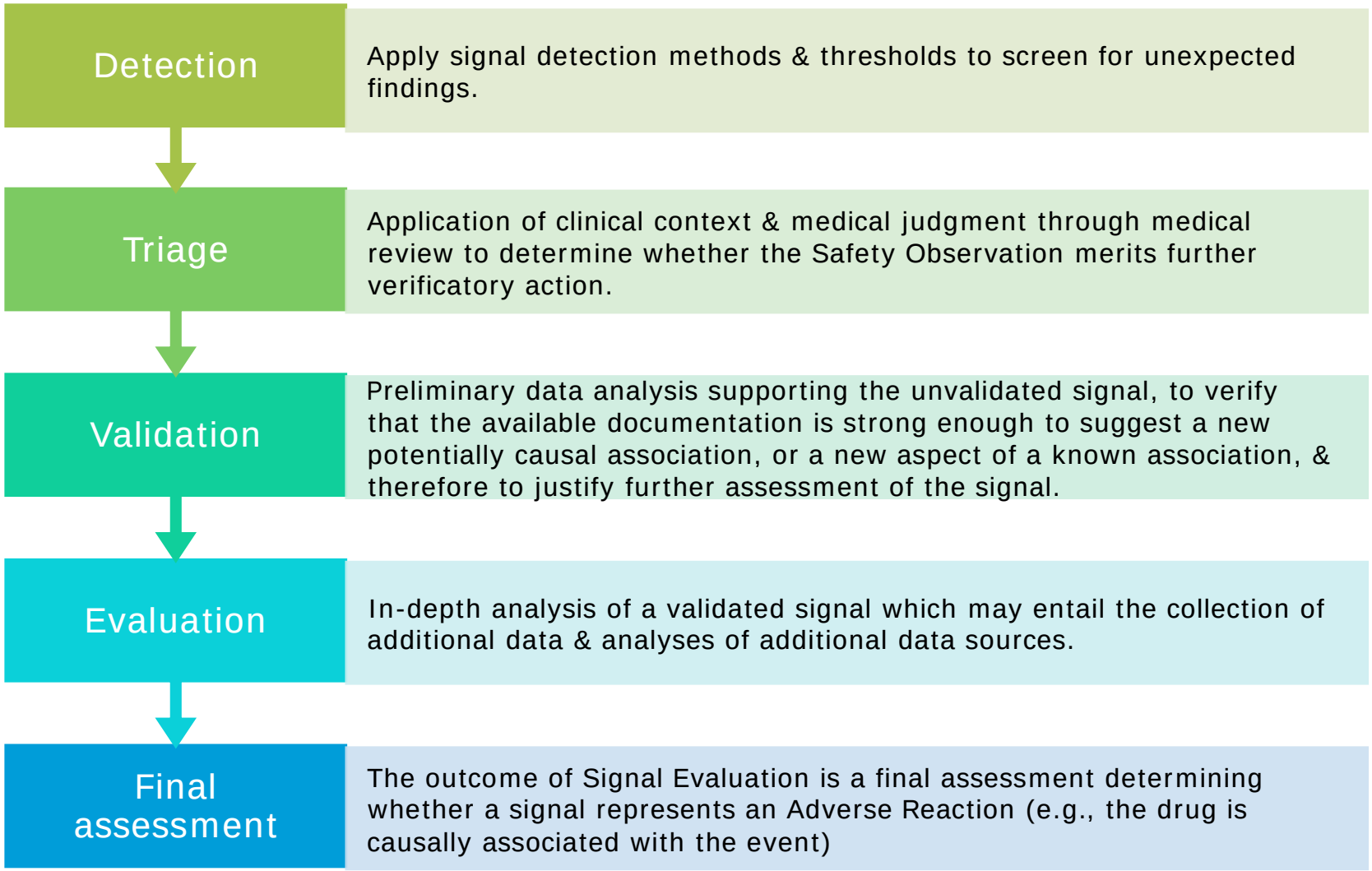
- little or no competitor data
- more cases on specific vaccines
- smaller overall data set size
- link to sales data and look at reporting rates
- comparison to background of an international database (with caveats)

Signal management process

Generic process aligned with
CIOMS VIII and GVP Module IX



Signal management process



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

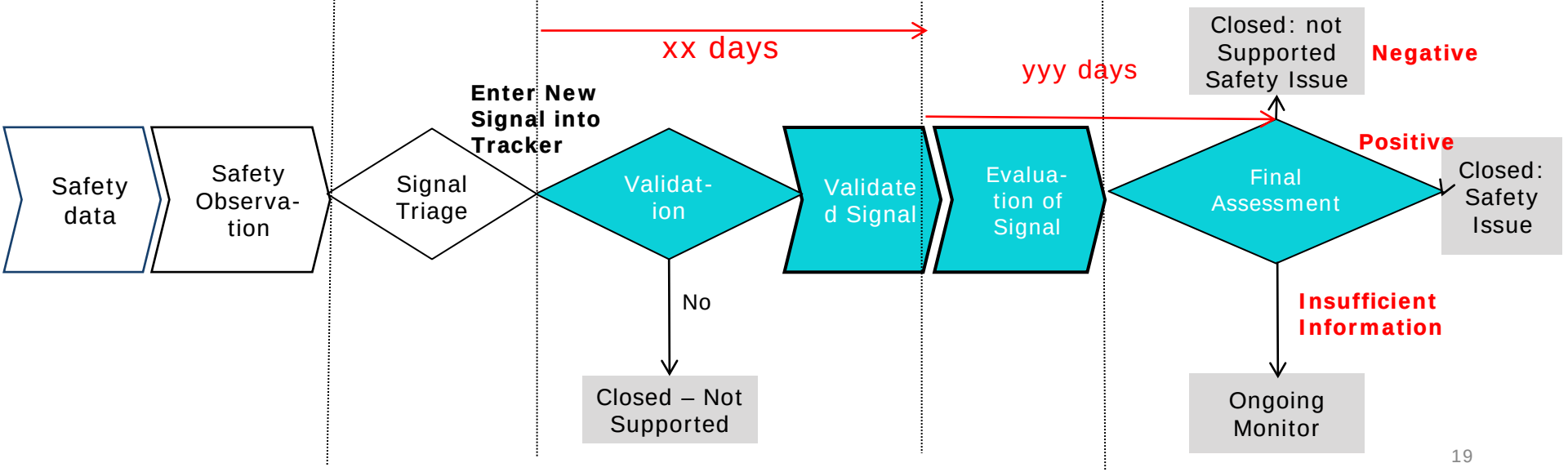
- Completion of the signal evaluation within defined timeline
- Safety meeting with different functions within the company to determine overall outcome:
  - Determination if evaluated signal constitutes a risk
  - Determination if identified or potential risk is important (i.e., of public health significance 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

DETECTION	TRIAGE	VALIDATION	EVALUATION	FINAL ASSESSMENT
Apply signal detection methods & thresholds to screen for unex-pected findings	SIGNAL TRIAGE: Application of clinical context & medical judgment through medical review to determine whether the Safety Observation merits further verificatory action	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, & therefore to justify further assessment of the signal	An in-depth analysis of a validated Safety Signal, which may entail the collection of additional data & analyses of additional data sources.	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 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	
Reviewed for	• Frequency • Severity • Prolonged duration • Unusual pattern or trends

Systemic AEFIs	
Reviewed for	• Frequency • Severity • Prolonged duration • Unusual pattern or trends • Events relevant in context of vaccine safety (see list of designated medical events DME)

SAEs	
Reviewed for	• Events relevant in context of vaccine safety (see list of DMEs) • Risk factors / interactions • Biological plausibility

Pregnancy	
Reviewed for	• Adverse outcome in mother • Adverse outcome in offspring

Known and potential risks with vaccines	
Reviewed for	• Anaphylaxis • Anxiety related responses incl. syncope • Evidence of transmission of infectious agents • Live attenuated vaccines: symptoms resembling wild-type disease • Vaccination errors • Vaccination failure (lack of efficacy) • Lot-related AEFIs

Designated Medical Events (Brighton case definitions)	
Reviewed for	• Abscess • Anaphylaxis • Cellulitis at Injection Site • Chronic fatigue • Convulsion / seizures • Diarrhea • Encephalitis / Myelitis / ADEM • Guillain Barré syndrome/ Fisher syndrome • Hypotonic hyporesponsive episodes (HHE) • Intussusception • Meningitis, aseptic • Narcolepsy • Thrombocytopenia / ITP / evidence of bleeding • Immune mediated disorders

Signal detection checklist

DATA SOURCE(S)

Product: ☐ AAAA

☐ BBBB

Data source: ☐ Clinical Trial Database: Study ID(s): _____

☐ Global Safety Database

☐ Other - please specify: _____

Cut-off date: _____

ITEMS REVIEWED

	Safety Observation?			
Solicited AEFIs	☐ Yes (see below)	☐ No	☐ N/A	☐ Not reviewed
Unsolicited AEFIs	☐ Yes (see below)	☐ No	☐ N/A	☐ Not reviewed
SAEs	☐ Yes (see below)	☐ No	☐ N/A	☐ Not reviewed
Pregnancies	☐ Yes (see below)	☐ No	☐ N/A	☐ Not reviewed
AESI / DMEs	☐ Yes (see below)	☐ No	☐ N/A	☐ Not reviewed
Other (specify) _____	☐ Yes (see below)	☐ No	☐ N/A	☐ Not reviewed
_____	☐ Yes (see below)	☐ No	☐ N/A	☐ Not reviewed

SAFETY OBSERVATION(S)

Description:

ACTIONS/SIGNATURE

☐ No safety observation (no action required)

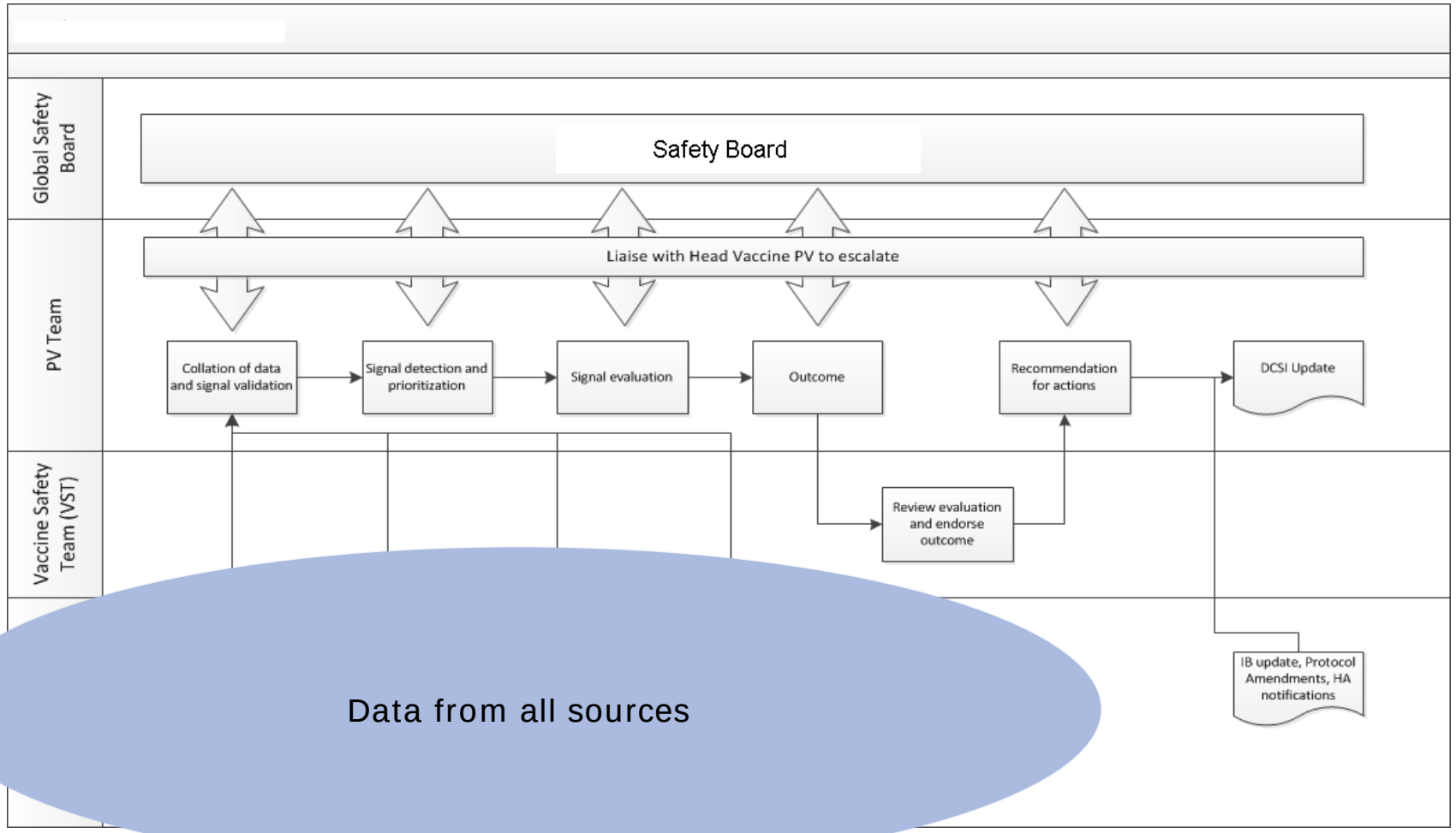
☐ Safety Observation: SMT Chair notified

☐ Emergent Safety Issue: Head Vaccine PV notified

_____ _____

Date Signature

Workflow Signal Management Example



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

ICH
harmonisation for better health

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

GVP
Module V

GVP
PI Vaccines

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

FDA

Risk Management

Purpose

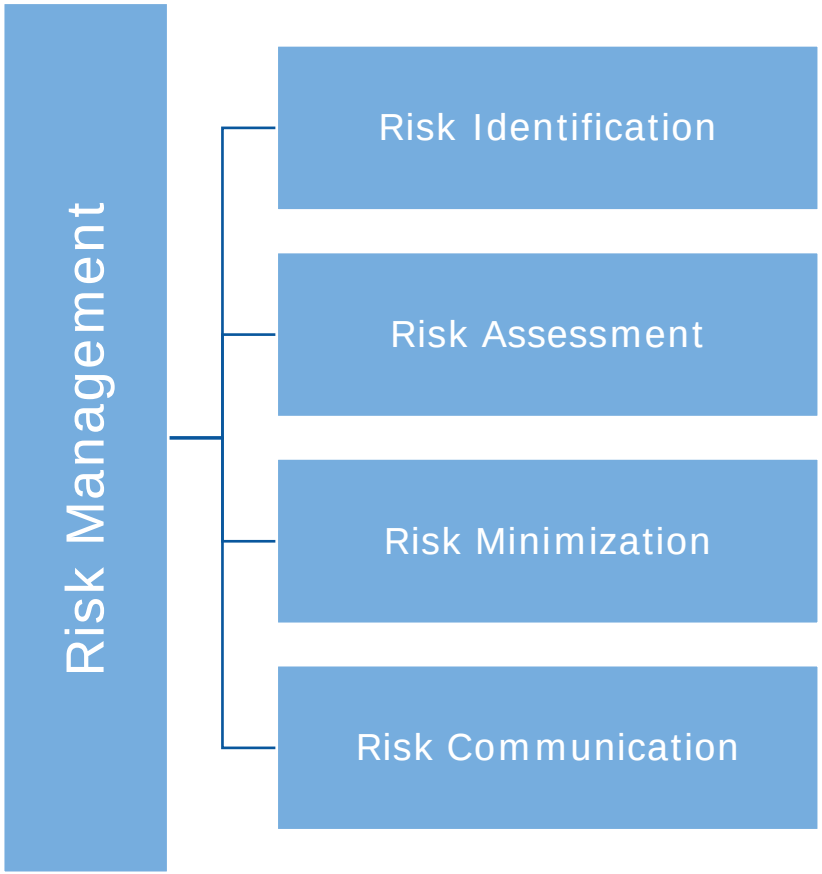
- The objective of a risk management strategy is to ensure a positive benefit risk balance over time in real world setting
- To propose a structure for a pharmacovigilance plan and safety specification that summarizes the identified and potential risk of a medicinal product

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

EU: In addition, assessment of the impact of pharmacovigilance activities



- 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?

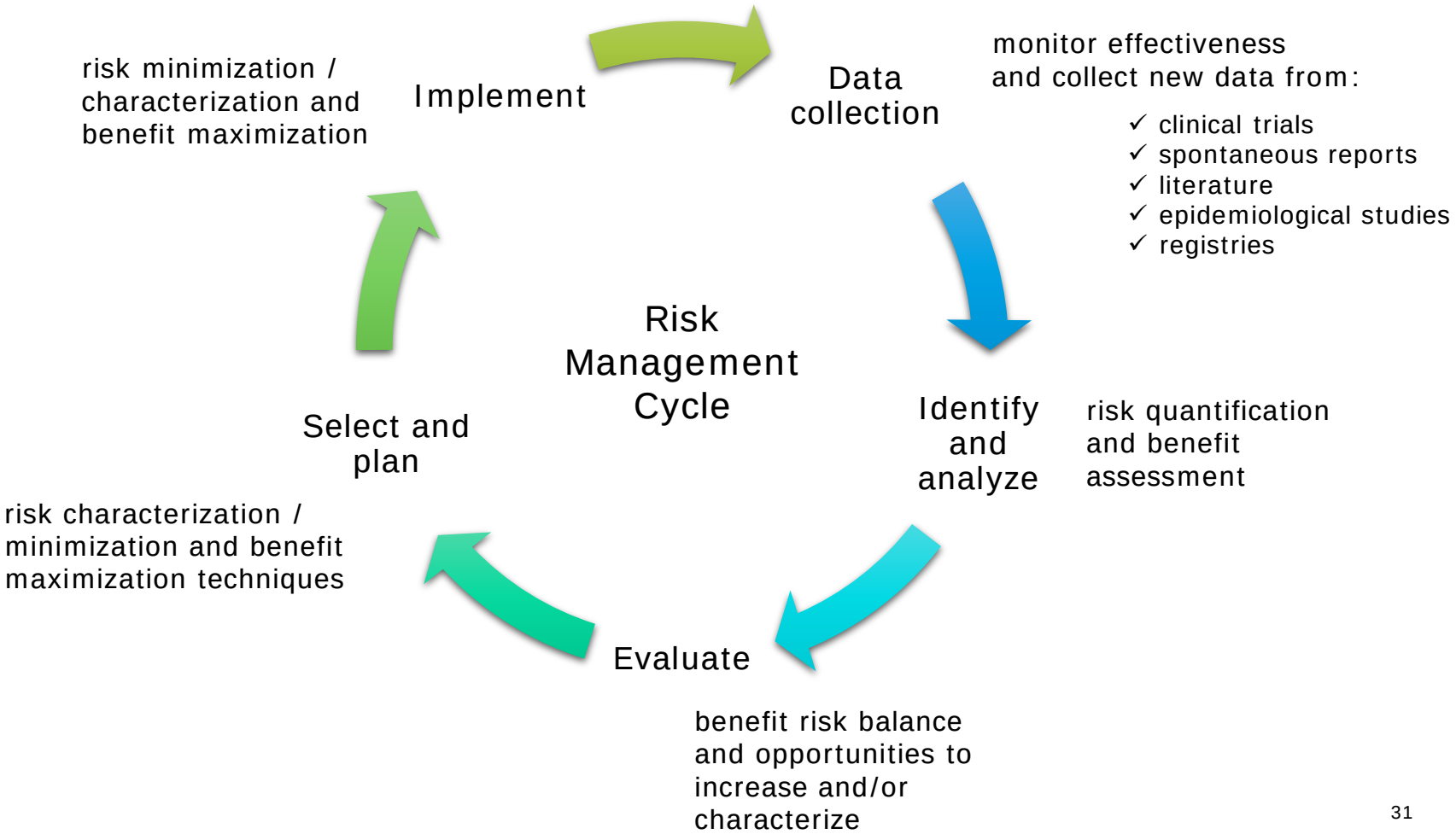
In general, an important risk is any risk that is likely to be included in the contra-indications / warnings and precaution section of the product information.

Clearly an important risk!

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 System (RMS)
Definition GVP Module V

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

Part II Safety Specification of EU RMP

- All identified or potential risks compiled, along with a record of what is missing in terms of safety information

Risk assessment / PV planning

Part III Pharmacovigilance Plan of EU RMP

- Plan for further identifying, characterizing, and assessing risks
- Planning contains both routine and additional pharmacovigilance activities

Risk Management Plan (RMP)

Part V Risk Minimization Measures of EU RMP

- Plan for minimizing the risk
- Integral part of the risk management plan
- Contains routine and additional risk minimization activities

Risk Management Plan (RMP)
Principles

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

Identify or characterize the safety profile of the medicinal product(s) concerned

Indicate how to characterize further the safety profile

Document measures to prevent or minimise the risks associated

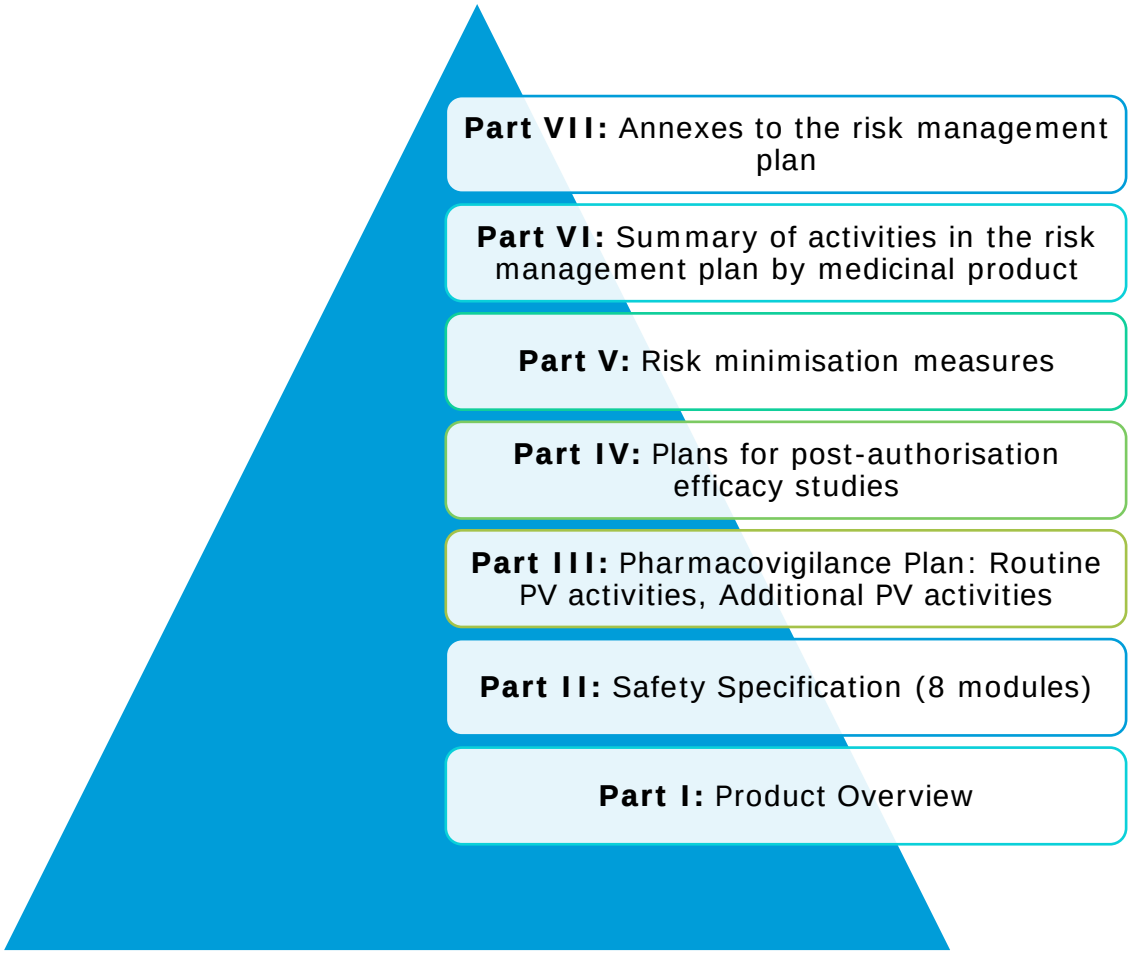
including assessment of effectiveness of the interventions

Document post-authorization obligations that have been imposed as a condition of marketing authorization

Implicit requirements:

- Describe what is known about the safety profile
- Indicate level of certainty that efficacy shown in clinical trials is seen in everyday practice
- Include how effectiveness of risk minimisation measures will be assessed

Structure of an EU Risk Management Plan for Vaccines



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

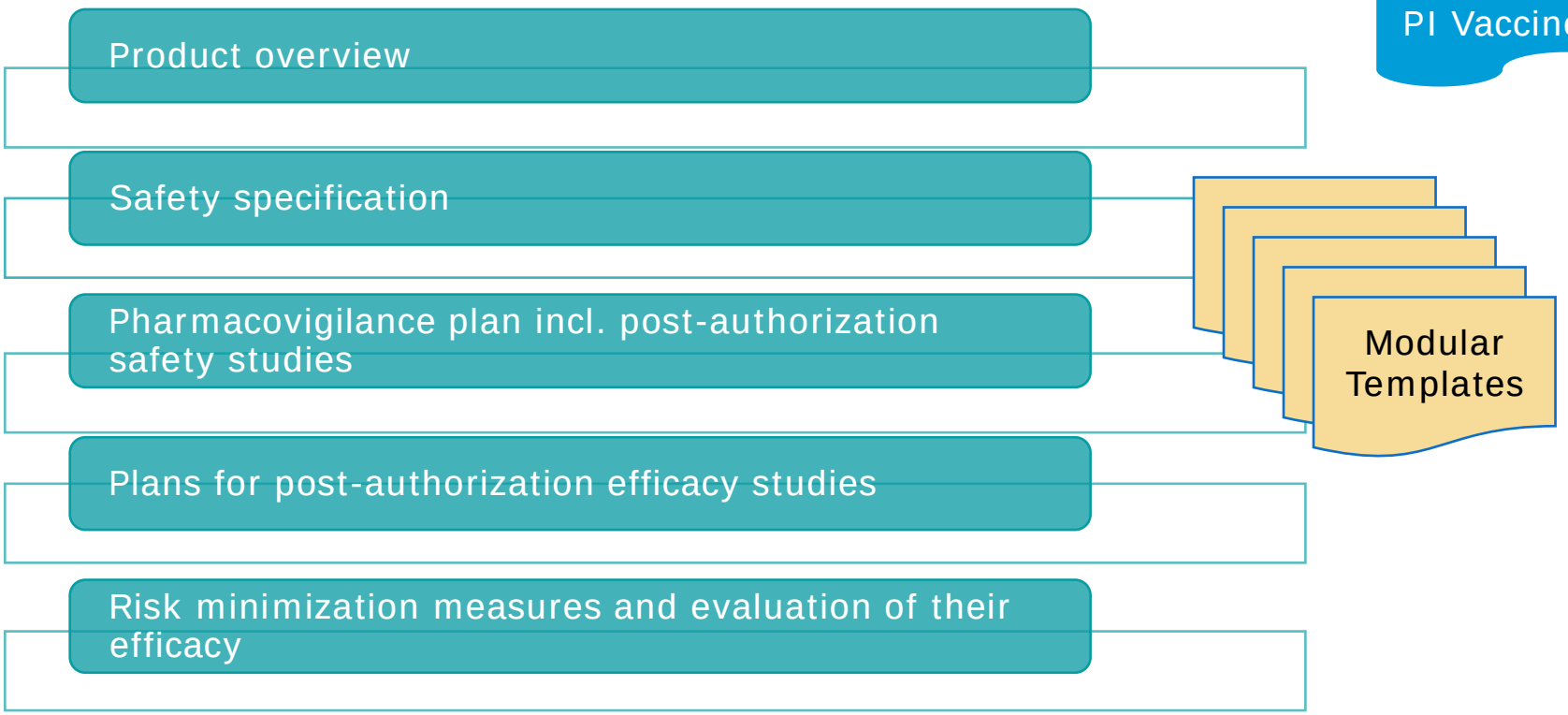
Preparation of RMP
Regulatory guidance and structure

Core RMP follows EU requirements

- GVP (Good Pharmacovigilance Practice) Module V
- GVP PI: Product- or Population-Specific Considerations I: Vaccines

GVP Module V

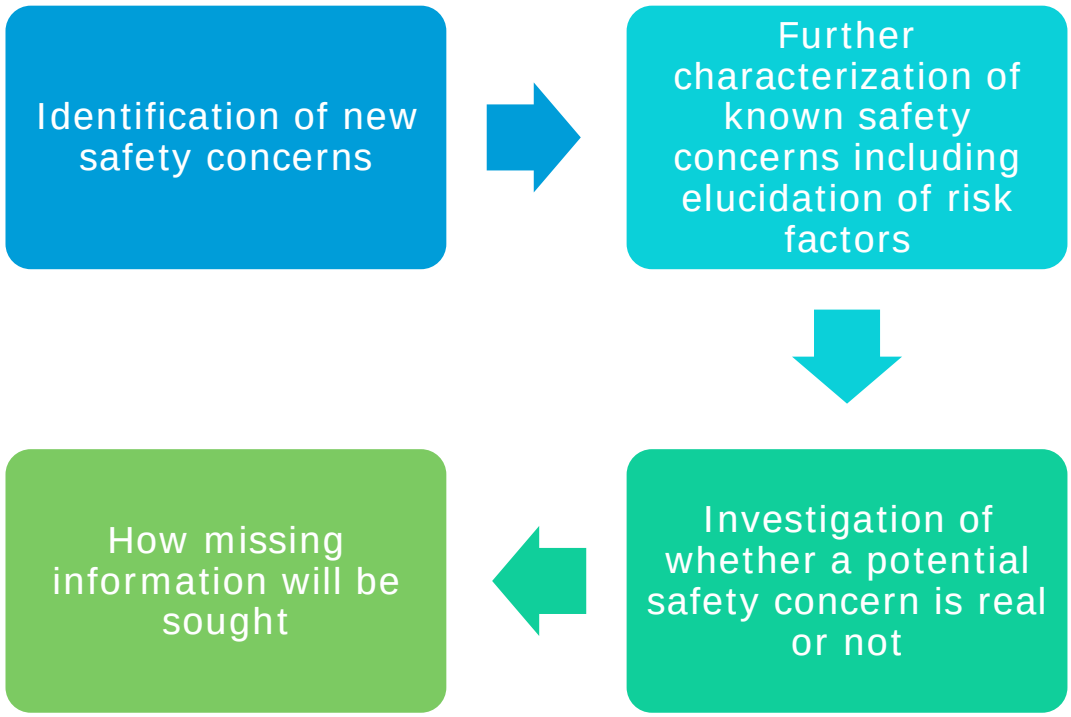
GVP PI Vaccines



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



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

GVP Module V

GVP PI Vaccines

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