Joint Working Group Workshop

Clinical – Regulatory – Pharmacovigilance
Delhi, February 16th – 17th 2026

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Signal Management
Risk Management
Benefit-Risk Management

An integrated framework

Protecting
people from
global diseases
since 2000.

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Agenda

01	Conceptual Framework - Signal / Risk / Benefit-Risk How the Three Domains interact
02	Signal Management
03	Risk Management
04	Benefit-Risk Management

The Integrated Conceptual Framework

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The Signal – Risk – Benefit-Risk Framework

The dynamic input-decision-action-re-assessment loop

Signal Management

- Evidence engine of risk management – signals trigger questions (risk?)
- The question is answered through risk and benefit-risk management tools

Benefit-Risk Management

- The continuous evaluation of the benefit-risk balance drives the RMP content and the PSUR / PBRER updates throughout the lifecycle.

Risk Management

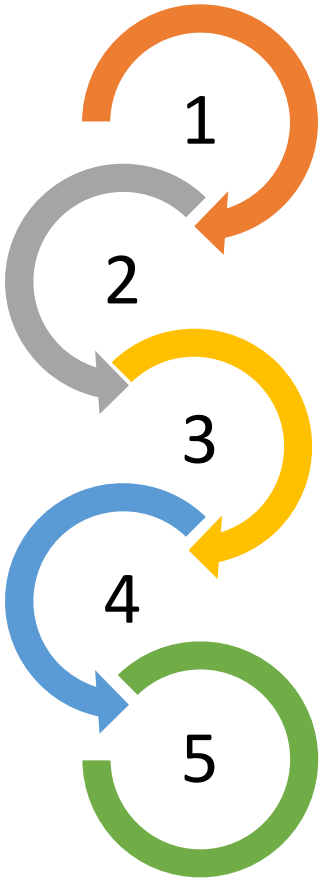
- Operationalization of the benefit-risk assessment – risks modify the benefit-risk balance

The Signal – Risk – Benefit-Risk Framework

The high-level end – to – end structure

1. Signal Detection

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



2. Signal Validation and Evaluation

- Alternative causes
- Verification of new information
- Priority assessment
- Causality assessment

3. Risk Assessment / Characterization

- Extent of risk
- Impact of risk
- Characterization of the risk

4. Benefit-Risk Evaluation

- Structured, clear explanation of methodology and reasoning
- Clear assumptions, considerations and judgment and weighing
- Supporting the B / R conclusions
- **DSUR / PSUR / RMP (update)**

5. Risk Minimization / PV Activities / Effectiveness Evaluation

- Risk mitigation strategy
- Risk mitigation plan

Signal Management

- Signals in Pharmacovigilance
- Signal Management Process
- Signal Detection Methods
- Signal Evaluation and Risk Assessment

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What is a Safety Signal?

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**"

A safety 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, WHO, EMA)

Relevance of Safety Signals

Early risk identification

- To detect previously unrecognized adverse events (AEs, AEFIs)
- To ensure that emerging safety concerns are not missed.

Real-world monitoring

- Vaccines administered to diverse populations not fully represented in clinical trials
- Signal detection captures “real-world” data, including rare or delayed effects.

Data-driven decisions

- To allow regulators and pharmaceutical companies to make evidence-based decisions
- May lead to changes, e.g., updating product labels, restricted use, withdrawal of product.

Public Health protection

- Timely detection of safety issues prevents harm and builds public trust in regulatory systems.

Sources of Safety Signals

Early / potential signals

Safety data from clinical development:

- ✓safety surveillance in clinical trials (incl. signal from pre-clinical)
- ✓look for anticipated risks
- ✓expected for new drugs / vaccines

Single case signals (“striking cases“)

Single important serious cases from any source

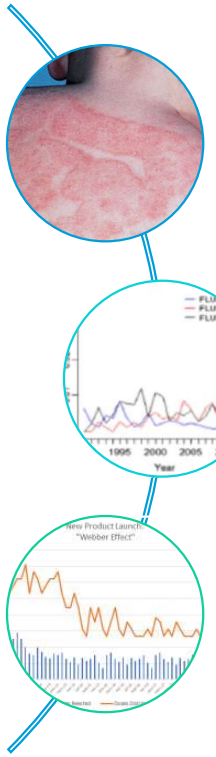
- ✓Focused medical evaluation

Multiple statistical signals

- ✓ Spontaneous reports from various safety databases:
  VigiBase, EudraVigilance, VAERS, NRA databases, Company databases
- ✓From case series, PSURs / PBRERs etc.
- ✓From registries, electronic health records (EHR), etc.

Information from other sources

- ✓Scientific literature
- ✓Reports from regulatory authorities
- ✓Media / internet
- ✓Other databases (e.g. insurance claim databases, patient databases etc.)
- ✓Competitive intelligence, etc.



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

Signal Management

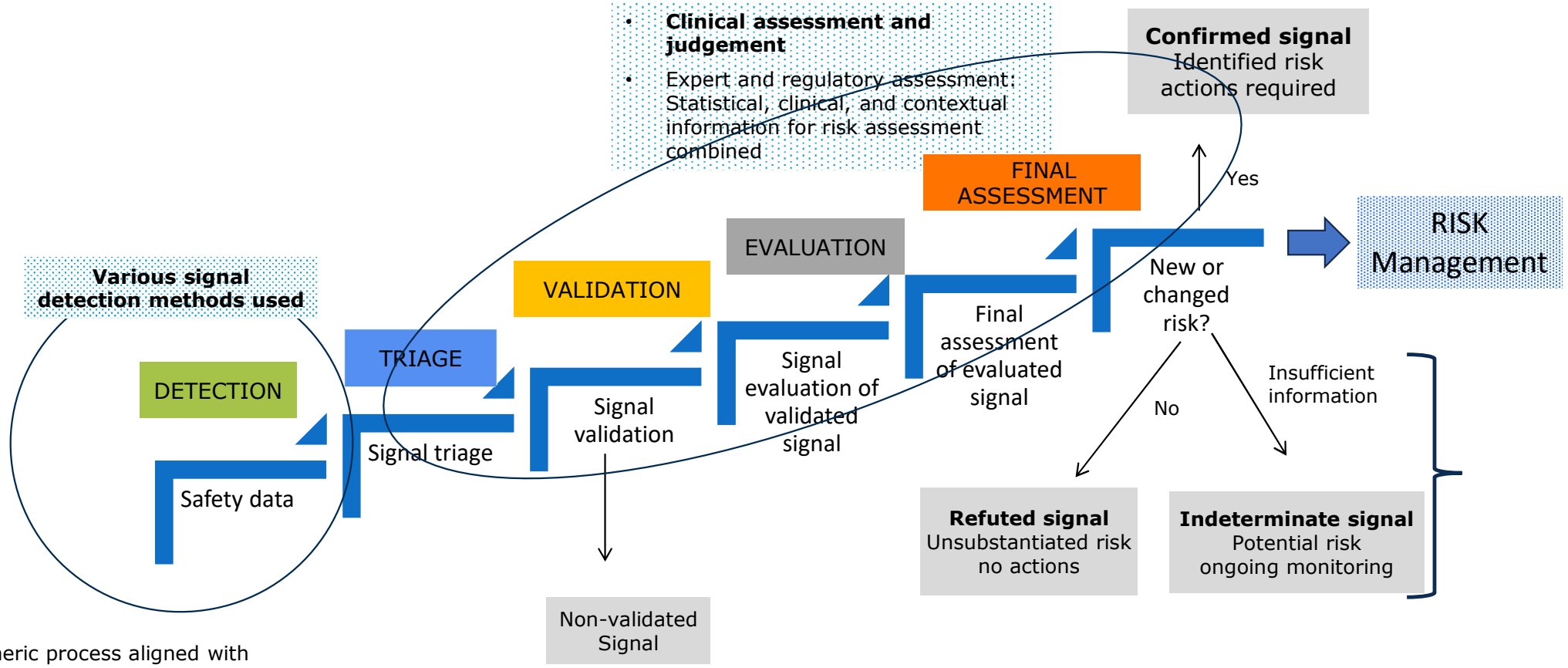
Continuous, life-cycle oriented systematic evaluation of data using evidence-based and risk-proportionate prioritized processes.

Signal management process: A set of **activities** performed **to determine** whether, based on an examination of individual case safety reports (ICSRs), aggregated data from active surveillance systems or studies, scientific literature information or other data sources, there are **new risks** associated with an active substance or a medicinal product or whether **known risks have changed**, as well as **any related recommendations, decisions, communications and tracking.** *EMA GVP Module IX (Rev1)*

Core Principles

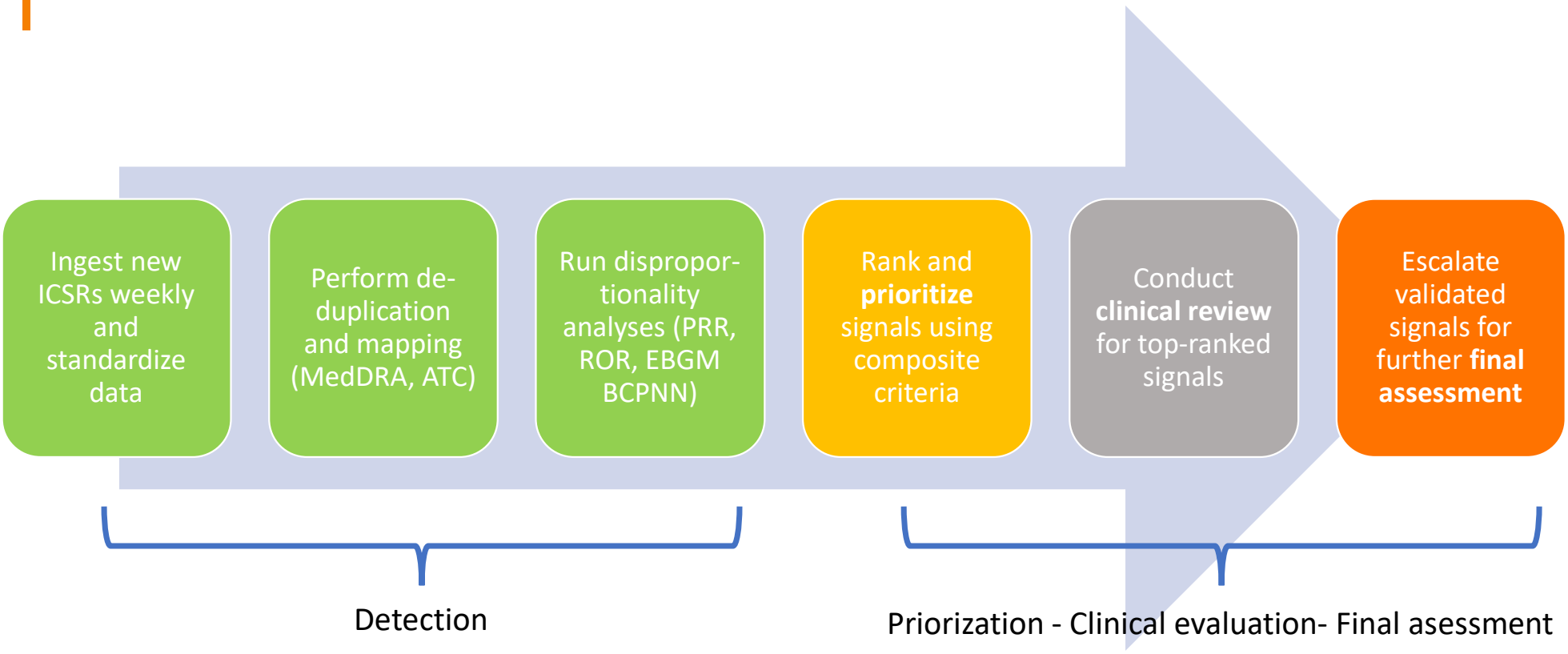
- Early identification of new or changing risks
- Scientific rigor
- Prortionality
- Timeliness
- Transparency and traceability
- Life-cycle approach
- Use of multiple data sources

Signal Management Process
Detection and Evaluation



Generic process aligned with
CIOMS VIII and GVP Module IX / Addendum I

Example of a Signal Management Workflow



Signal Detection and Evaluation
Supporting Tools

Standardized nomenclature to describe event	MedDRA: which granularity screening level (e.g.,SOC, HLT, PT)
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 Methods

- **EU GVP** Module IX R1 and GVP IX Addendum on Signal Management and CIOMS WG Report 2010 **provide guidance on methods and structures**
- **No gold standard**, methods need to be adapted respective data sets as not all methods may be appropriate

Qualitative Detection

- Case-by-case analysis
- Case series analysis

Method preferred when performing signal detection in small data sets: Flagging issues of interest when a report is first received

Quantitative Detection

- Disproportionality analysis (Spontaneous reports / Data mining)
- Observed versus expected analysis ((O/E)
- Rapid Cycle Analysis (RCA)
- Self-controlled Designs - epidemiological method used in Active Safety Surveillance
- Machine Learning (ML) – evolving research

Case – by Case Analysis

Definition:

- Refers to the manual screening and **systematic, non-statistical review of individual case safety reports (ICSRs)** and other sources of safety data to identify new, potential causal relationships between a vaccine and an adverse event.
- Relies on expert clinical, pharmacological, and epidemiological judgment.

Data Sources

- **Spontaneous reports** (e.g., from HCP, patients / consumers, national pharmacovigilance centers, manufacturers, or EudraVigilance/VigiBase,)
- **Published literature**
- **Regulatory agency communications**
- **Scientific meetings, news reports**
- **Non-standard data sources** (emerging area:social media, web fora)

Core Priniples:

- **Clinical review:** Evaluation of ICSRs for clinical plausibility (causality), consistency, and specificity.
- **Pattern recognition:** Looking for unusual or repeated adverse events, unexpected clusters, or temporal trends.
- **Expert judgment:** Medical assessment that integrates pharmacology, pathophysiology, and background epidemiology.
- **Contextual interpretation:** Considering exposure, background rates, and confounding factors.

Case - Series Analysis

Definition:

- Case-series report and analyze the clinical, demographic, therapeutic and outcome characteristics of several patients with the same disease or exposure, without control group
- In **Pharmacovigilance**: Structured synthesis of multiple case reports describing the same event – vaccine / drug pair to identify consistent patterns and evaluate signal strength.
- Bridges qualitative assessment and early epidemiologic quantification

Best practices

- **Standardized qualitative review of cases** - e.g., use of a signal review template
- **Multidisciplinary review panels:** clinicians, epidemiologists, data scientists
- **Structured case assessment forms** for consistency
- **Traceability** of the expert reasoning (audit ready signal management process)

Case selection criteria:

- Same drug / vaccine event pair:
- defined timeline,
- inclusion of all medically confirmed cases

Structured data extraction:

- demographics
- event-type and outcome,
- time to onset,
- for drugs de- / rechallenge
- causality assessment,
- concomitant exposures

Pattern analysis:

- Temporal patterns: Cluster after product introduction
- Clinical patterns: similar symptoms, onset and pathology.
- Pharmacological / immunological patterns: mechanism plausibility, dose-response
- Geographical pattern: Isolated, regional, global

Qualitative Signal Detection
Strengths and limitations

Strengths

- Ability to detect novel, rare and unexpected events
- Inexpensive and easy – preferred method in small data sets
- Lays groundwork for future active safety surveillance studies
- Integrates clinical, pharmacological / immunological context
- Can identify complex syndromes missed by algorithms

Limitations

- Data quality often questionable – missing or inaccurate data
- Underreporting and / or selective reporting
- No controlled environment, not a true epidemiologic study
- Difficult to quantify magnitude of risk
- Causality assessment difficult
- Confounding: disease linked with outcome; diagnostic bias
- Time and resource intensive
- Not suited for the detection of
  - Delayed reactions
  - Adverse reactions with high background incidence

Quantitative Signal Detection

Disproportionality analysis (Data source: Spontaneous reporting databases)

- Established method used in Pharmacovigilance by regulators and industry to identify potential signals.
- Many software tools available (signal detection analytics with respective dashboards) included in commercial electronic safety databases (e.g., Oracle Empirica).

Observed versus Expected analysis O/E (Data source: Data with exposure denominators, e.g., vaccine registries, EHRs, claims data, spontaneous reports with denominator available)

- Analyses of risk disproportions.
- Quantitative estimation of excess risk.
- Complementary to analyses of reporting disproportions (Disproportionality analyses).
- Rapid Cycle Analysis RCA.

Disproportionality Analysis

Definition:

- Refers to the **systematic use of statistical and data mining methods** to identify disproportionately reported drug / vaccine – event pairs in **large pharmacovigilance databases.**
- Goal to **detect unexpected reporting patterns** indicating a new safety issue (hypothesis generation).
- Goal to **prioritize potential safety signals** for clinical review.
- Disproportionate analysis is the *starting point* — confirmation requires **clinical judgment and robust epidemiological evidence**.
- Results are highly situation-dependent, influencing factors, e.g.:
  - reporting sources / collection methods
  - type of medicinal products in the database
  - medicinal terminology / coding
  - date of creation of database

Core Priniple:

- "Is what we observe different from what we expect?"
- Compare the **observed number of reports** of a specific vaccine – event combination with the **expected number of reports**, assuming independence between vaccine and event.
- If the event is reported **more frequently** with the vaccine than with other pairs, further review is warranted.

Disproportionality Analysis
2 x 2 Contingency Table

	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

Proportional Reporting Rate (PRR) = [A/(A + B)]/[C/(C + D)]
Reporting Odds Ratio (ROR): (A/C) / (B/D

Interpretation:

- **PRR > 2**, with ≥ 3 cases and chi-square ≥ 4 is often **used as threshold** for the statistical signal (signal of disproportionate reporting SDR)
- **No gold standard**, signal must be evaluated in the clinical context
- PRR and ROR with 95% CI: lower bound of 95% CI ≥ 1 and number of individual cases: ≥ 3

Statistical Methods
Disproportionality Analysis

- Many pairs have **very low counts**, especially for rare events leading to false positive signaling.
- Classical measures like **PRR** or **ROR** can be **unstable** for small numbers.
- Bayesian statistics have been introduced for more robust and reliable measures than simpler frequentist PRR and ROR measures.
    - An Empirical Bayes approach is the **Empirical Bayes Geometric Mean model EBGM** developed by FDA and used e.g., by FDA and MHRA**.**
    - The **Bayesian statistical model BCPNN** used by WHO Uppsala Monitoring Center UMC for signal detection in VigiBase.

Bayesian Statistics
(based on Bayes theorem)

- Without including prior knowledge, we are over-sensitive to data - leads to false (positive) signals
- Combines prior knowledge (a priori) with new data
    - Data consistently updated on addition of new data
- Update prior beliefs (priors) with observed data (likelihood) to obtain updated beliefs (posterior).
- Gives results as probabilities of outcomes or effects:
    - Produces full posterior distributions, enabling direct probability statements (e.g., "There's a 95% probability that the effect size exceeds zero").

Disproportionality Analysis
Strengths and Limitations

Strengths

Hypothesis generation (screening tool): Early identification of potential rare and unexpected safety signals in spontaneous reporting systems .

Scalable and automated use: Continuous near real-time monitoring and applied automatically.

Objective and transparent: Explicit statistical rules.

Quantification of association: Numeric measures with credibility intervals.

Noise reduction: false positive signals reduced and more reliable prioritization through statistical shrinkage.

Standardization across systems: Global signal comparison and collaboration.

Limitations

Dependent on reporting quality: Biased by underreporting, duplicate, or incomplete reports.

Not proof of causality: A signal means *"more reports than expected,"* not that the vaccine *caused* the event.

Influenced by external factors: Media attention, regulatory actions, or vaccination campaigns can distort reporting rates.

Denominator uncertainty: The true number of exposed individuals is often unknown or imprecise.

Masking and confounding: Common or severe events can mask other signals; co-administered products may confound results.

Instability for rare events: Small numbers can produce spurious or highly variable estimates.

No control for time trends: Cannot easily distinguish new versus ongoing risks.

Simulated Disproportionality Analysis
Example

Simulated analysis of 200 spontaneous reports (ICSRs) from 3 vaccines (VaxA, VaxB, VaxC).
Event-vaccine pairs with higher reporting rates (PRR and EBG) identified. Top 10 ranked signals below.

Rank	Product	Event (PT)	Reports	Countries	EBGM	EB05	PRR
1	VaxA	Anaphylaxis	8	4	12.3	9.5	5.2
2	VaxB	Fever	15	5	6.8	5.1	3.4
3	VaxC	Rash	12	6	4.1	3.0	2.5
4	VaxA	Headache	10	4	3.9	2.9	2.2
5	VaxB	Myocarditis	5	3	3.7	2.8	2.0
6	VaxA	Fatigue	14	5	3.2	2.4	1.9
7	VaxC	Seizure	4	2	2.8	2.0	1.8
8	VaxB	Arthralgia	6	3	2.7	1.9	1.7
9	VaxC	Lymphadenopathy	7	4	2.6	1.8	1.6
10	VaxA	Injection site pain	9	4	2.5	1.8	1.5

Priorization table.

Product	Event	EB05	PRR	Reports	Action
VaxA	Anaphylaxis	9.5	5.2	8	Expedited review
VaxB	Fever	5.1	3.4	15	Clinical triage
VaxC	Rash	3.0	2.5	12	Monitor

Decision thresholds:
- EB05 ≥ 2 and ≥3 distinct reports: potential signal.
- PRR ≥ 2 and chi-square ≥ 4: supportive evidence.
- Reports from ≥2 countries: higher priority.

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Observed to Expected Analysis /1

- O/E analysis distinct but complementary to disproportionality analysis.
  - "do we see more actual cases than we would expect given exposure volume and known background rates?"
- O/E analysis relies on aggregate data without individual linkage.
- O/E analysis compares observed rates calculated from spontaneous reporting systems or cohort event monitoring CEM with expected background incidence rates from independent sources.
- O/E analysis is often used for vaccines when the AEFI is acute and short term to refine safety signals or within the signal management process.

Background rates

- **Historic comparisons** of adverse event rates with the expected rate within a general population is a common vaccine safety surveillance method.
- **Background rate comparison** methods using observational data (e.g., electronic health records, administrative claim data etc.) may generate high numbers of false positive signals.
- **Within-database background rate comparisons** using observational data is sensitive (low type 2 error) but unspecific (high type 1 error) to identify safety signals.
- **Age and sex-adjusted rates** and "time of risk" are crucial to minimize false-positive safety signals.
- **Caution when comparing background rates** across literature and data sources, analysis methods, healthcare systems and populations.
- Availability of "**locally relevant" background rates** of disease incidence important for vaccine safety surveillance.

Observed to Expected Analyses /2

Calculation of the expected number of cases for an AESI Y – Example:

- 3,000,000 doses of vaccine X sold world-wide
- Increased risk of Y within 30 days p.v., whatever dose
- Vaccination schedule: 3 doses at 2,4,6 months
- Assumptions: no dose effect and all 3 mio doses administered:
- **Person-time at risk**: 3,000,000 x 30 person-day= **2.46 / 100,000 person-years** (3,000,000 x 30/365 x 1/100,000)
- **Background incidence rate** for event Y is **4.8 cases per 100,000 person-years** (measured on unvaccinated population sharing similar demographic characteristics with the exposed population)
- **Expected number of cases of event Y:** 2.46 x 4.8 = **11.8**

Conclusions rely on multiple assumptions:

- Number of administered doses administered to population known.
- Cases presenting the adverse event are mainly spontaneously (passively) reported (e.g., in registries, EHRs).
- Background rate in the vaccinated population the same as in the population used to calculate the expected rate.
- Population on which the background incidence was measured is not exposed to the vaccine of interest.
- Risk period considered focuses on time period for which an excess of risk occurs in case of causal association.

Safety concerns for O/E analysis from:

- literature review data,
- medical reviews,
- disproportionate reporting,
- unexpected temporal relationship,

may trigger O/E analyses of spontaneous reports where clear knowledge on causality or magnitude of risk is lacking.

Observed to Expected Analysis
Strengths and limitations

Strengths

Real risk estimation: Accounts for exposure denominators.

Useful for vaccines and new products with massive rollouts.

Can stratify by age, sex, dose and region.

Bridge between spontaneous signal detection (complements disproportionality methods) and formal epidemiologic investigation.

Limitations

Requires reliable data on exposure and background incidence.

Sensitive to misclassification or under-ascertainment.

Needs harmonized definitions and time-at-risk assumptions.

Overview of the Complementary Methods
Disproportionality – Observed / Expected

Feature	Disproportionality (PRR, ROR, BCPNN, EBGM)	Observed vs Expected
Data type	Spontaneous reports	Data with exposure denominators (registries, EHRs, vaccine surveillance)
Denominator	Number of reports	Number of exposed persons / doses
Reference	All other drugs / vaccines or events	Background incidence rate
Output	**PRR / ROR**	**Relative risk (observed/expected)**
Use case	**Hypothesis generation**	**Hypothesis confirmation / signal validation**
Level of inference	**Suggestive of association**	**Quantitative estimation of excess risk**

Extension of the Observed to Expected Analysis Rapid Cycle Analysis RCA

Definition:

- A near real-time method to compare observed vs expected rates of pre-specified adverse events after exposure.
- Performs O/E comparisons repeatedly as data accumulats (e.g., weekly, monthly).
- Outcome definitions and windows pre-specified.
- Sequential testing for continuous monitoring, e.g., using sequential hypothesis testing.
- Widely used by e.g., VAERS, vaccine safety monitoring networks, EU Data Analysis and Real-World Interrogation Network (DARWIN EU), EMA during the pandemic to monitor COVID vaccine.

Strengths

- Rapid signal detection with statistical rigor.
- Continuous monitoring without waiting for full data set.
- Adjusts for changing background rates.
- Controls type-1 error (false-positives).
- Formal quantitative trigger for follow-up investigation.

Limitations:

- Requires well-defined exposures and outcomes.
- Potential for confounding by indication, age, etc.

Machine Learning ML Approaches

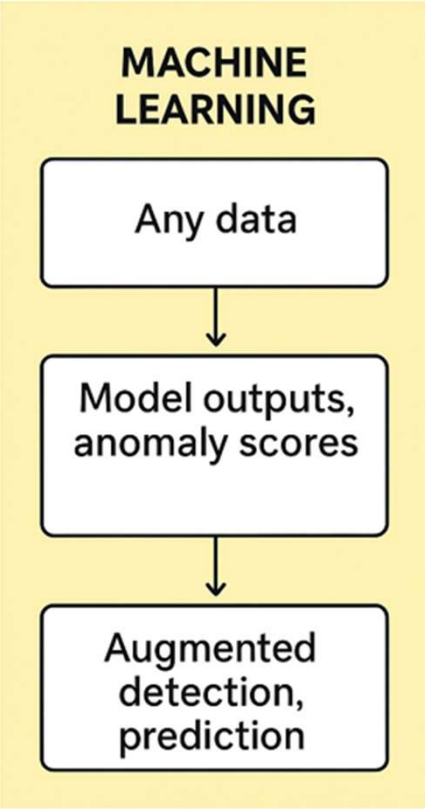
Machine Learning ML approaches are in an **emerging research stage**

Strengths:

- Increasingly explored for signal detection, risk prediction and pattern recognition across high dimensional data.
- Handles non-linear relationships, and large, complex and unstructured data:
  - Text / deep learning models to understand meaning from unstructured text, e.g., automatic extraction from case narratives, detecting emerging signals from social media, literature etc.
- Can detect multivariate associations and automate prioritization of potential signals detected with risk prediction and pattern recognition.

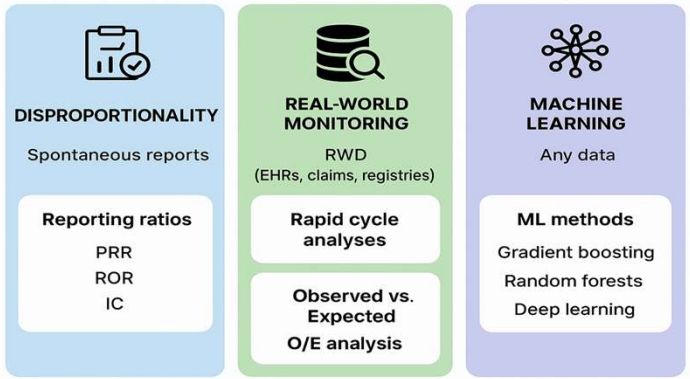
Challenges:

- Explainability and regulatory transparency
- Need for robust validation
- Risk of overfitting spurious correlations



Quantitative Safety Signal Detection
Summary Table

Dimension	Disproportionality	O/E / Rapid Cycle / Self-Controlled	ML-Based
Data	Spontaneous reports	EHRs, claims, registries	Any (structured + unstructured)
Metric	Reporting ratios (PRR, ROR, BPCNN/IC, EBM)	Risk ratios, incidence rates	Model outputs, anomaly scores
Timing	Passive, delayed	Near real-time	Potentially real-time
Confounding control	Minimal	Strong (esp. self-controlled)	Varies by method
Use case	Early signal detection	Active surveillance	Augmented detection, prediction
Regulatory use	Established	Increasingly used (FDA Sentinel, EMA DARWIN EU)	Emerging, research-stage



Early detection methods depend on available **data source** and **timing** of surveillance.

Signal validation

Evaluation of the data supporting the detected signal to verify that the available documentation contains **sufficient evidence** to demonstrate the **existence of a new potentially causal association, or a new aspect of a known association**, & therefore to justify further assessment of the signal.

Clinical review activity:
SNIP Criteria to support validation

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 be seriousness and severity

Prevention

- Potential for preventive measures

Signal Evaluation
Clinical Context

- Disproportionate analysis is the *starting point* in the signal management process.
- Signal evaluation needed for confirming if **detected signal** represents a **“true” (causally associated) signal** for further work-up and risk assessment.
- In-depth evaluation analysis of the validated signal requiring **clinical judgment and robust epidemiological evidence** by multidisciplinary teams (e.g., Safety Management Teams)

Signal Evaluation
Clinical Review

Clinical Review (multidisciplinary):

- Understand the clinical pattern (e.g, case-series clinical assessment)
- Assess the signal at population level (aggregate data review)
- Contextualize the signal (literature and external evidence)
- Understand the clinical impact – robust clinical conclusion with recommendation of appropriate actions

Case Series Clinical Review performed for all relevant cases

- Case narratives reviewed
- Clinical phenotype described
- Time-to-onset distribution analyzed
- Dose number (1, 2, booster) assessed
- Dechallenge / rechallenge reviewed (where applicable)

Aggregate & Epidemiological Evidence Review

- Disproportionality analyses (PRR/ROR/IC)
- Observed vs expected analyses
- Stratification by age, sex, dose
- Comparison with background rates

Literature & External Evidence -Sources

- Clinical trials
- Post-authorization studies
- Case reports
- Immuno-pathological plausibility
- Class /platform effects

Signal Evaluation
Prioritization

High

- Signal with important impact on public health / patient health
- 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

- **Severity, seriousness, outcome** and **reversibility** of the adverse reaction and the potential for prevention.
- Patient exposure and the estimated **frequency** of the adverse reaction-
- Patient exposure in **vulnerable populations** and/or in populations with different patterns of use, where appropriate;
- Expected extent of **regulatory actions** (e.g. label change, addition of adverse reactions, warnings, contraindications, additional risk minimization measures, suspension, revocation).
- Whether the signal is likely to apply to other substances of the same class of medicinal products.

Final Signal Evaluation
Determination if evaluated signal constitutes a risk

Confirmed signal	• **Risk identified** • Vaccine reaction supported by sufficient evidence – action required
Indeterminate signal	• **Inconclusive / potential risk** • Inconclusive / lacking information - ongoing monitoring
Refuted signal	• **Unsubstantiated risk** • Validated signal determined to be “false”, causal association not established – no action required

Effective signal evaluation requires an integrated approach combining robust data collection, qualitative and quantitative methodologies, scientific clinical rigor, regulatory compliance, and technology-enabled monitoring.

Following best practices **allows timely identification and management of emerging safety concerns** – thereby protecting patients / population and maintaining regulatory oversight.

Signal Evaluation Report
Key Principles

A well-structured Signal Evaluation Report should follow best practices:

- Robust assessment of the evaluated signals
- Scientific rigor
- Consistent decision making (e.g., by Safety Management Teams)
- Regulatory compliant
- Traceable
- Timely communication to regulatory authorities as appropriate

Transparency

Clearly report sources, methods, reasoning

Traceability

Maintain the report for regulatory inspection and audit

Consistency

Use standardized formats /templates ensure signal com-parability and over time.

Regulatory alignment

GVP Module IX, CIOMS WG VIII, EMA best practices

Signal Evaluation Report
TOC Example

1. **Signal Identification and Background**
   - Source of signal
   - Signal description
   - Background information
   - Rationale for evaluation
2. **Methods of Evaluation**
   - Data sources analyzed
   - Search criteria and strategies
   - Analytical approaches
   - Causality assessment methods
3. **Results**
   - Summary of evidence
   - Case descriptions
   - Aggregate data evaluation
4. **Discussion**
   - Interpretation of data
     - Strength of association
     - Consistency across sources
     - Alternative explanation
     - Clinical relevance for patients / population
   - Integration with known risks
   - Identification of knowledge gaps
5. **Conclusions**
   - Validation status: Validated, Non-validated, Uncertain / Pending
   - Assessment of Public Health impact
   - Indication of next steps or follow-up monitoring
6. **Recommendations for action**
   - Proposed regulatory or internal action
   - (e.g. Emerging Safety Issue?)
   - Timelines for actions and re-evaluation
7. **Documentation and Traceability**
8. **Supporting Material**

Regulatory Aspects in Signal Management

Regulatory frameworks define how signals must be detected, assessed and communicated by MAHs and authorities.

Regulatory outcomes:

- Label updates (SmPC, PIL, in clinical trials IB update)
- Direct Healthcare Professional Communication (DHPCs)
- RMP update
- PBRER / PSUR update
- Additional monitoring or restriction
- In extreme cases suspension or withdrawalases

Documentation and Audit Requirements

- MAHs must maintain
  - Signal detection procedurse
  - Validation ratiponale
  - Assessment reports
  - Decision logs
- Subject to inspection by regulatory authorities

Signal Management
GVP Module IX

EMA Definition Emerging safety issue:

- Requires urgent attention by the NRA because of the potential **major impact on the risk-benefit balance and/or on patients' or public health.**
- Potential **need for prompt regulatory action and communication** to patients and healthcare professionals.

Examples include:

- Unexpected increased rate of fatal or life-threatening adverse events in a clinical trial.
- Major safety issues identified through spontaneous reporting or scientific literature potentially leading to considering contraindication, restriction / suspension or withdrawal.

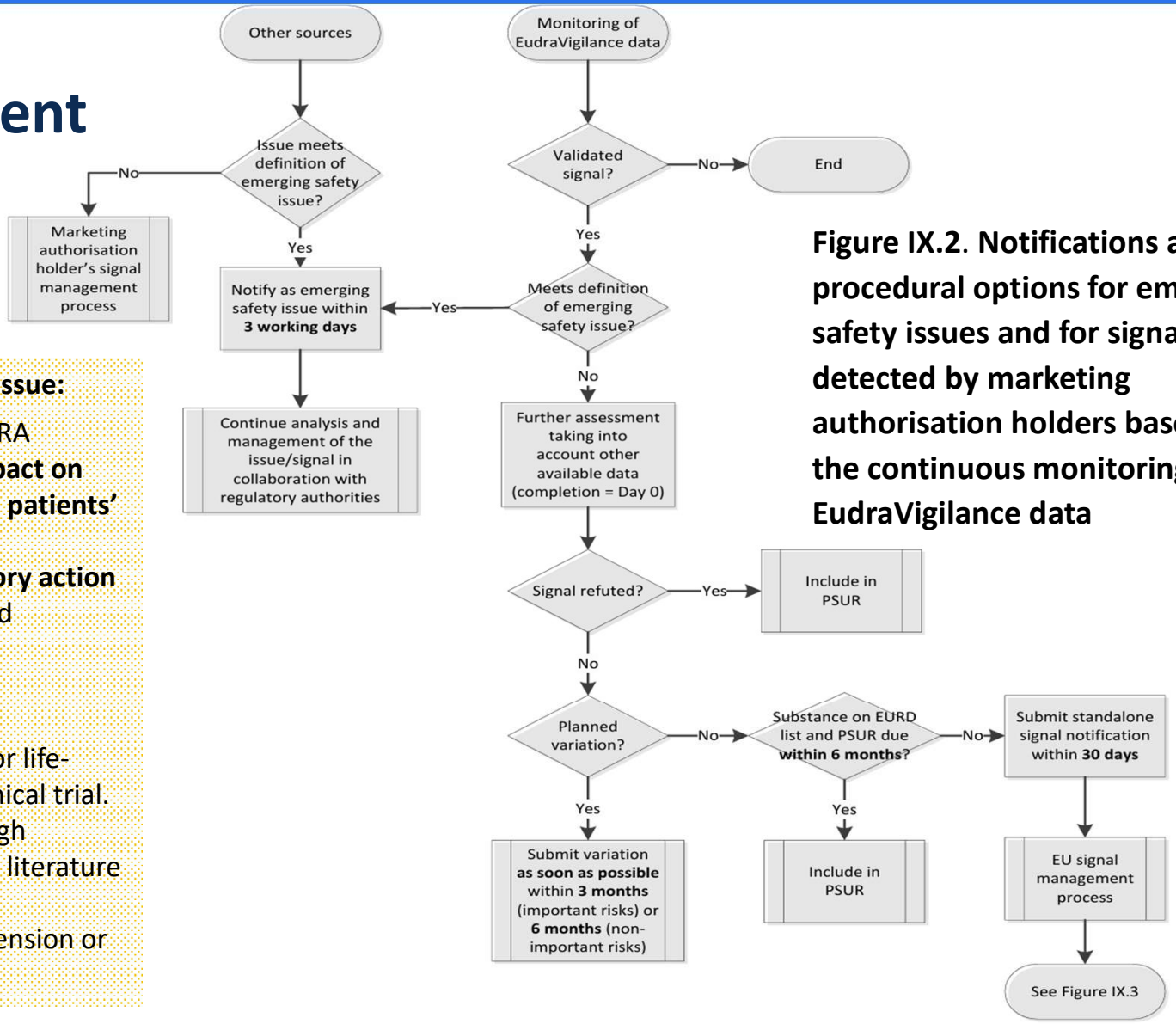


Figure IX.2. Notifications and procedural options for emerging safety issues and for signals detected by marketing authorisation holders based on the continuous monitoring of EudraVigilance data

Tabular Summary of Safety Signals in PBRER /PSUR ICH E2C(R2)

ICH E2C (R2): Appendix C – Example of a Tabular Summary of Safety Signals, ongoing or closed during Reporting Interval

Signal term	Date detected	Status (ongoing or closed)	Date closed (for closed signals)	Source of signal	Reason for evaluation & summary of key data	Method of signal evaluation	Action(s) taken or planned
Stroke	month/ year	ongoing	month/year	meta-analysis (published trials)	statistically significant increase in frequency	review meta-analysis and available data	pending
SJS	month/ year	closed	month/year	spontaneous case reports & one case report in Phase IV trial	Rash already an identified risk SJS not reported in pre authorisation CTs. 4 apparently unconfounded reports within 6 months of approval; plausible time to onset.	targeted follow up of reports with site visit to one hospital. Full review of cases by MAH dermatologist and literature searches	RSI updated with a Warning and Precaution DHPC sent to oncologists Effectiveness survey planned 6 months post DHPC. RMP updated.

Risk Management

- Risk Assessment
- Risk Management
- Risk Managment Process
- Risk Managment Plan
- Generic Life-cycle Risk Managment Model

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Risks in the Context of Pharmacovigilance

Any risk relating to the quality, safety or efficacy of the medicinal product as regards patients' health or public health and any risk of undesirable effects on the environment

EMA GVP Definitions[DIR 2001/83/EC Art 1(28)].

Risk Identification
Assessment

Identified risk	• An untoward occurrence for which there is adequate evidence of an association with the medicinal product (see **confirmed signal)**
Potential risk	• An untoward occurrence for which there is some basis for suspicion of an association with the medicinal product of interest but where this association has not been confirmed (see **indeterminate signal)**.
Missing information*	• Gaps in knowledge about a medicinal product, related to safety or use in particular patient populations, which could be clinically significant.

*ICH E2C(R2) definition: Critical gaps in knowledge for specific safety issues or populations that use the marketed product.

EMA GVP Risk Definitions

Risk Identification
Important Risk

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

An important risk is any identified or potential risk that could have an impact on the risk-benefit balance of the product or have implications for public health

An important risk depends upon several factors, including the impact on the individual, the seriousness of the risk and the impact on public health.

Normally, **any risk that is likely to be included in the contraindications or warnings and precautions section of the product information should be considered important**

EMA GVP Definitions 2025

What is 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
Purpose and Core Principles

Continuous, iterative, proactive process to identify, characterize, prevent and minimize / mitigate risk while ensuring safe use during the product's life-cycle.

The overall and continuing process of minimizing risks and the measurement of the effectiveness of the risk minimizing measures throughout the product's life-cycle to optimize its benefit/risk balance.

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 System (RMS)
Definition

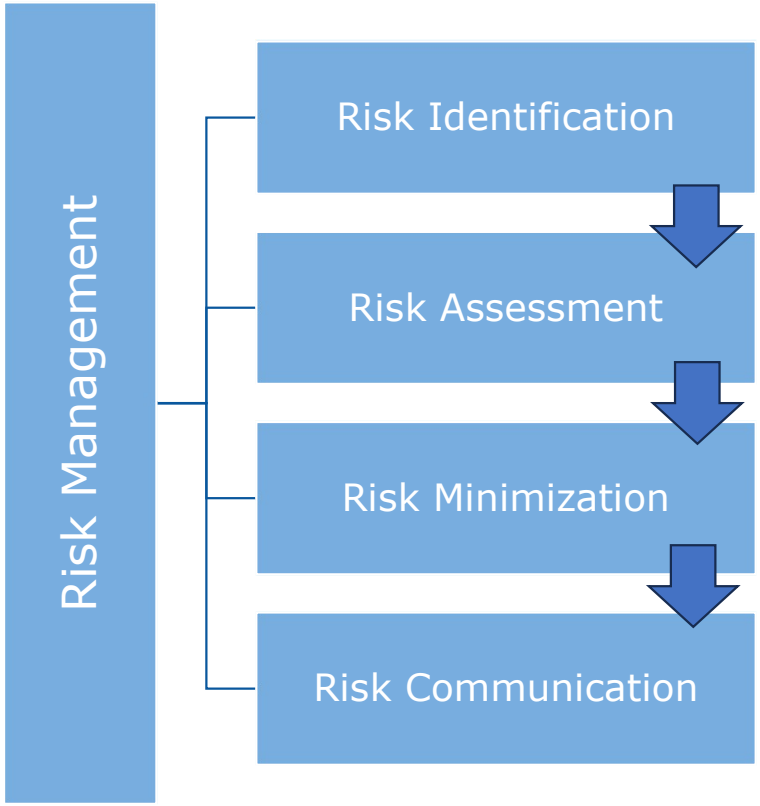
GVP Module V

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 Managment Process



- Risk Management is a complex process which needs a governance structure.
- Safety Management Teams (SMTs) are the operating model to ensure vaccine safety during a vaccine product's life-cycle and to document continuous and permanent safety evaluation of a vaccine product.

Risk Management Process

Risk management is the process of measuring or assessing and developing strategies to manage the risk.

Risk management is based on the three pillars which are covered in the Risk Management Plan.

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

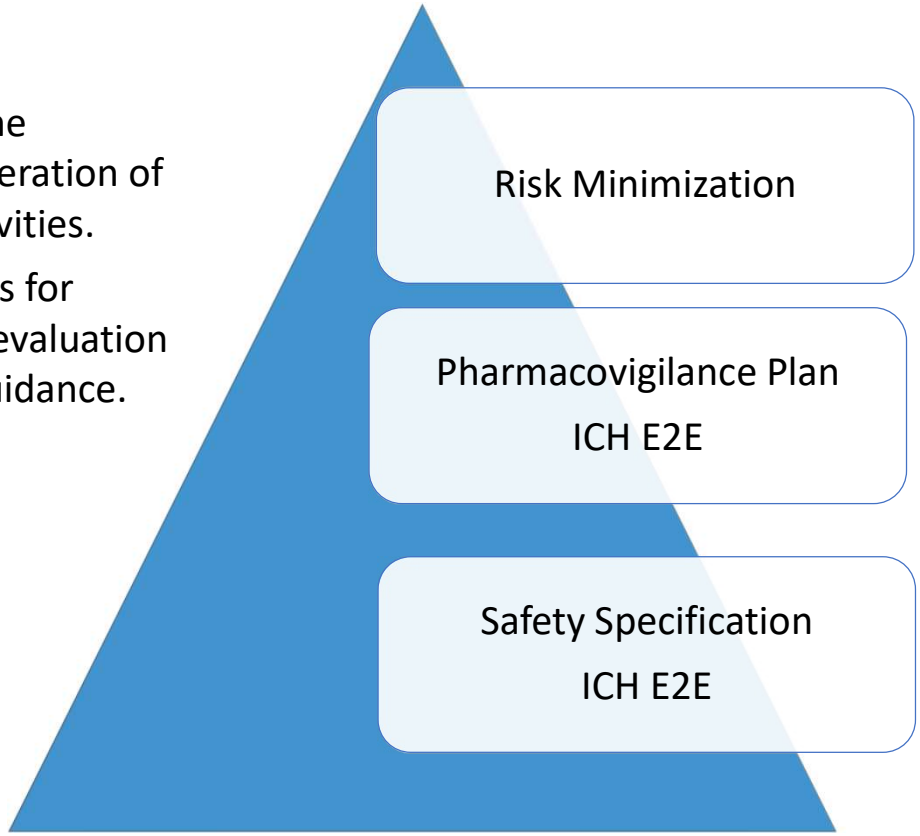
Risk Management Planning (RMP)

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

Pharmacovigilance Planning
ICH E2E

- ICH E2E establishes the principles incl. consideration of risk minimization activities.
- Detailed requirements for implementation and evaluation defined in regional guidance.

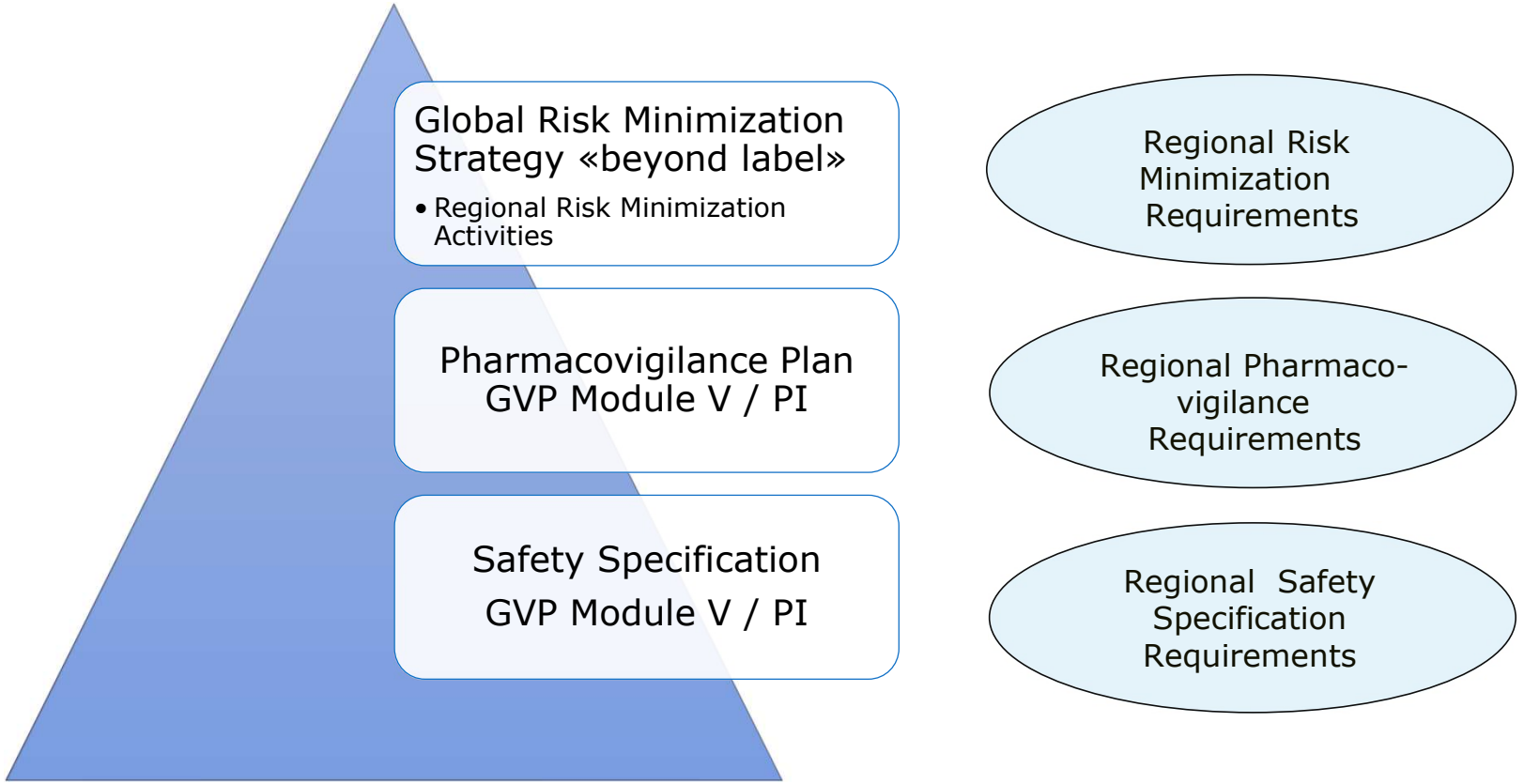


Activities to be taken to minimize the impact of specific safety concerns on the benefit-risk balance, incl evaluation of the effectiveness

Planning of actions to minimize risks based on safety specification; Routine PV practices and specific action plan to investigate specific safety concerns (ICH E2E)

Summary of important identified risks, important potential risks and missing information (ICH E2E)

Global Risk Managment Plan
EU RMP GVP Module V / PI with Regional Variations



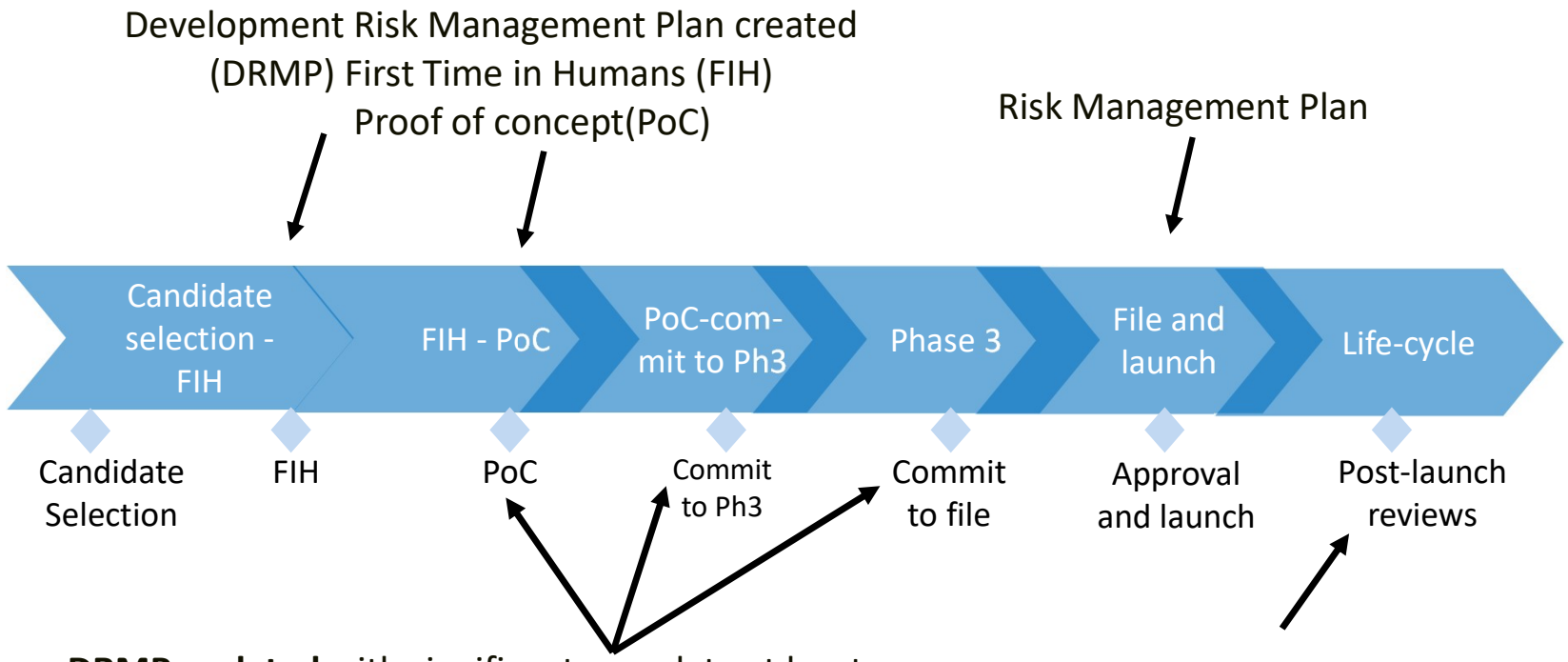
RMP – Consistency with (e)CTD

- RMP Modules modules to map with the CTD
  - Mainly to CTD Modules 2.3, 2.4, 2.5, 2.6, 2.7, 3, 4 and 5
- Consistent information from the RMP to be discussed in the CTD and vice versa

Table V.2. Mapping between RMP modules and information in eCTD

RMP Module	eCTD
Part I Product(s) overview	Module 2.3 Quality overall summary Module 3 Quality
Module SI Epidemiology of the indication(s) and target population(s)	Module 2.5 Clinical overview
Module SII Non-clinical part of the safety specification	Module 2.4 Non-clinical overview Module 2.6 Non-clinical written and tabulated summaries Module 4 Non-clinical study reports
Module SIII Clinical trial exposure	Module 2.7 Clinical summary Module 5 Clinical Study reports
Module SIV Populations not studied in clinical trials	Module 2.5 Clinical overview
Module SV Post-authorisation experience	Module 2.5 Clinical overview
Module SVI "Additional EU requirements for the safety specification"	Data not presented elsewhere in eCTD
Module SVII Identified and potential risks	Module 2.5 Clinical overview (including benefit-risk conclusion) Module 2.7 Clinical summary (SPC)
Module SVIII Summary of the safety concerns	Module 2.5 Clinical overview Module 2.7 Clinical summary
Part III Pharmacovigilance plan (including post-authorisation safety studies)	Module 2.5 Clinical overview Module 2.7 Clinical summary
Part IV Plans for post-authorisation efficacy studies	Module 2.5 Clinical overview Module 2.7 Clinical summary
Part V Risk minimisation measures (including evaluation of the effectiveness of risk minimisation activities)	Module 2.5 Clinical overview Module 2.7 Clinical summary

Generic Life-Cycle Risk Management Planning Model



Risk Management – RMP
Summary

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

Main focus of RMP:

- Post-authorization safety studies.
- Risk minimization plan.
- Risk minimization measures with ensuring effectiveness of measures.
- Pre-and post-marketing benefit-risk management and planning.

Benefit - Risk Management

- Benefit Risk Framework
- Methodologies in Benefit-Risk Assessment
- Benefit Risk Assessment Challlenges

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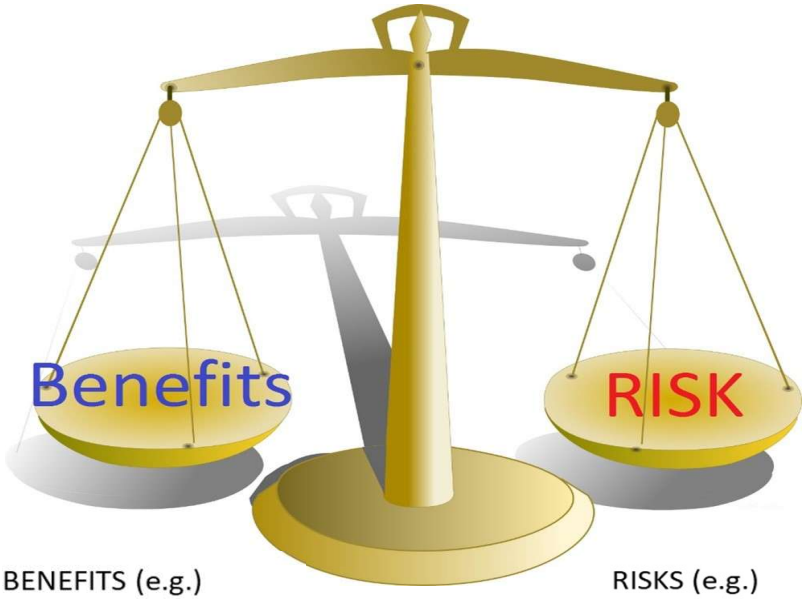
Benefit – Risk Framework

A continuous evaluation of the positive therapeutic effects of the medicinal product in relation to the risks, i.e. any risk relating to the quality, safety or efficacy of the medicinal product as regards to patients' health or public health *(Directive 2001/83 Article 1– Definition of risk and risk/benefit balance).*

Assessment of Safety = Assessment of the Benefit- Risk Balance



BENEFITS (e.g.)

- Severe disease prevention
- Reduced transmission
- Mortality / hospitalisation reduced
- …. etc.

RISKS (e.g.)

- Guillain Barre syndrome
- Thrombcytopenia / VTTS / TTS
- Vasculitis
- Myocarditis
- Encephalopathy
- ADEM (acute disseminated encephalomyelitis
- …. etc.

Benefit – Risk Framework Core Principles

Life-cycle Approach

Benefit-risk assessment (BRA) is continuous, beginning in preclinical development, extending through clinical trials and post-authorization surveillance.

Reflects that the **safety and the efficacy / effectiveness profile evolves over time as new data emerges**. Periodic re-assessment ensures that decisions remain evidence-based.

Evidence-Based Evaluation:

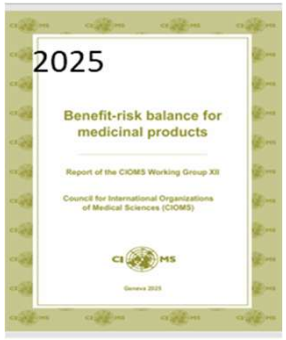
- An **integrated benefit-risk management** relies on **qualitative judgement** (e.g., clinical and contextual interpretation) and **quantitative evidence** (e.g., numerical risk and benefit estimates):
  - Clinical trial data (phase 1-3),
  - Safety data from post-authorization surveillance
  - Epidemiological studies, registries and meta-analyses,
  - Scientific literature
- **Weight of evidence** for benefits versus potential harms (risks) explicitly evaluated **using structured methodologies**.
- The BRA integrates
  - data on the effectiveness,
  - frequency and severity of adverse event / AEFIs,
  - variability among patient population and regions.

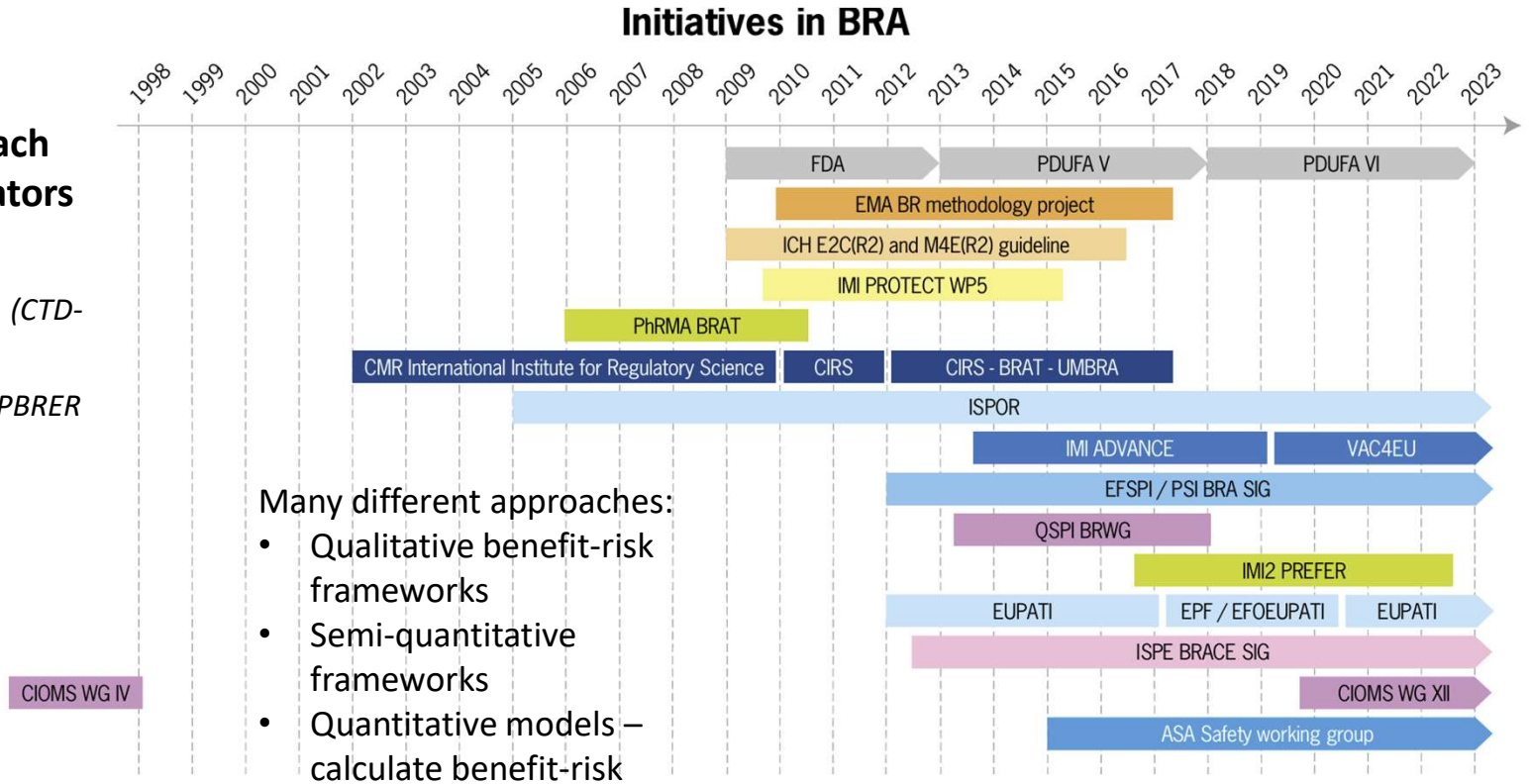
Benefit – Risk Assessment
General concepts

All available data should be considered in benefit – risk assessment	
The nature of the disease to be taken into account for benefit – risk balance	e.g., self-limiting diseases versus diseases with high mortality
Absolute versus relative benefit – risk balance	e.g., alternative therapies to be considered, interpretation of the B / R to involve comparisons (consideration of alternative sources of risk)
Benefit – risk balance is dynamic and evolves over time	
Require cross-functional safety management teams	

Benefit-Risk Assessments
International Key Initiatives

- **No Gold-Standard**
- **No specific approach required by regulators**
- **Guidelines:**
  - **ICH M4E (R2)** *(CTD-pre-approval)*
  - **ICH E2C(R2)** *(PBRER -post-approval)*



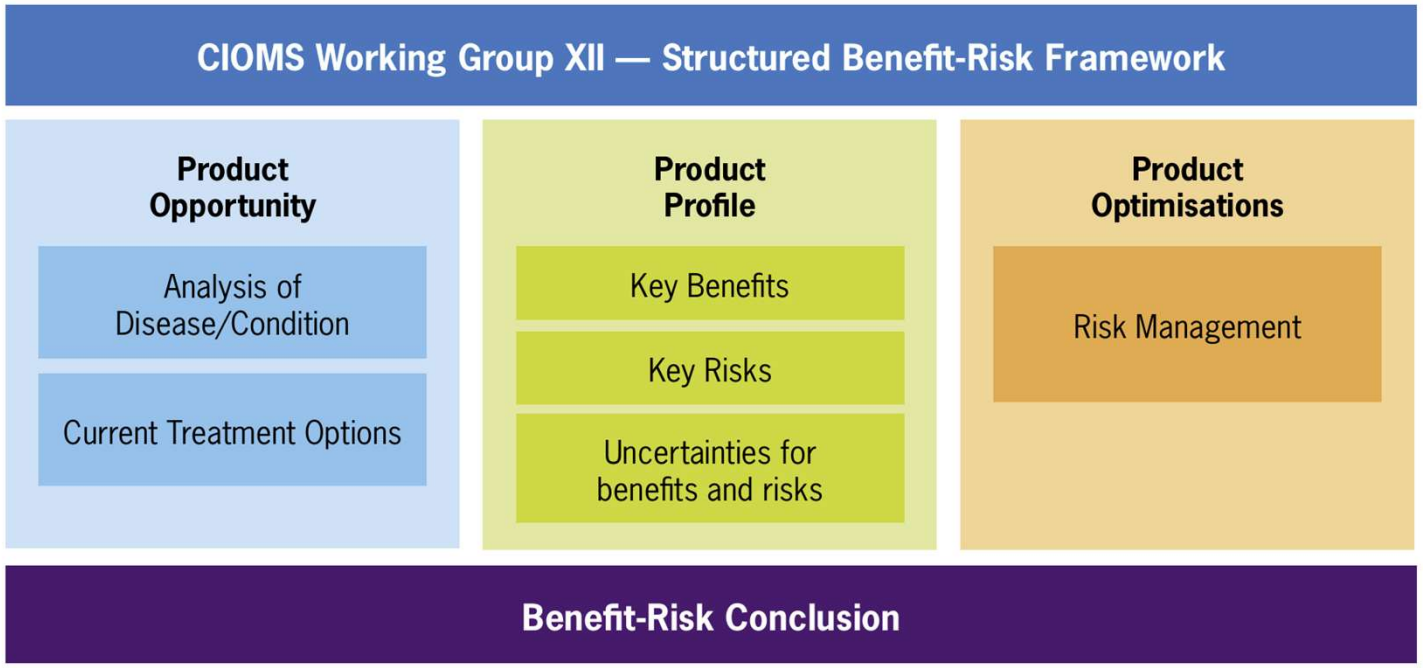


Many different approaches:

- Qualitative benefit-risk frameworks
- Semi-quantitative frameworks
- Quantitative models – calculate benefit-risk

Benefit-Risk Framework
Components of a Structured Framework

Source: Modified from ICH M4E(R2),[12] EMA PROACT-URL, and other BR frameworks [4, 6]



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The US FDA Benefit-Risk Framework

The US FDA Benefit-Risk Framework is a draft guideline. Designed to consider:

- **the therapeutic context** including the condition being treated and treatment alternatives,
- **the evidence on benefits and risks** which are either being submitted for a NDA / BLA or found in the post marketing period,
- **the uncertainties** of the benefits and risks, and
- **the regulatory options** the US FDA has at its disposal to manage risks or reduce uncertainties

Figure 1: FDA Benefit-Risk Framework

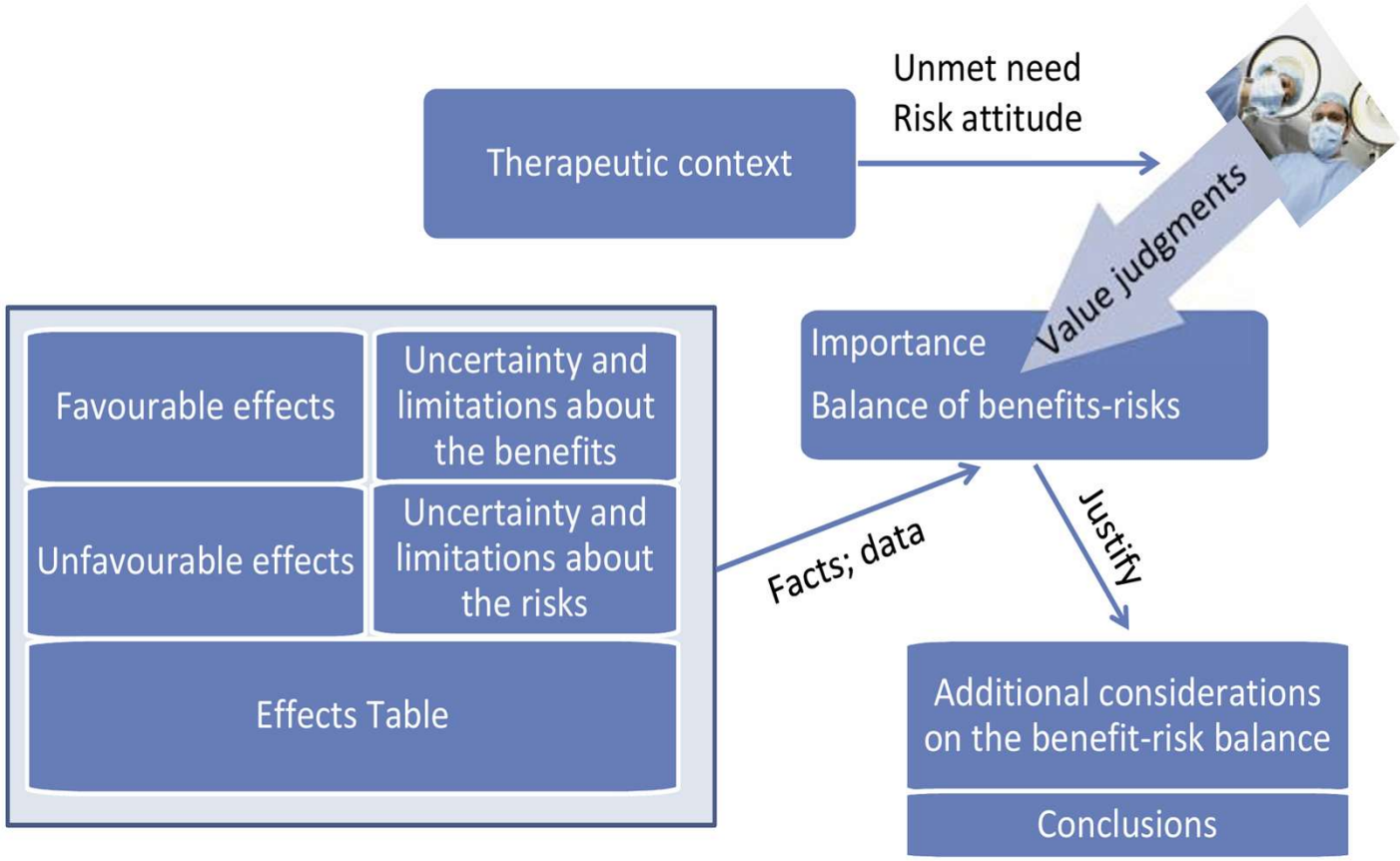
Decision Factor	Evidence and Uncertainties	Conclusions and Reasons
Analysis of Condition		
Current Treatment Options		
Benefit		
Risk		
Risk Management		
Benefit-Risk Summary Assessment		

Benefit-Risk Assessment for New Drug and Biological Products
FDA Guidance for Industry 2023

Qualitative Benefit-Risk Framework
EMA 4-fold Qualitative Model

EMA Benefit-Risk Methodology Project:

EMAs four-fold qualitative model	
favourable effects	uncetainty of favourable effects
unfavourable effects	uncetainty of un-favourable effects



Benefit/risk assessment of medicinal products
Andreas Kouroumalis
EMA Human Medicines Evaluation Division
Scientific and Regulatory Management Department, 2019

Qualitative Benefit-Risk Framework
The EMA PrOACT-URL Framework

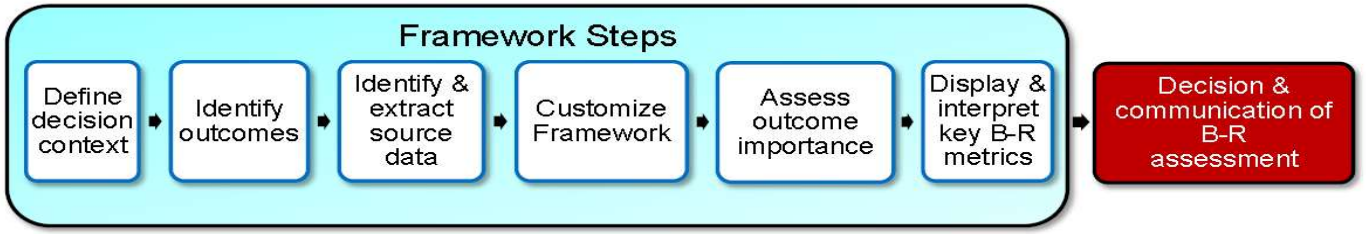
Problem	• Determine the nature of the problem and its context. • Frame the problem
Objective	• Establish objectives that indicate the overall purposes to be achieved. • Identify criteria for (a) favourable effects, and (b) unfavourable effects
Alternatives	• Identify the options to be evaluated against the criteria.
Consequences	• Describe how the alternatives perform for each of the criteria, i.e., the magnitudes of all effects, and their desirability or severity, and the incidence of all effects.
Trade-off	• Assess the balance between favourable and unfavourable effects.
Uncertainty	• Report the uncertainty associated with the favourable and unfavourable effects. • Consider how the balance between favourable and unfavourable effects is affected by uncertainty.
Risk tolerance	• Judge the relative importance of the decision maker's risk attitude for this product. • Report how this affected the balance reported in step 9.
Linked decisions	• Consider the consistency of this decision with similar past decisions, and assess whether taking this decision could impact future decisions.

The EU / CHMP Benefit-Risk Day 80 Assessment Report

5. Benefit risk assessment	5.1. Therapeutic Context	5.1.1. Disease or condition	5.1.2. Available therapies and unmet medical need	5.1.3. Main clinical studies
5.2. Favourable effects	5.3. Uncertainties and limitations about favourable effects	5.4. Unfavourable effects	5.5. Uncertainties and limitations about unfavourable effects	5.6. Effects Table
5.7. Benefit-risk assessment and discussion	5.7.1. Importance of favourable and unfavourable effects	5.7.2. Balance of benefits and risks	5.7.3. Additional considerations on the benefit-risk balance	5.8. Conclusions

Structured Benefit Risk Assessment
The Semi-quantitative BRAT Framework

Coplan et al 2010
Levitan et al 2012

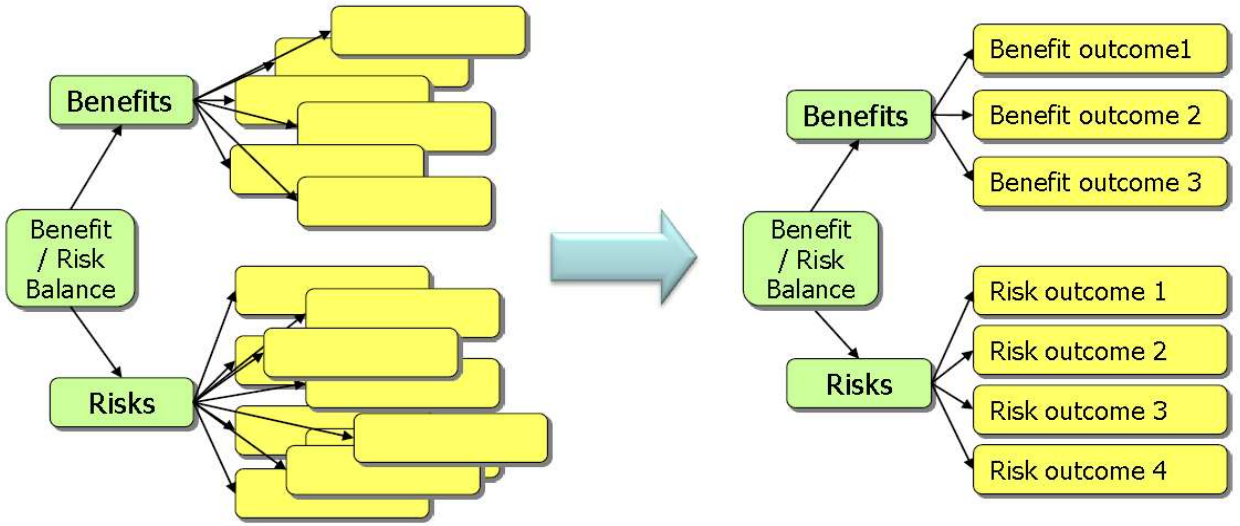


1. **Defining the decision context** involves specifying the therapeutic context, comparator to use of the product, time horizon for exposure, measurement of benefit and risk, and specifying the perspective of stakeholders (sponsor, regulators, prescribers, patients, etc.).
2. **Identifying benefit and risk outcomes**: **building the value tree** includes defining – preferably prospectively – the benefit and risk outcomes which will be considered in the assessment (select – define – document).
3. **Identifying data sources** for the framework refers to the information or data which will be input into the framework (e.g. clinical trials,literature, observational studies etc.) .
4. **Customizing the framework** requires taking into account the quality and characteristics of the data which will be used and **updating the value tree** accordingly.
5. **Assessing relative importance of different outcomes** recognizes that outcomes will have different weights or importance based on their severity or relative benefit to the patient.
6. **Displaying and interpreting key benefit-risk metrics** involves the creation of a Key Benefit-Risk Summary (KBRS) table and **foster plots** to help users to readily grasp the key issues.

Qualitative Benefit-Risk Framework
BRAT Value Tree

Requires expert clinical / medical judgement – to be operationalized by cross-functional teams (Safety Management Team SMT)

Establish a preliminary scope for the benefit-risk assessment by identifying and paring down potential benefit/risk outcomes

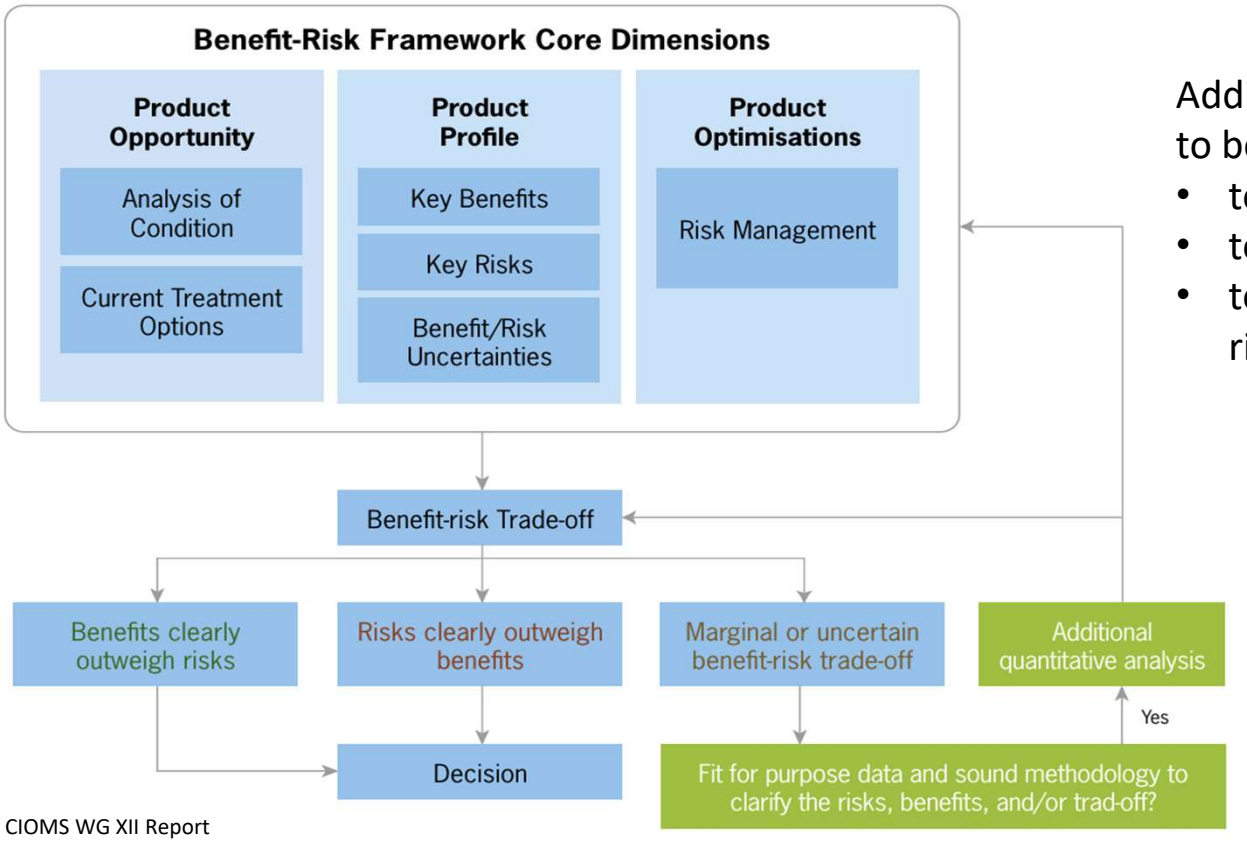


Framework can serve as basis for discussion with health authorities to prospectively frame the benefit-risk assessment

Framework Steps:

Decision Context → Value Tree → Data Sources & Statistical Methods → Benefits → Risks and Mitigations → Weights/ Clinical Impact → Integrated B-R Assessment

Benefit-Risk Assessment
Decision Tree for Additional Quantitative Analysis



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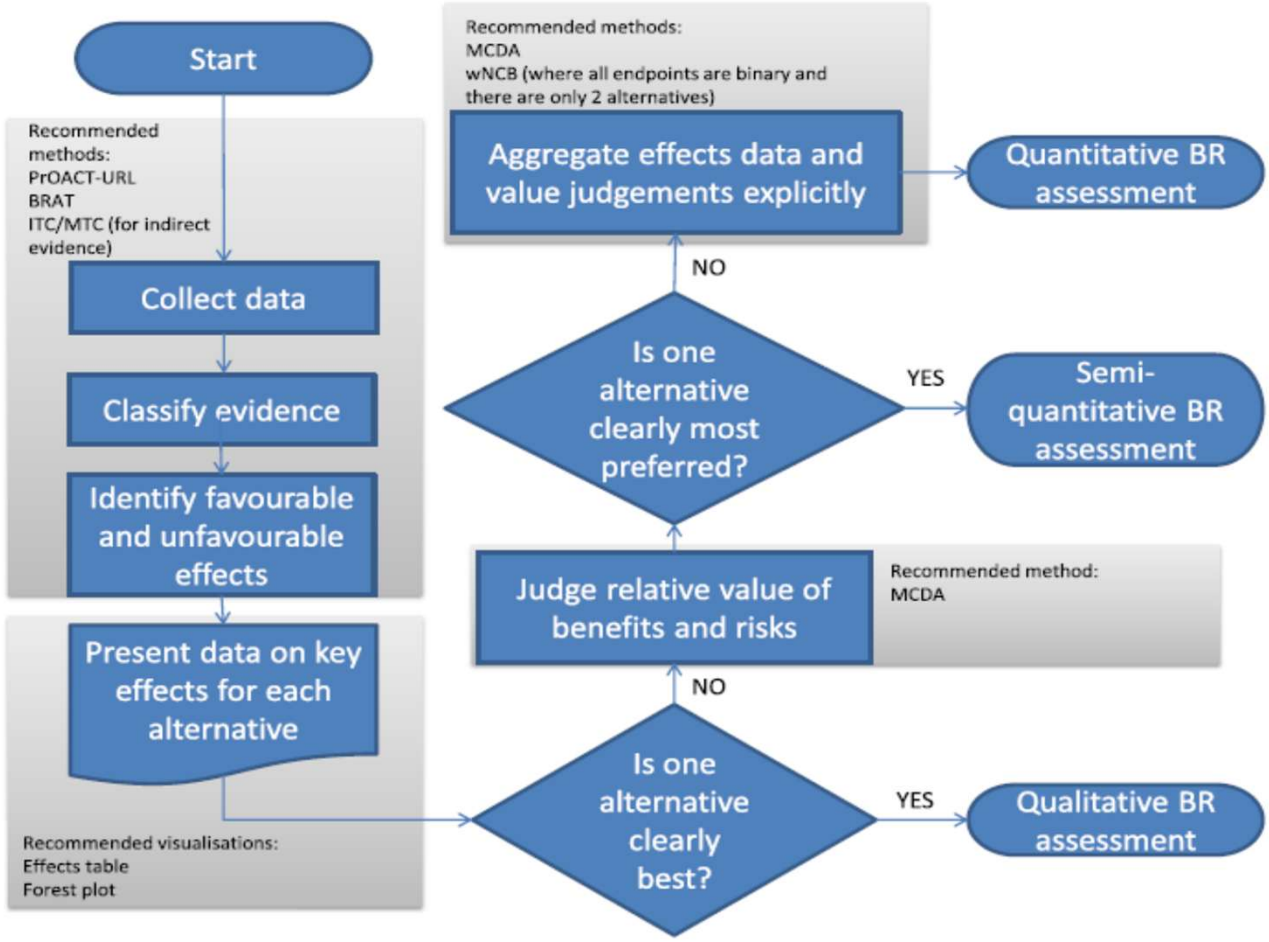
Additional quantitative analyses to be used for different purposes:

- to facilitate discussion
- to inform decisions
- to communicate benefits and risks (e.g. by foster plots etc.)

Qualitative and Quantitative Benefit-Risk Assessment

Flowchart indicating **qualitative and additional quantitative benefit-risk assessment** with recommended methods

Hughes 2016



Format - ICH E2C PBRER / GVP Module VII PSUR

9. Information from other clinical trials and sources

10. Non-clinical data

11. Literature

12. Other periodic reports

13. Lack of efficacy in controlled clinical trials

14. Late-breaking information

15. Overview on signals: New, ongoing or closed

16. Signal and risk evaluation
16.1. Summaries of safety concerns
16.2. Signal evaluation
16.3. Evaluation of risks and new information
16.4. Characterization of risks
16.5. Effectiveness of risk minimization (if applicable)

17. Benefit evaluation
17.1. Important baseline efficacy / effectiveness information
17.2. Newly identified information on efficacy / effectiveness
17.3. Characterization of benefits

18. Integrated benefit-risk analysis for authorized indications
18.1. Benefit-risk context – medical need and important alternatives
18.2. Benefit-risk analysis evaluation

19. Conclusions and actions

20. Appendices to the periodic safety update report

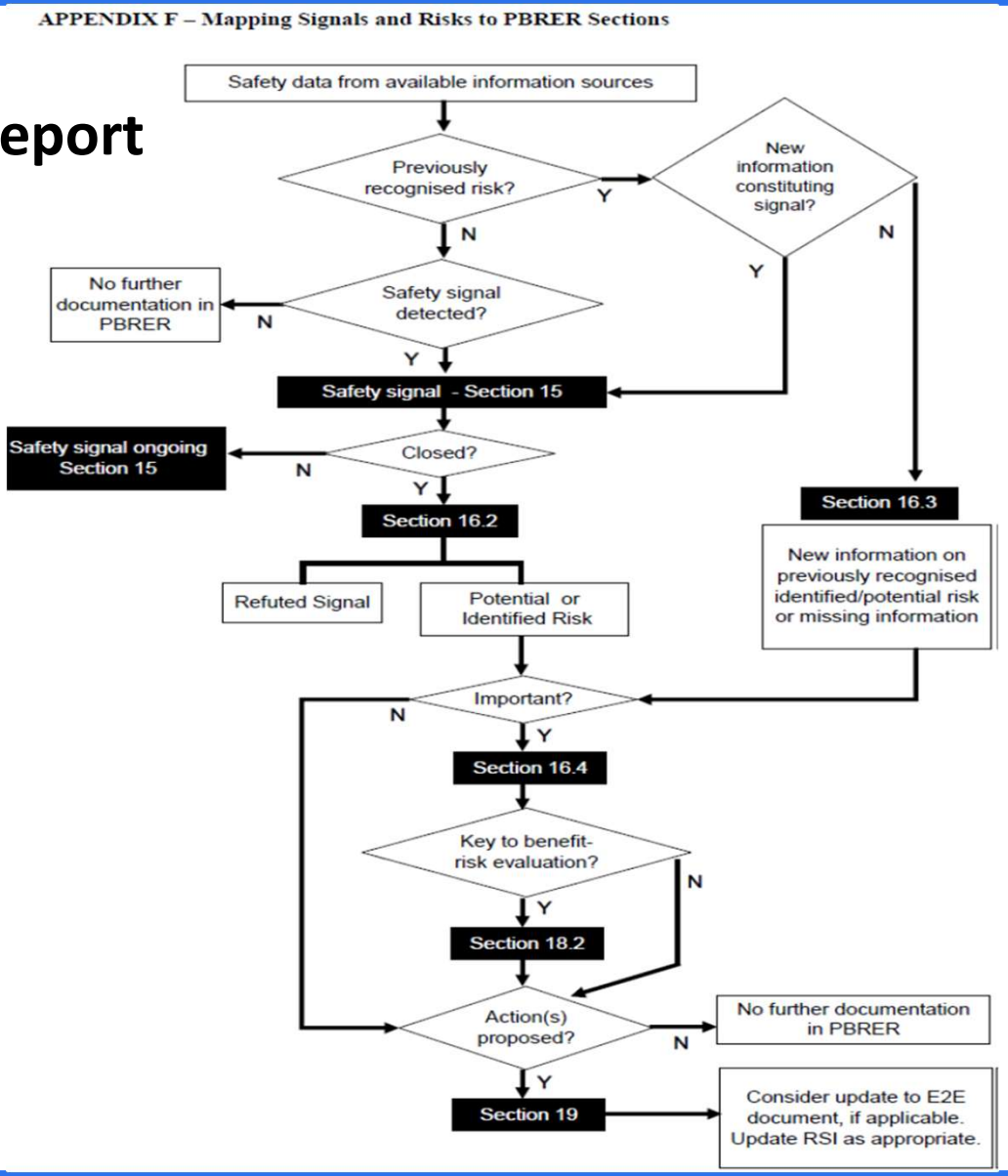
Section 16 – 18 NEW in PBRER

Periodic Benefit-Risk Evaluation Report (PBRER) - ICH E2C (R2)

Flowchart mapping signal and risks to different PBRER sections (Appendix F)

ICH: Periodic Benefit Risk Evaluation Report (ICH E2C (R2)

EMA: Guideline on good pharmacovigilance practices (GVP) Module VII – Periodic safety update report



Benefit Risk Assessment
Challenges

Benefit-risk analysis seems conceptually easy but hard to operationalize – in particular:

- **Data-related challenges**: e.g. Data quality and availability; Integration of multiple data sources “squash the messy complexity of real life into a simple model”.
- **Methodological challenges**: Framework variability, handling uncertainty, subjectivity in weighing / elicit defined consistent criteria across decision options in value judgements
- **Regulatory and Compliance Challenges**: No, evolving or new regulations, documentation and transparency, regulatory harmonization
- **Operational and Resource Challenges**: Cross-functional expertise requirements / Safety Management teams, complexity and volume of data, frequency of assessment
- **Stakeholder and Decision-making Challenges**: Balancing benefits and risks, communication of results, patient / vaccinees perspectives
- **Technological and Analytical Challenges**: Integrated analytical tools, visualization dashboards, automated alerts, B/R model limitations.

Continuous B/R assessment is a multifaceted challenge combining

- Data quality
- Methodological rigor
- Regulatory adherence
- Operational capacity
- Effective stakeholder management

	Periodic Benefit Risk Evaluation Report / Periodic Safety Update Report PBRER / PSUR	**Risk Management Plan RMP**
Legal Basis (EMA GVP)	GVP Module VII	GVP Module V
Primary purpose	To **periodically evaluate the benefit–risk balance** of a medicinal product based on cumulative safety and efficacy data	To **identify, characterize, prevent, or minimize risks** associated with a medicinal product throughout its lifecycle
Timing/ frequency	Submitted at **defined intervals** (e.g., 6-monthly, yearly, or per EU reference dates)	**Living document**: submitted at initial authorization and **updated when new safety information emerges**
Lifecycle focus	**Retrospective and cumulative review** of safety and benefit–risk	**Prospective and proactive risk management**
Key questions answered	"Based on all available data, **does the benefit–risk balance remain positive?**"	"What are the **important risks**, and **how will they be monitored and minimized**?"
Scope of data	Worldwide cumulative data: clinical trials, post-marketing, literature, epidemiology, effectiveness (if applicable)	Known and potential risks, missing information, and planned pharmaco-vigilance and risk minimization activities
Role in regulatory decision making	Supports **regulatory re-assessment**, label changes, or additional risk measures	Defines **required safety activities and risk minimization measures**
Audience	Regulators evaluating ongoing benefit–risk	Regulators overseeing risk control strategy

Main focus of the PSUR:

- ✓ Integrated post-authorization benefit-risk assessment
- ✓ Ensuring benefit-risk balance remains favorable
- ✓ Signal detection and evaluation
- ✓ Establishing and documenting "core safety profile"
- ✓ Ensuring up-to-date product information

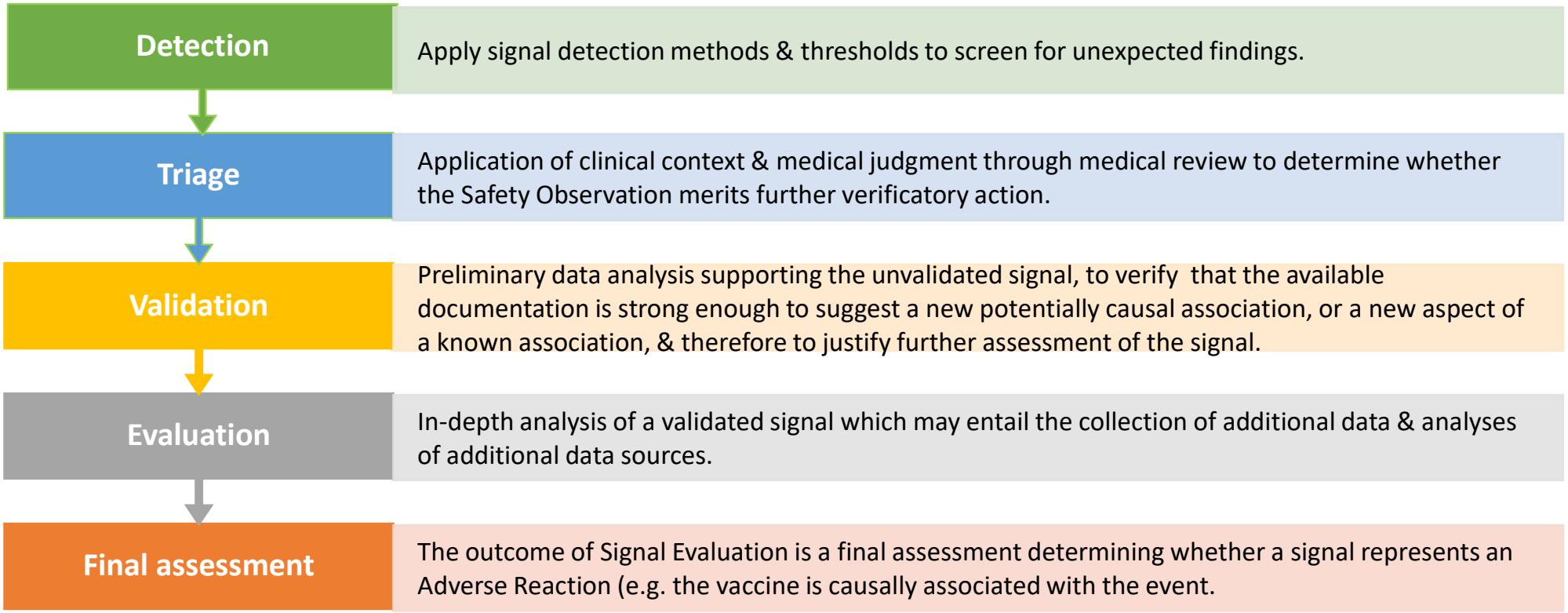
- Benefit-risk balance of a vaccine can change over time and there could be a need for re-adjustment
- PBRERS / PSURs permit the periodic re-assessment of the benefit-risk balance
- Legal actions can be taken from the PSUR assessment
- Minimizing risks and optimizing benefits throughout the lifecycle of a vaccine will promote and protect public health and enhance patient safety by avoiding unnecessary risks to vaccinees.

THANK YOU

Questions ?

Back-up Slides

Signal Management Process



Empirical Bayes Geometric Mean EBGM

Concept:

- An **Empirical Bayes approach** is the **EBGM model** developed by **FDA** and used e.g., by FDA and MHRA**.**
- Statistical measure derived from Bayesian data mining techniques in analyzing contingency tables.
- EBGM is derived from Relative Reporting Ratio RR, the observed–to-expected count ratio (unlike PRR)
  - Drug/vaccine-event combination of interest included in comparator group
- Refined version of the RR incorporating Bayesian adjustments (shrinkage) to stabilize the increased variability associated with small observed and / or expected report counts esp. in small sample sizes.

Downloadable software package(free): Empirical Bayes Metrics with openEBGM

Interpretation:

- **EBGM >1:** drug/vaccine – event pair reported more often than expected
- **EB05 >2:conservative signal measure** (FDA signal threshold - lower limit of CI 90%)
- The interval from **EB05** to EB95 is the 90% CI interval

Bayesian Confidence Propagation Neural Network BCPNN

Concept:

- The **Bayesian statistical model BCPNN** used by **WHO Uppsala Monitoring Center UMC** for signal detection in VigiBase.
- A Bayesian approach for the detection of statistical associations (signals) between a drug / vaccine and an event on observed and expected reporting frequencies, beyond what would be expected by chance, while accounting for uncertainty due to sparse data.
- Propagates probabilistic information through a network of nodes representing drugs / vaccines and adverse events.
- Model estimates the **Information Component (IC),** a Bayesian measure of disproportionality.

Downloadable software package (calculates PRR, ROR and IC):
pvda package - RDocumentation

Interpretation:

- **IC > 0:** drug/vaccine – event pair reported more often than expected
- **IC_{025} > 0: signal of disproportionate reporting** (lower limit of 95% CI >0)

Disproportionality Analysis
Comparison of different methods

PRR / ROR fast, simple, easy to compare – good for *screening* but overestimates signal values leading to false-positive signals

EBGM / BCPNN more statistically principled and reliable – better for *decision-making and long-term signal management*

- Strongly improved signal detection method
- Reduces spurious signals / control of false positives
  - Shrinks the disproportionality estimate of single observations in large databases
- Directly interpretable
- Incorporation of prior information
- Gradual data-driven learning / Bayesian driven updating over time
- Transparent and comparable
- Used by FDA (FAERS / VAERS), WHO (VigiBase)
- Commercial electronic safety databases provide these signal detection analytics

Example of a signal detection workflow:

1. Ingest new ICSRs weekly and standardize data.
2. Perform deduplication and mapping (MedDRA, ATC).
3. Run disproportionality analyses (PRR, EBGM ROR, IC).
4. Rank and prioritize signals using composite criteria.
5. Conduct clinical review for top-ranked signals.
6. Escalate validated signals for further assessment

Rapid Cycle Analysis RCA
Statistics

Sequential hypothesis testing method allows for repeated testing of accumulating data without inflating the false-positive rate.

Concept:

H_0 (null): event rate after exposure equals expected background rate

H_1 (alternative): event rate after exposure higher than expected

After each data refresh method evaluates

Reject H_0 - Signal enough evidence of elevated risk

Accept H_0 - Stop enough evidence no elevated risk

maxSPRIT is the statistical engine that powers rapid, ongoing signal detection in real-world real-time vaccine/drug safety monitoring

maxSPRIT statistics:

- Does not require a fixed alternative hypothesis
- Is more flexible and powerful for unknown effect sizes, as
  - likelihood is maximized across all possible elevated risks
- log-likelihood ratio (LLR) calculated
- Signal is generated if LLR exceeds pre-specified critical value
  - Derived from the desired α-level and number of sequential looks

Statistics in Signal Detection
Main Tools

Descriptive Statistics

Used to summarize data and detect patterns.

- **Frequency counts and percentages:** Number of adverse events (AEs) per vaccine or system organ class (SOC).
- **Rates and proportions:** Incidence of AEs per number of patients or person-time.
- **Cross-tabulations:** Compare events across subgroups (age, sex, dose).
- **Measures of central tendency and dispersion:** Mean, median, standard deviation, e.g., for safety laboratory values or AE onset times.

Statistics in Disproportionality Analysis

Used mainly in spontaneous reporting systems (e.g., VAERS, EudraVigilance, VigiBase. Detects **unexpected reporting patterns**.

- **Proportional Reporting Ratio (PRR):** Compares proportion of a specific AE – drug/vaccine pair vs all other drugs / vaccines.
- **Reporting Odds Ratio (ROR):** Odds of a specific AE occurring with a drug/vaccine compared to all other drugs / vaccines
- **Information Component (IC, used in BPCNN):** Measures disproportionality using Bayesian shrinkage.
- **Empirical Bayes Geometric Mean (EBGM):** Shrinkage-based signal detection to reduce false positives.

Future Trends in Safety Signal Detection

- Integration of **AI and NLP** for unstructured data (social media, clinical notes).
- Use of **federated analytics** (data stays local, analysis is centralized only analytical results or summary statistics are shared, e.g., DARWIN EU).
- **Automated dashboards** for real-time monitoring (e.g., RShiny, Power BI tools).
- Combination of **passive + active surveillance** (hybrid pharmacovigilance).

Signal validation

Evaluation of the data supporting the detected signal to verify that the available documentation contains **sufficient evidence** to demonstrate the **existence of a new potentially causal association, or a new aspect of a known association**, & therefore to justify further assessment of the signal.

Clinical relevance:

- Strength of evidence
- Seriousness/severity of reaction/outcome
- Novelty
- Drug interactions
- Special populations

Previous awareness:

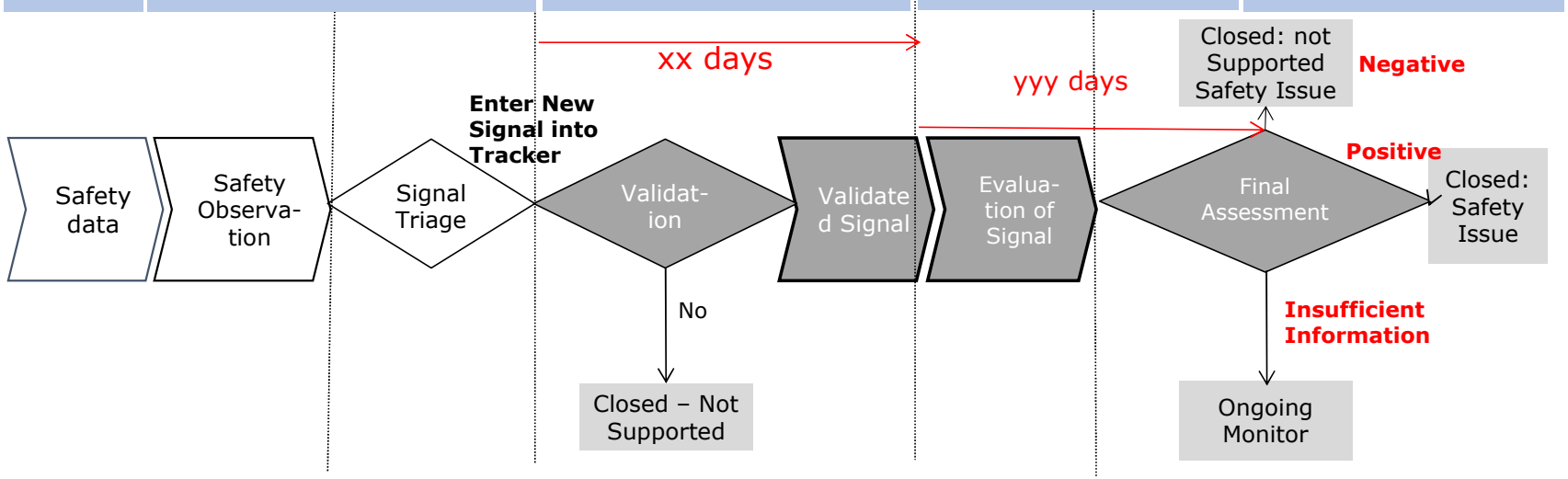
- Inclusion in Company Core Data Sheet and product label
- Assessed in previous Periodic Benefit Risk Evaluation Report/Periodic Safety Update Report or Risk Management Plan

Other relevant information

- Literature reports of similar cases
- Experimental findings or biological mechanisms
- Screening of databases with larger datasets (if relevant)

Signal Tracking Workflow
Example from Industry

DETECTION	TRIAGE	VALIDATION	EVALUATION	FINAL ASSESSMENT
Apply signal detection methods & thresholds to screen for un-expected 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

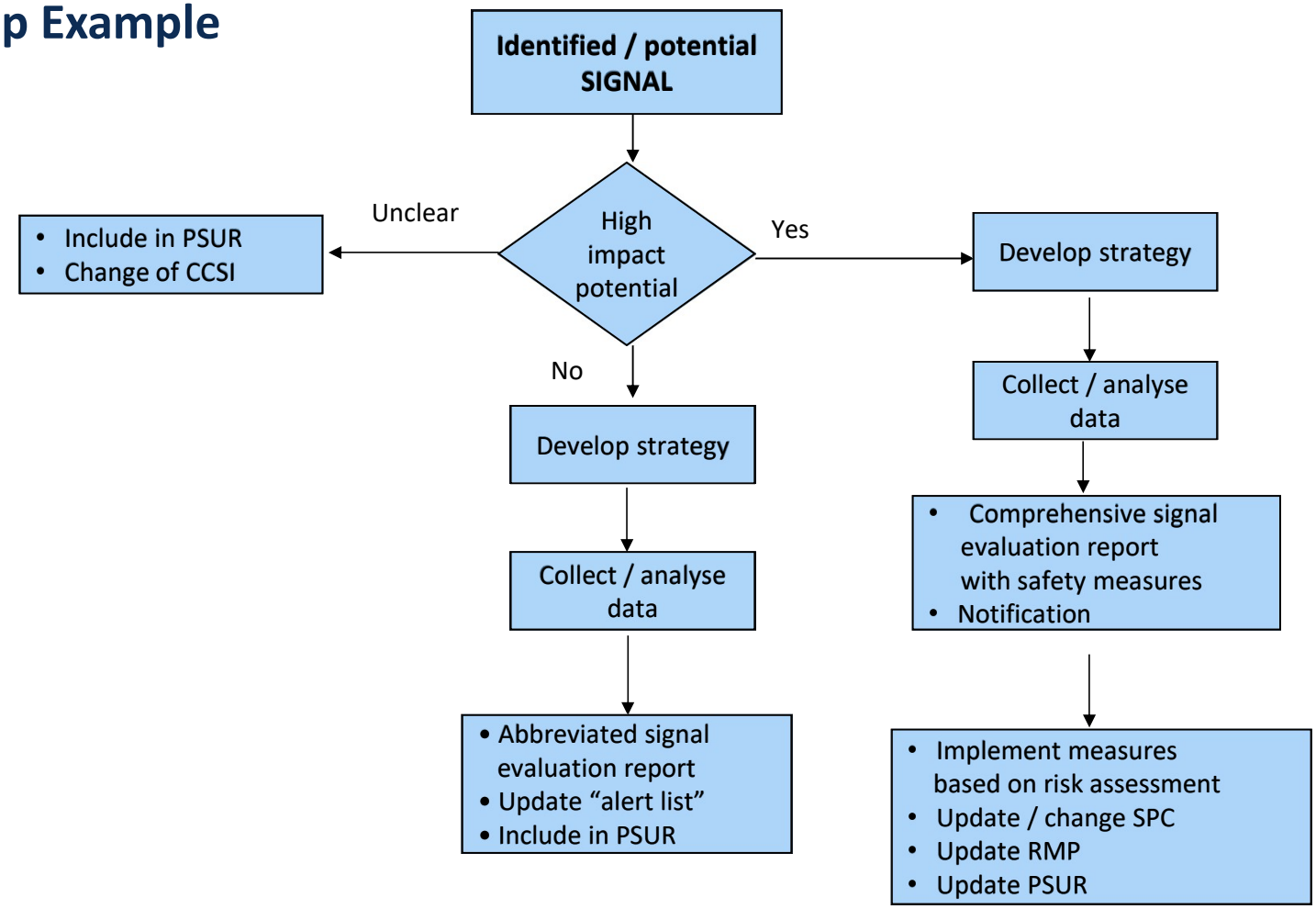


Signal Detection Toolkit Example

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

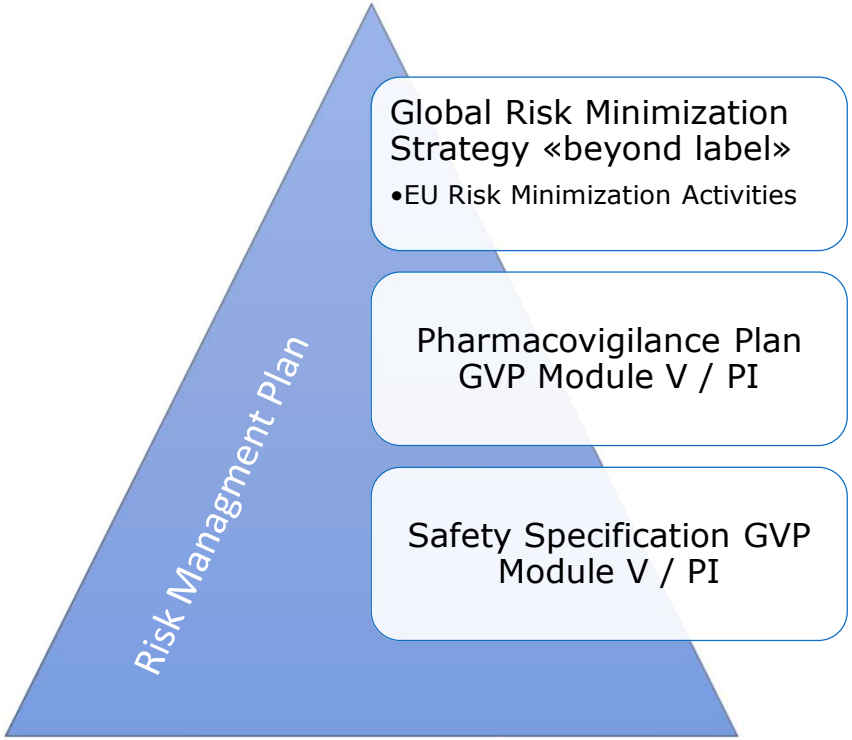
ith vaccines
esponses incl. syncope smission of infectious agents vaccines: symptoms type disease s re (lack of efficacy) s
Brighton case definitions)
ction Site zures velitis / ADEM ndrome/ Fisher syndrome esponsive episodes (HHE) tic ia / ITP / evidence of bleeding ed disorders

Identified / Potential Signal
Workup Example

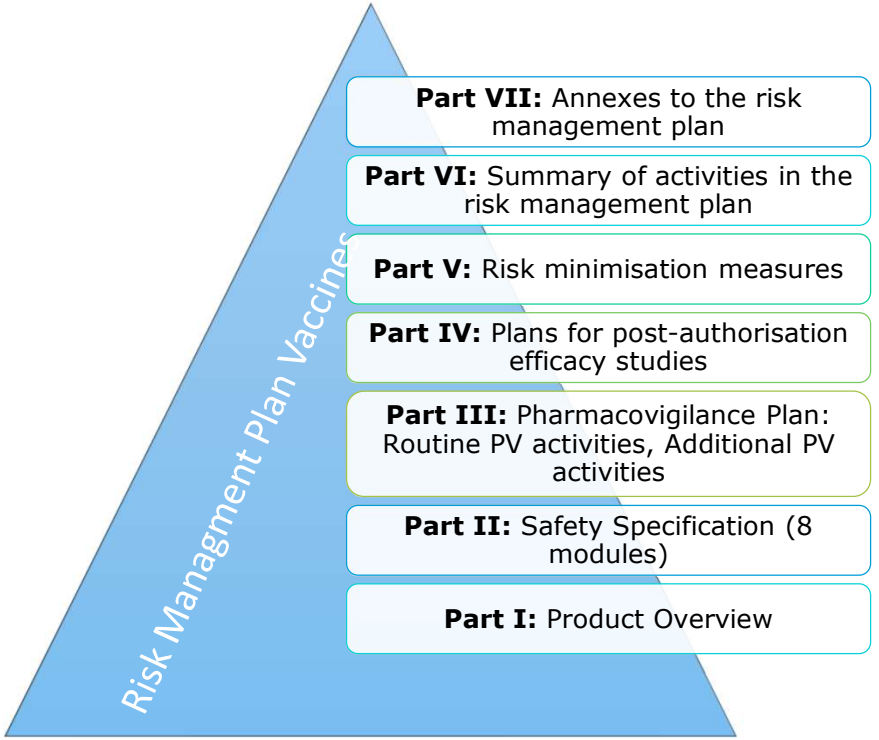


EU Risk Management Plan
GVP Module V / XVI

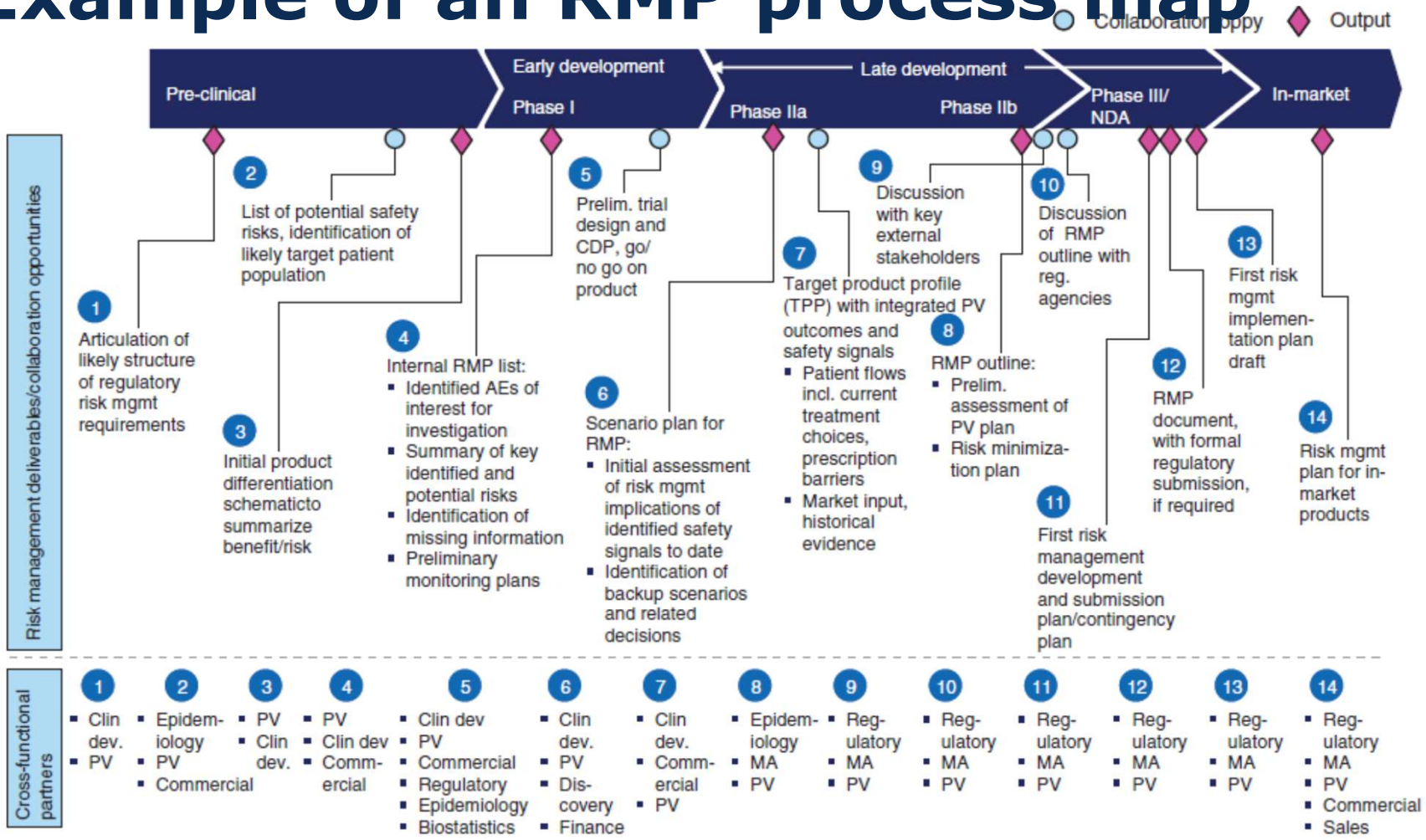
General Structure



Detailed Structure



Example of an RMP process map



Benefit-Risk Assessment
Principles

Many initiatives and tools to standardize and improve consistency, transparency and communication of B/R assessment

Benefits

- ✓Beneficial effects (e.g., prevention of severe disease, lowering or preventing mortality, hospitalization or serious AEFIs, etc.)
- ✓Uncertainty in the knowledge about beneficial effects

Risks

- ✓Unfavorable effects (e.g., AEFIs, lack of effectiveness etc.)
- ✓Uncertainty in the knowledge about unfavorable effects

Assessment of Benefit / Risk Balance

- ✓Should be performed in a structured approach (qualitative / quantitative?)
- ✓Focus on the individual and population benefits and risks
- ✓Assess frequency of benefits (e.g., vaccine efficacy) and risks (e.g., frequency of serious AEFIs, vaccination failures)
- ✓Weigh frequency and importance of favorable and unfavorable effects appropriately
- ✓Assess benefit – risk balance
- ✓Discussion on the benefit-risk assessment
- ✓Conclusions

Qualitative Benefit-Risk Framework
The PrOACT-URL Framework

Problem: Determine the nature of the problem and its context

Objectives: Establish objectives and identify criteria of favorable and unfavorable effects

Alternatives:- Identify the options to be evaluated against the criteria

Consequences: Describe how the alternatives perform for each of the criteria

Trade-offs- Assess the balance among favorable and unfavorable effects

Uncertainty: Assess the uncertainty associated with the effects

Risk tolerance: Judge the relative importance of the decision maker's risk attitude

Linked decisions: Consider the consistency of this decision with past/future decision(s)

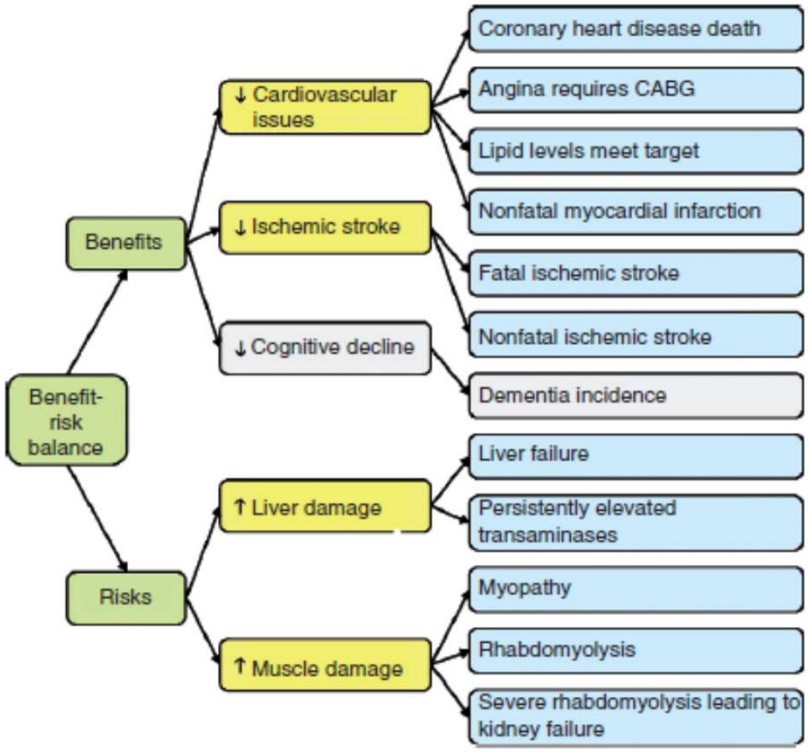
The Semi-quantitative BRAT Framework

Define decision context	• Define drug, dose, formulation, indication, patient population, comparator(s), time horizon for outcomes, perspective of the decision makers (regulator, sponsor, patient, or physician)
Identify outcomes	• Select all important outcomes and create the initial value tree. • Define a preliminary set of outcome measures/endpoints for each. • Document rationale for outcomes included/excluded
Identify data sources	• Determine and document all data sources (e.g. clinical trials). • Extract all relevant data for the data source table, including detailed references and any annotations, to help the subsequent interpretations create summary measures.
Customise framework	• Modify the value tree on the basis of further review of the data and clinical expertise. • Refine the outcome measures/endpoints. May include tuning of outcomes not considered relevant to a particular benefit-risk assessment or that vary in relevance by stakeholder group.
Assess outcome importance	• Apply or assess any ranking or weighting of outcome importance to decision makers or other stakeholders.
Display & interpret key benefit-risk metrics	• Summarise source data in tabular and graphical displays to aid review and interpretation. • Challenge summary metrics, review source data, and identify and fill any information gaps. • Interpret summary information.

Coplan et al 2010
Levitan et al 2012

Value Tree

Benefit-Risk outcomes for inclusion in a comparative B/R assessment

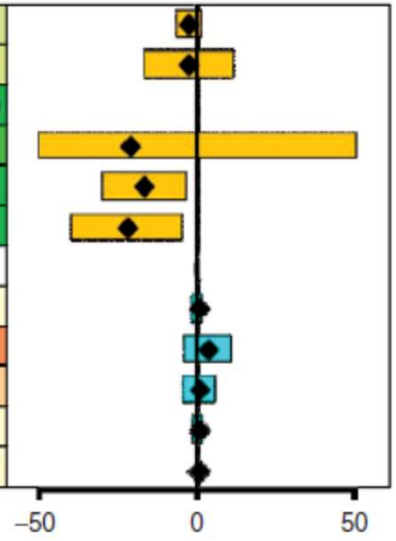


CABG: Coronary artery bypass graft

Coplan et al 2010
Levitan et al 2012

Key Benefit-Risk Summary Table
Presentation from Value Tree Example

		Outcome	Study drug risk[a]	Placebo risk[a]	Risk difference per 10,000 person-years		Risk difference forest plot[a]
Benefits	Cardio-vascular issues	Angina requiring CABG	3.7	6.4	−2.6	(−6.4, 1.2)	
		Coronary heart disease death	31.0	33.6	−2.7	(−16.9, 11.6)	
		Lipid levels meet target	6700	2900	3800	(2,691, 4,909)	
		Nonfatal myocardial infarction	22.1	43.3	−21.2	(−95.2, 52.8)	
	Ischemic stroke	Fatal ischemic stroke	18.6	35.4	−16.8	(−29.9, −3.6)	
		Nonfatal ischemic stroke	97.5	119.8	−22.3	(−39.8, −4.8)	
Risks	Liver damage	Liver failure	0.6	0.6	0.0	(−1.6, 1.6)	
		Persistently elevated transminases	13.6	10.1	13.5	(−3.8, 10.9)	
	Muscle damage	Myopathy	5.9	5.3	0.6	(−4.5, 5.6)	
		Rhabdomyolysis	0.6	0.5	0.1	(−1.5, 1.6)	
		Severe rhabdomyolysis → kidney failure	0.029	0.026	0.003	(−0.07, 0.08)	



[a]Risk per 10,000 person-years strong risk strong benefit

Coplan et al 2010
Levitan et al 2012

Methodologies for assessing Benefit - Risk

Qualitative benefit-risk frameworks:

- Relies on expert clinical / medical judgement

Semi-quantitative and Quantitative Benefit-Risk Frameworks:

- Various quantitative methods involving modelling, based on pharmaco-epidemiological principles
- No single agreed upon formal method for vaccine B/R assessment.
- A number of initiatives under way that involve regulators, industry and academia to harmonize evaluations at a global level:
  - ✓IMI-PROTECT to harmonize project : Assessing available methodologies and developing tools for visualization of B/R; development of recommendation roadmap
  - ✓ADVANCE (Accelerated Development of Vaccine B/R Collaboration in Europe) project: To establish a prototype of a sustainable system to provide best available scientific evidence on vaccination B/R
  - ✓Benefit-risk action team (BRAT) framework: Standardization and communication of B/R assessments between pharmaceutical companies and regulators
  - ✓Multi-criteria decision analysis framework (MCDA) integrates multiple benefits and risk criteria

Trend and Pattern Analysis /2

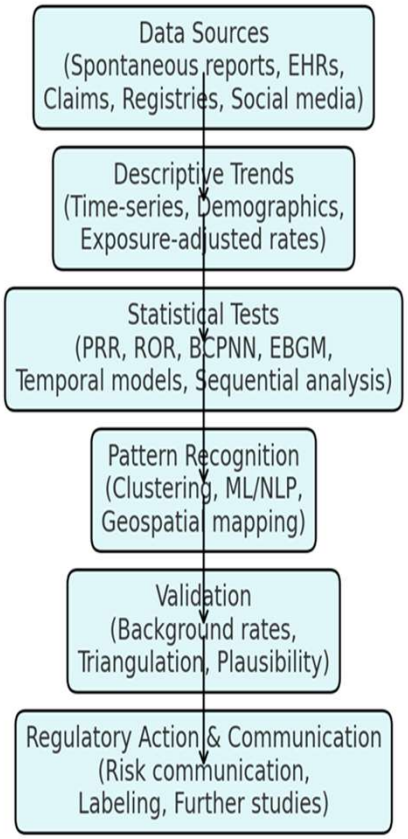
Applications in PV

- **Signal detection:** spotting unexpected safety issues (e.g., myocarditis after COVID-19 mRNA vaccines).
- **Comparative safety monitoring:** trends of ADRs across drug classes.
- **Public health monitoring:** seasonal or outbreak-related patterns (e.g., adverse events after flu vaccines).
- **Regulatory risk communication:** detecting shifts in risk perception through spikes in reporting.
- **Long-term monitoring:** chronic use drug risks (e.g., hepatotoxicity trends).

Challenges

- Underreporting and reporting bias.
- Data heterogeneity across regions.
- Confounding by indication/comorbidity.
- Difficulty separating true signal vs noise (media-driven spikes).

Framework for trend and pattern analyses in Pharmacovigilance



Trend and Pattern Analysis /1

Why Trends & Pattern Analyses in PV?

- To identify emerging safety signals (new or rare adverse drug reactions, ADRs).
- To detect changes in reporting behavior (e.g., underreporting, media-triggered spikes).
- To compare drug/vaccine classes or patient subgroups.
- To support regulatory decision-making (label changes, risk management).

Data Sources Used

- Spontaneous Reporting Systems (SRS): e.g., WHO VigiBase, FDA FAERS, EMA EudraVigilance.
- Electronic Health Records (EHRs): longitudinal, real-world clinical data.
- Claims databases & registries: population-level healthcare utilization.
- Social media & digital platforms: detecting early "sentinel" signals of patient-reported outcomes.
- Clinical trial & post-marketing surveillance data.

Approaches to Trend Analysis

a. Descriptive Trends

- Time-series of case counts (monthly/quarterly reports of specific ADRs).
- Demographics: age, sex, geography distribution.
- Drug/vaccine exposure: reports normalized by sales or doses distributed.

b. Statistical Trend Detection

- Disproportionality Analysis (DPA)
- Change-point analysis: detects sudden increases in reporting frequency.
- Temporal trend tests: e.g., Chi-square for trend, regression models (Poisson, logistic).

Pattern Recognition

- Clustering: identify drug-event pairs with similar reporting profiles.
- Association rules mining: find hidden associations between multiple drugs / vaccines drugs and event.
- Geospatial patterns: mapping event hotspots (helpful for vaccines in outbreak settings)
- Machine learning & NLP: applied to narrative case reports to extract recurring themes.