Developing Countries Vaccine Manufacturers Network

Vaccine Safety Monitoring
DCVMN Regional Training Workshop
Sao Paulo 27 - 30 May 2019

Signal Detection and Signal Management

An Introduction

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Signal – WHO (1992)

Reported information on a possible causal relationship between an adverse event and a drug, the relationship being unknown or incompletely documented previously.

Usually more than a single report is required to generate a signal, depending upon the seriousness of the event and the quality of the information. *(WHO defined 3 similar reports)*

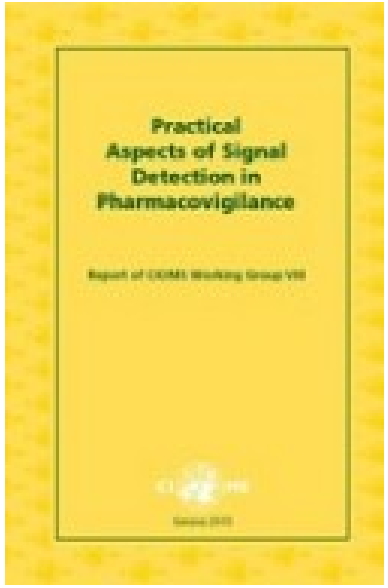
Signal – CIOMS VIII (2010)

Practical Aspects of Signal Detection in Pharmacovigilance

Report of CIOMS Working Group VIII

Definition:

Information that arises from one or multiple sources (including observations and experiments), which suggests a new potentially causal association or a new aspect of a known association, between an intervention and an event or a set of related events, either adverse or beneficial, that is judged to be of sufficient likelihood to justify verificatory action.



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 process
- Documentation of decision making and communication

Signal Management
Principles for Industry

Signal management process goals:

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

GVP Module IX Rev 1 2017 / Addendum 1
Signal management

HMA Heads of Medicines Agencies

EUROPEAN MEDICINES AGENCY SCIENCE MEDICINES HEALTH

9 October 2017
EMA/827661/2011 Rev 1*

Guideline on good pharmacovigilance practices (GVP)
Module IX – Signal management (Rev 1)

Date of coming into effect of first version	2 July 2012
Draft Revision 1* finalised by the Agency in collaboration with Member States	30 June 2016
Draft Revision 1 agreed by the European Risk Management Facilitation Group (ERMS FG)	18 July 2016
Draft Revision 1 adopted by Executive Director	4 August 2016
Release for public consultation	8 August 2016
End of consultation (deadline for comments)	14 October 2016
Revised draft Revision 1 finalised by the Agency in collaboration with Member States	27 September 2017
Revised draft Revision 1 agreed by the EU Network Pharmacovigilance Oversight Group (EU-POG)	4 October 2017
Revised draft Revision 1 adopted by Executive Director as final	9 October 2017
Date for coming into effect of Revision 1*	22 November 2017**

HMA Heads of Medicines Agencies

EUROPEAN MEDICINES AGENCY SCIENCE MEDICINES HEALTH

9 October 2017
EMA/209012/2015

Guideline on good pharmacovigilance practices (GVP)
Module IX Addendum I – Methodological aspects of signal detection from spontaneous reports of suspected adverse reactions

Draft finalised by the Agency in collaboration with Member States	30 June 2016
Draft agreed by the European Risk Management Facilitation Group (ERMS FG)	18 July 2016
Draft adopted by Executive Director	4 August 2016
Released for public consultation	8 August 2016
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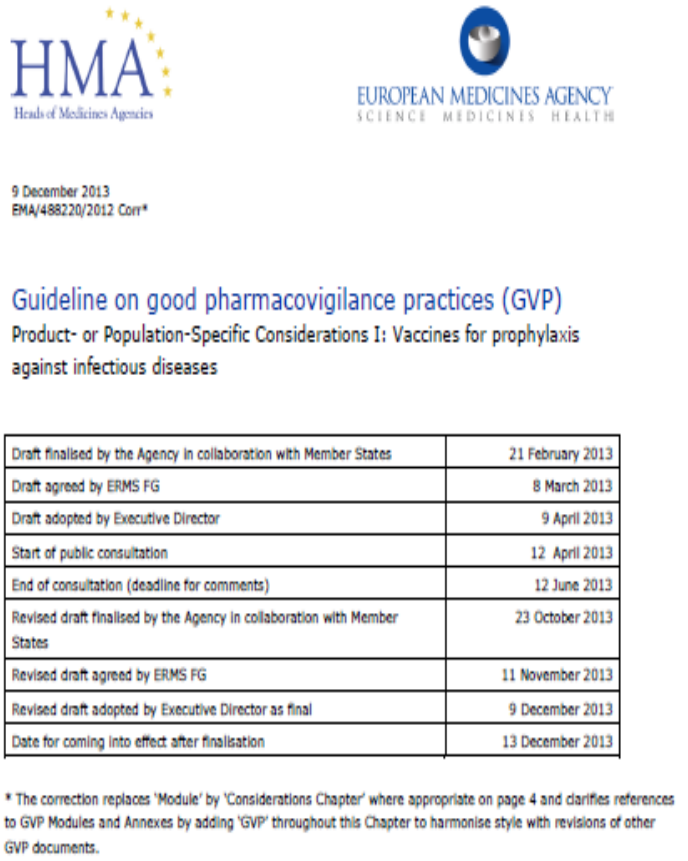
Revised draft agreed by the EU Network Pharmacovigilance Oversight Group (EU-POG)	4 October 2017
Revised draft adopted by Executive Director as final	9 October 2017
Date for coming into effect of final version	22 November 2017

Note: This guidance extends and updates some of the information given in the Guideline on the Use of Statistical Signal Detection Methods in the EudraVigilance Data Analysis System (EMEA/106464/2006 rev. 1) and supersedes the previous advice in the areas addressed by this new guidance.

6

GVP P I Product-specific considerations:
PV for vaccines for prophylaxis against infectious disease

- Module relevant to vaccines used in pre- and post-exposure prophylaxis of infectious diseases.
- Module focuses on vaccine-specific aspects to be respected when designing and implementing PV activities for vaccines.
- Module provides guidance specific for vaccines in relation to PV processes described in the following GVP Modules:
  - Module V: Risk Management System
  - Module VII: Periodic Safety Update Report
  - Module VIII: Post-authorisation Safety Studies
  - Module IX: Signal Management
  - Module XV: Safety Communication
- Module provides guidance on „Batch recall and quarantine“ (legal basis: EMA GMP and GDP compliance)



9 December 2013
EMA/488220/2012 Corr*

Guideline on good pharmacovigilance practices (GVP)
Product- or Population-Specific Considerations I: Vaccines for prophylaxis against infectious diseases

Draft finalised by the Agency in collaboration with Member States	21 February 2013
Draft agreed by ERMS FG	8 March 2013
Draft adopted by Executive Director	9 April 2013
Start of public consultation	12 April 2013
End of consultation (deadline for comments)	12 June 2013
Revised draft finalised by the Agency in collaboration with Member States	23 October 2013
Revised draft agreed by ERMS FG	11 November 2013
Revised draft adopted by Executive Director as final	9 December 2013
Date for coming into effect after finalisation	13 December 2013

* The correction replaces 'Module' by 'Considerations Chapter' where appropriate on page 4 and clarifies references to GVP Modules and Annexes by adding 'GVP' throughout this Chapter to harmonise style with revisions of other GVP documents.

GVP Module IX – P I: Signal management - Vaccines

- 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.
- Signal validation, as described in the report of the CIOMS/WHO Working Group on Vaccine Pharmacovigilance.

Signal Management Process
GVP Module IX

- Signal detection
- Signal validation
- Signal confirmation
- Signal analysis
- Signal prioritization
- Signal assessment
- Recommendations for action
- Exchange of information

Roles and responsibilities of the MAH:

- Continuously monitor the safety of their medicinal products and inform authorities of any changes that might have an impact on MA
- Monitor the data in EudraVigilance
- Keep an audit trail of the signal detection activities

Signal detection /1
Where can we find signals?

- Reports of unexpected and serious AEFIs
- Expected AEFIs with
    - increased frequency
    - greater severity
    - long-term sequelae
    - new risk factors
- Evidence from formal studies
- Change in effectiveness
- Risks are greater than with competitor vaccines

Signal detection /2
Where can we find signals?

- Early / potential signals
  - Pre-clinical data
    - safety surveillance in pre-clinical studies
    - look for anticipated risks
    - expectation for new vaccine
- Single case signals (“striking cases“)
  - single SAEs / SUSARs / SARs 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, authorities, media, internet, claims databases, competitive intelligence, etc.

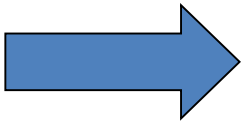
Qualitative Signal Detection

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

Qualitative Signal Detection
Limitations

- Data quality often questionable
- Missing and / or inaccurate data
- Underreporting and / or selective reporting
- Causality assessment difficult
- Confounding: disease linked with outcome
- Diagnostic bias
- Channeling: susceptible patients switched to a new drug
- Not suited for the detection of
  - delayed reactions
  - ADRs with high disease background incidence



no denominator - cannot calculate:
incidence / prevalence
relative risk

Quantitative Signal Detection
Disproportionality analysis

- „Is what we observe different from what we expect?“
- Identification of statistically prominent reporting associations between pairs of drugs / vaccines and events
  - Screening (data mining) of large databases composed of spontaneous reports for disproportionate associations or dependencies between variables, i.e., drug/event combination compared with a control, i.e., observed / expected probability of occurrence
- Data mining has enhanced signal detection performance and possibly replaced some traditional approaches
- 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

2 x 2 Contingency Table:

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

PRRs = [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)

Signal of Disproportionate Reporting SDR

- No gold standard for establishing threshold for “statistical signals”
- SDR applied in queries of EudraVigilance Data Analysis:
  - PRR with 95% CI: lower bound of 95% CI ≥ 1; number of individual cases: ≥ 3
  - PRR displayed with Chi-square statistics: PRR ≥ 2; $X^2 \geq 4$
- All SDRs must be evaluated in their clinical context.

GVP Modul IX Signal detection:

“Use of statistical tools may not be appropriate in all situations…..”

“The method should be appropriate for the data set; … the use of complex statistical tools may not be appropriate for smaller data sets….”

Bayesian Statistics / Mathematical Modelling

- Bayesian method:
  - Without including prior knowledge we are over-sensitive to data
    - leads to false signals
  - Uses „probability“ to express subjective belief in a specific outcome
  - Current probability based on
    - prior belief (a priori)
    - data consistently updated on addition of new data
- Mathematical modeling of disproportionality methods using Bayesian methods
  - Empiric Bayesian Screening (EBS):
    - Multi-item Gamma Poisson Shrinker (MGPS): FDA
    - Used by a number of pharmaceutical companies
  - Bayesian Confidence Propagation Neural Network (BCPNN):
    - WHO Uppsala Monitoring Centre (UMC): WHO-ADR Coding

Quantitative Signal Detection
Limitations

- Frequentist signal detection methods support the analysis of AEFI reporting rates
- 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.

Signal Detection Systems
Safety databases

- WHO: Vigibase - WHO Bayesian confidence propagation neural network (BCPNN)
- EU: EudraVigilance – within their data warehouse activities PRR
- FDA: VAERS - Screening algorithms, e.g., Multi-Item Gamma Poisson Shrinker (MGPS) program
- National Authority databases
- ....
- Company databases
    - little or no competitor data
    - more cases on specific drugs
    - smaller overall data set size
    - link to sales data and look at reporting rates
    - comparison to background of an international database (with caveats)

Approaches to signal detection
Example from industry

Quantitative

- Statistical methods used to identify signals in databases such as VAERS and VigiBase using Empirica Signal (Oracle based software)
- Threshold approach to identify Vaccine-Event combinations to review – cases ≥ 3, EB05 ≥ 2

Qualitative

- Other sources of data
- Including company safety database as product profile of database means background is 'skewed' and may mask signals

Signal evaluation
Strength of evidence

Signal evaluation strategy:

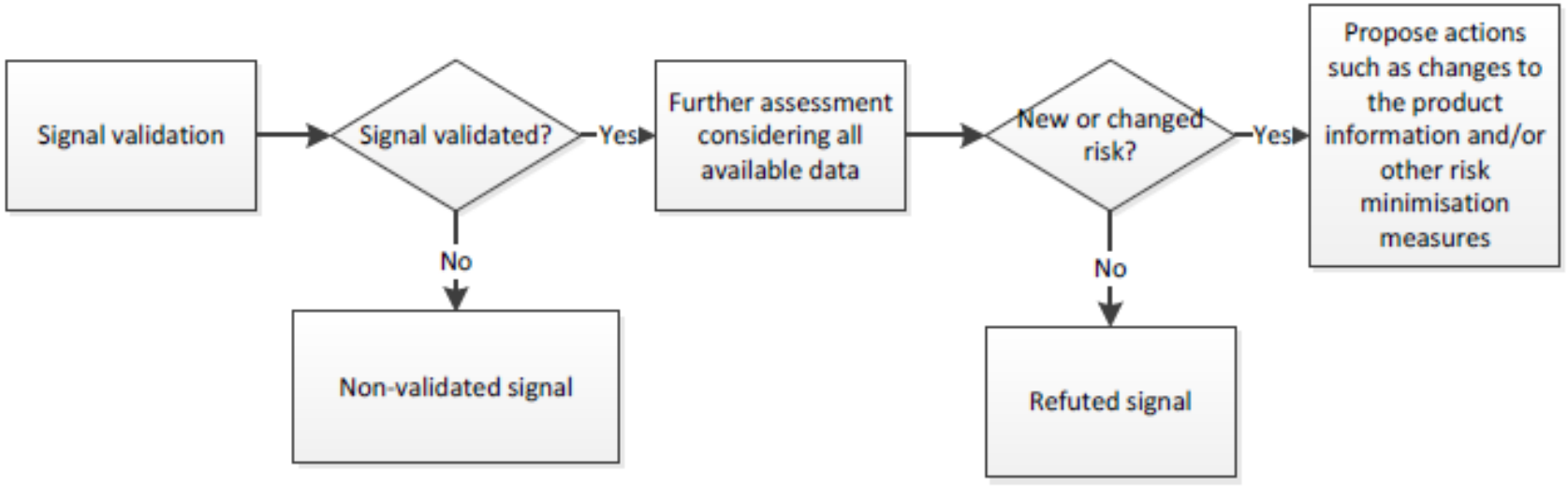
- Data gathering:
  - Generate case series, literature reviews, clinical and pre-clinical data review
  - Additional sources of information
- Methodology including search strategy (qualitative / quantitative methods)
- Data analysis:
  - SMQSs used
  - Case series analysis (descriptive narratives of the cases)
    - are all relevant facts present
    - other risk factors present
    - Clinical relevance
  - Conclusion regarding signal confirmation
  - Ad hoc report

SNIP criteria:

- Strength of association
- Newness of event
- Clinical importance at event
- Potential for preventive measures

Signal evaluation

Generic process (GVP Module IX)



Signal Tracking Workflow
Example from Industry

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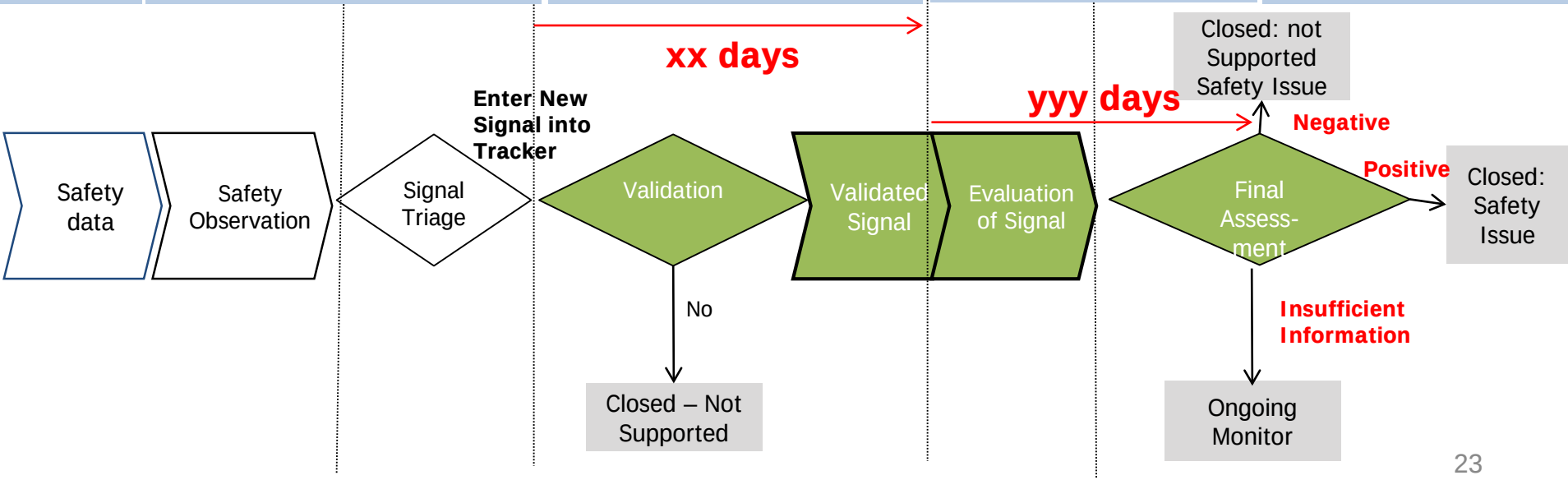
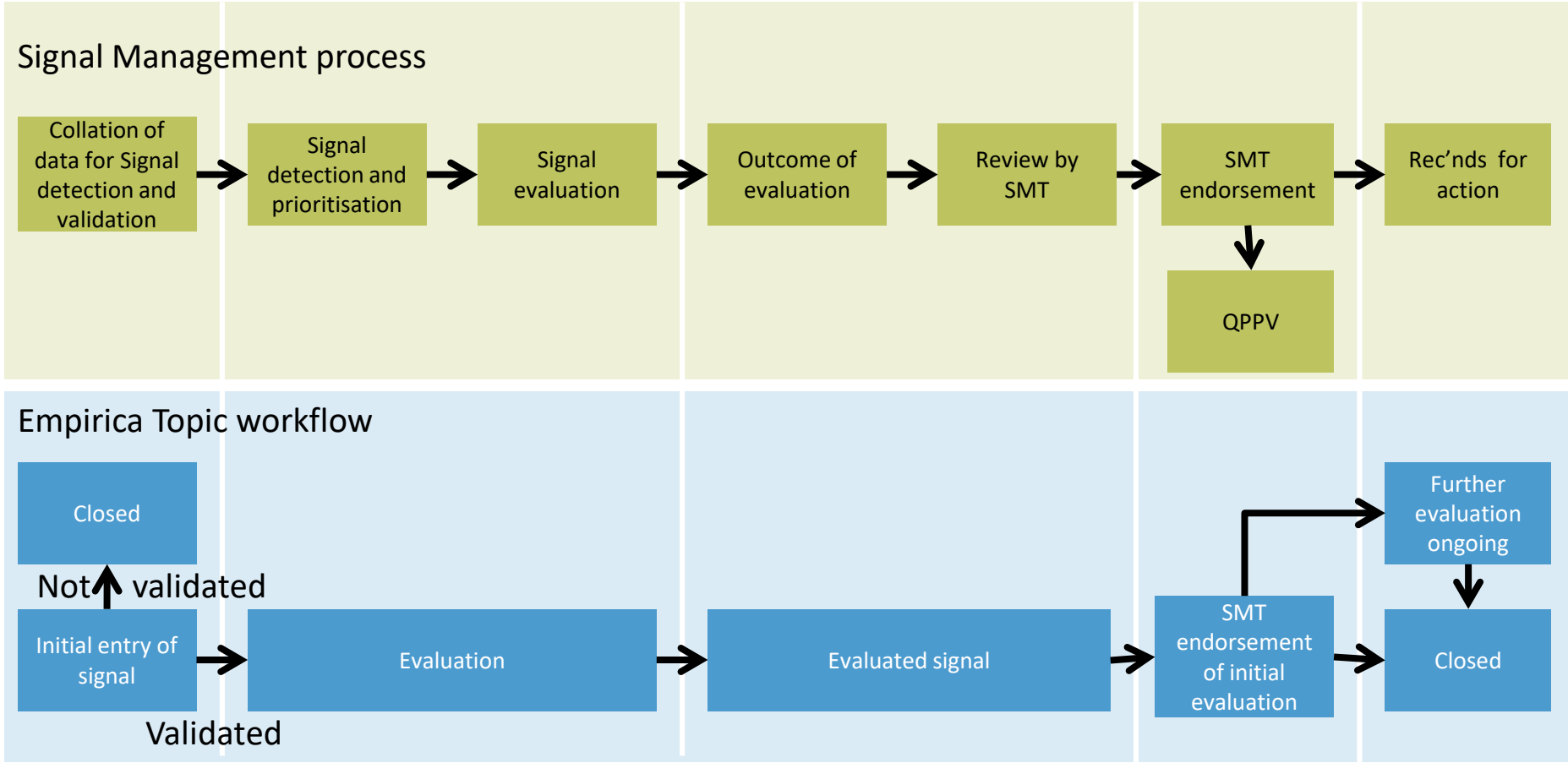
DETECTION	TRIAGE	VALIDATION	EVALUATION	FINAL ASSESSMENT
Apply signal detection methods & thresholds to screen for unexpected findings.	SIGNAL TRIAGE: Application of clinical context & medical judgment through medical review to determine whether the Safety Observation merits further verificatory action	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 Management process aligned with Empirica Topics

- Process aligned with CIOMS VIII and GVP IX
- Changes regarding recording of non-validated signals



Signal priorities and timelines

High

- Signal with important impact on public health / patient health for very 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 evaluation outcome

Communication / Escalation / Recommendation

- Completion of the signal evaluation within defined timeline
- Safety meeting to determine overall outcome
- 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 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

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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