Vaccine Safety Monitoring and Pharmacovigilance Tools
Advanced Pharmacovigilance Mini E-Workshop
16-18 March 2020

dcvmn
Developing Countries Vaccine Manufacturers Network

AEFI Case Management Best Practices

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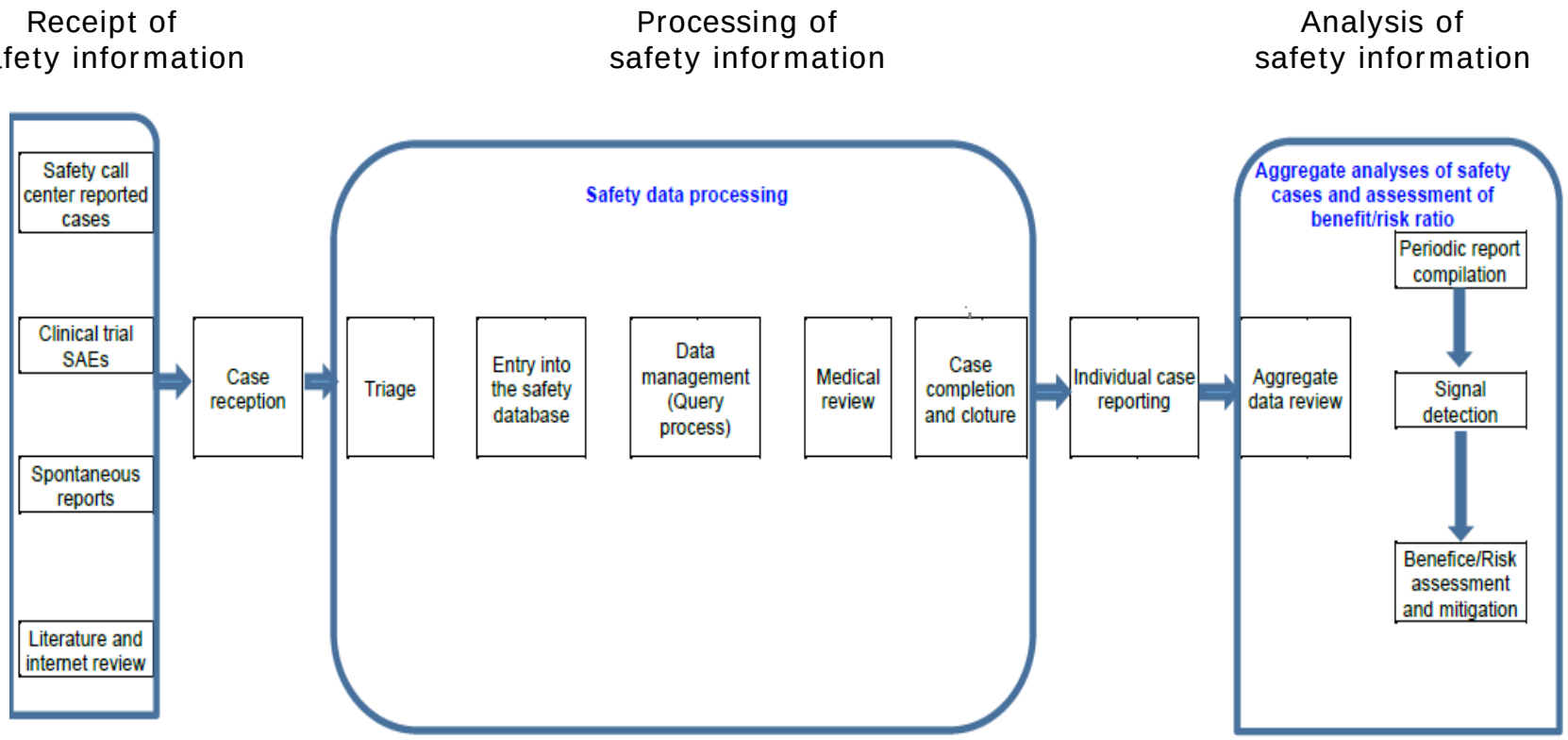
Understanding the terminology
Important definitions

Serious	Severe	Adverse event following immunization AEFI	Adverse event AE
Adverse reaction AR	Serious adverse event SAE	Serious adverse reaction SAR	Expected / Unexpected
	Minimum criteria for reporting to regulatory authority	Frequency definitions	

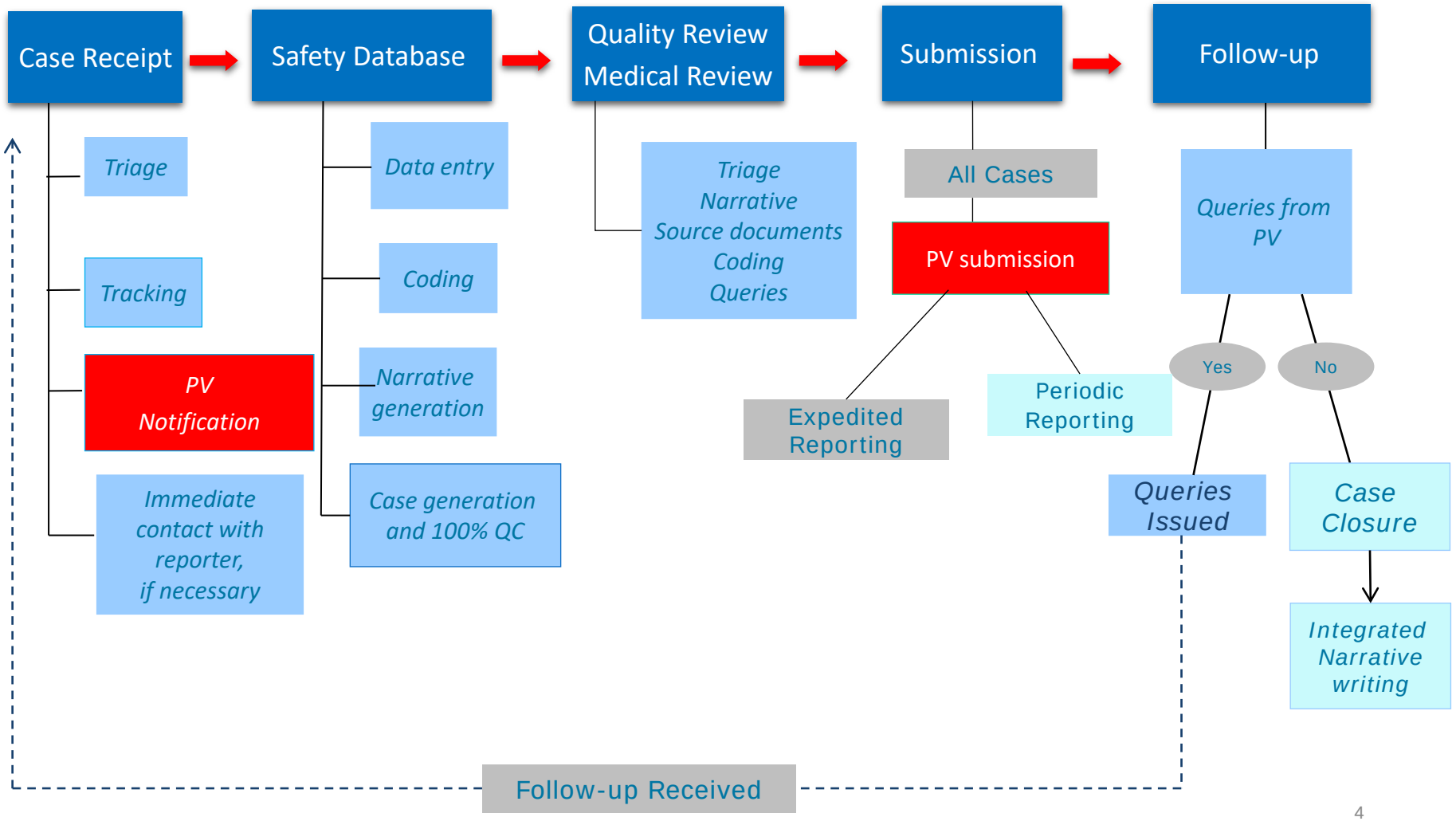
Definitions in national legislation are in general consistent (not verbatim) with ICH definitions (ICH E2A and ICH E6)

Pharmacovigilance activities Workflow

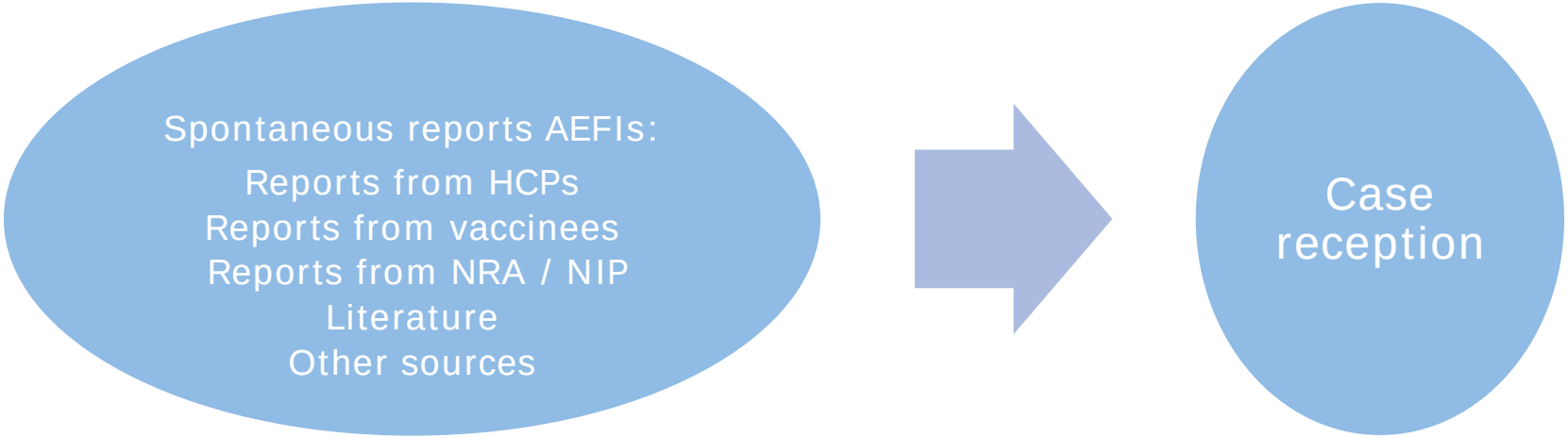


Chapalain 2014

Safety data processing
AEFI case handling workflow



Case Receipt

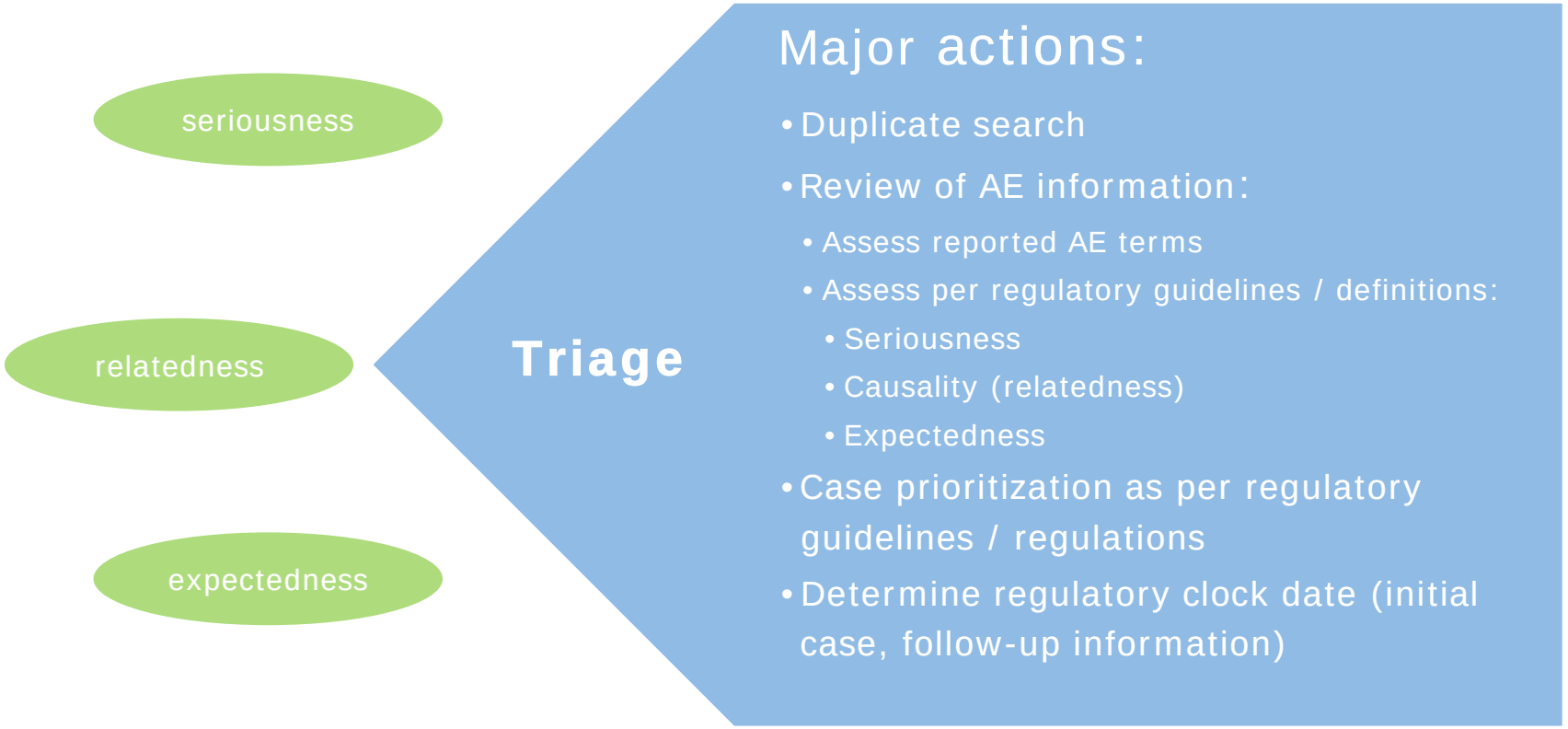


Major actions:

- Case intake / date of receipt (clock date)
- Acknowledge receipt
- Assign case number *
- Tracking of case receipt
- First check of case validity
- Request additional information, where necessary
- Translate AEFI into English, if appropriate

* depending on the PV database system (manual or electronic)

Case Triage


seriousness
relatedness
expectedness
Triage
Major actions:
• Duplicate search
• Review of AE information:
• Assess reported AE terms
• Assess per regulatory guidelines / definitions:
• Seriousness
• Causality (relatedness)
• Expectedness
• Case prioritization as per regulatory guidelines / regulations
• Determine regulatory clock date (initial case, follow-up information)

Seriousness assessment

- Assessment based on **outcome** of the AEFI
- ICH E2A seriousness criteria:
  - results in death
  - is life threatening — Requires medical judgement
  - requires hospitalization or prolongation of hospitalization
  - results in persistent or significant disability — Requires medical judgement
  - is a congenital anomaly
  - is medically important — Requires medical judgement

Determines expedited regulatory reporting of AEFI

Specificities of seriousness assessment

- Death: only serious if event caused death
- Hospitalization: only serious if inpatient stay (e.g., overnight), not emergency room
- Life-threatening / medically important (i.e., serious in the medical sense): requires individual medical assessment
- Company (MAH): Adverse Events of Special Interest (AESI) / designated AEFIs (MedDRA coded)
- CIOMS V / WHO Critical Term List (MedDRA coded)
- EU: Important Medical Event (IME) List (MedDRA coded)

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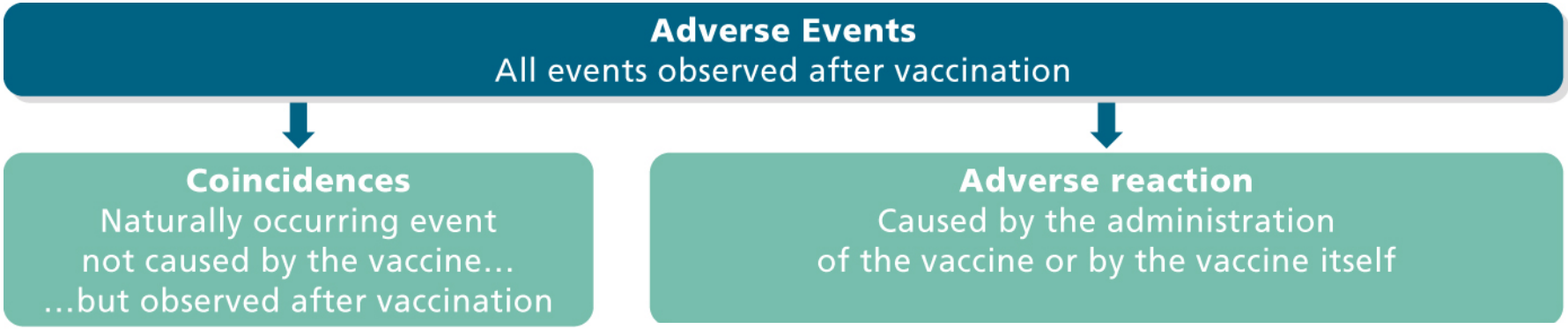
Relatedness (Causality)
Adverse Events following immunization AEFI



- Vaccine product related reaction
- Vaccine quality defect related reaction
- Immunization error related reaction
- Immunization anxiety related reaction

AEFI (WHO/CIOMS): Adverse medical occurrence following immunization and which does not necessarily have a causal relationship with the usage of the vaccine (**ICH E2A)**

Methods for assessment of relatedness (causality)

Clinical evaluation

- Global introspection: causality inference obtained via clinical judgement, such as with an expert panel
- Most common approach for causality assessment of individual case safety report; process is known to be subjective

Algorithm

- Causality classes: Sets of specific questions with associated scores for calculating the likelihood of a cause-effect relationship
- Standardized instrument to assess causality in a structured way (“reliable and reproducible measurement of causality”)

Probability theory

not useful for assessing single case reports

- Probability of a causal association calculated from available knowledge (observed versus expected)

Causality in vaccine safety
Main criteria

Biological plausibility

Examples:

- Fever after endotoxin containing vaccine
- Acute flaccid paralysis after oral polio vaccine

Laboratory evidence of vaccine involvement

Examples:

- Disseminated BCG in an immuno-compromised patient
- Urabe mumps vaccine in CSF of a patient with meningitis symptoms

Evidence of increased risk after vaccination

Examples:

- Clustering in a post vaccination period
- Higher risk in vaccinated compared to unvaccinated

Evidence across studies

Examples:

- Consistent increased risk of aseptic meningitis with MMR vaccines within 15-35 days post vaccination
- Consistent inability to find evidence of an association between vaccination and incidence (e.g., MMR vaccines and autism)

Components of causality assessment

Eligibility	Determine if information collected in AEFI case investigation is sufficient for conducting causality assessment (e.g, Brighton case definition available?)
Data review	Review of specific and essential information to assess causality (e.g., good case quality)
Algorithm	Guide in the interpretation of available data and review their consistency
Classification	Classify the AEFI in one of the four final WHO categories to facilitate appropriate actions (unclassifiable, consistent, indeterminate, inconsistent)

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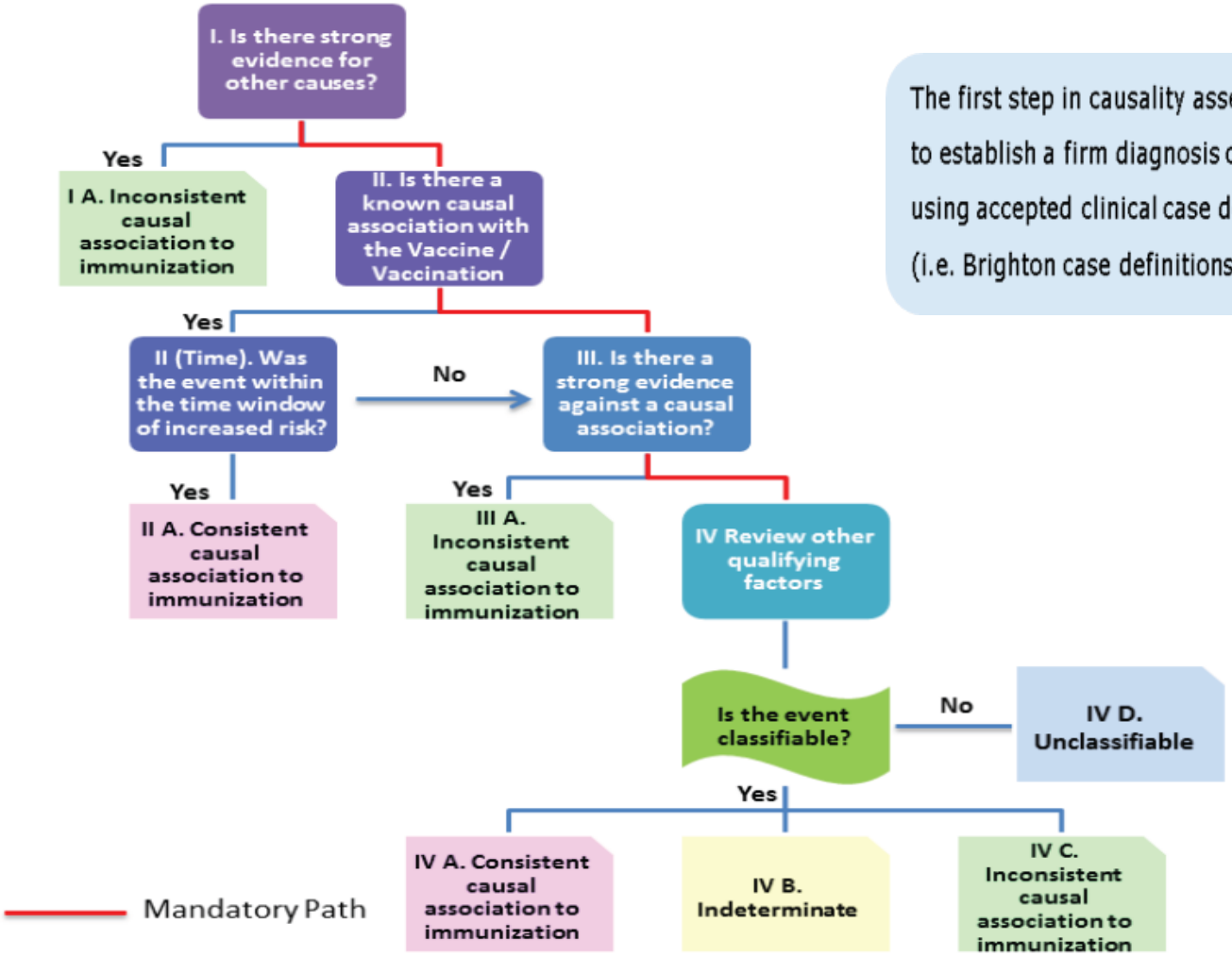
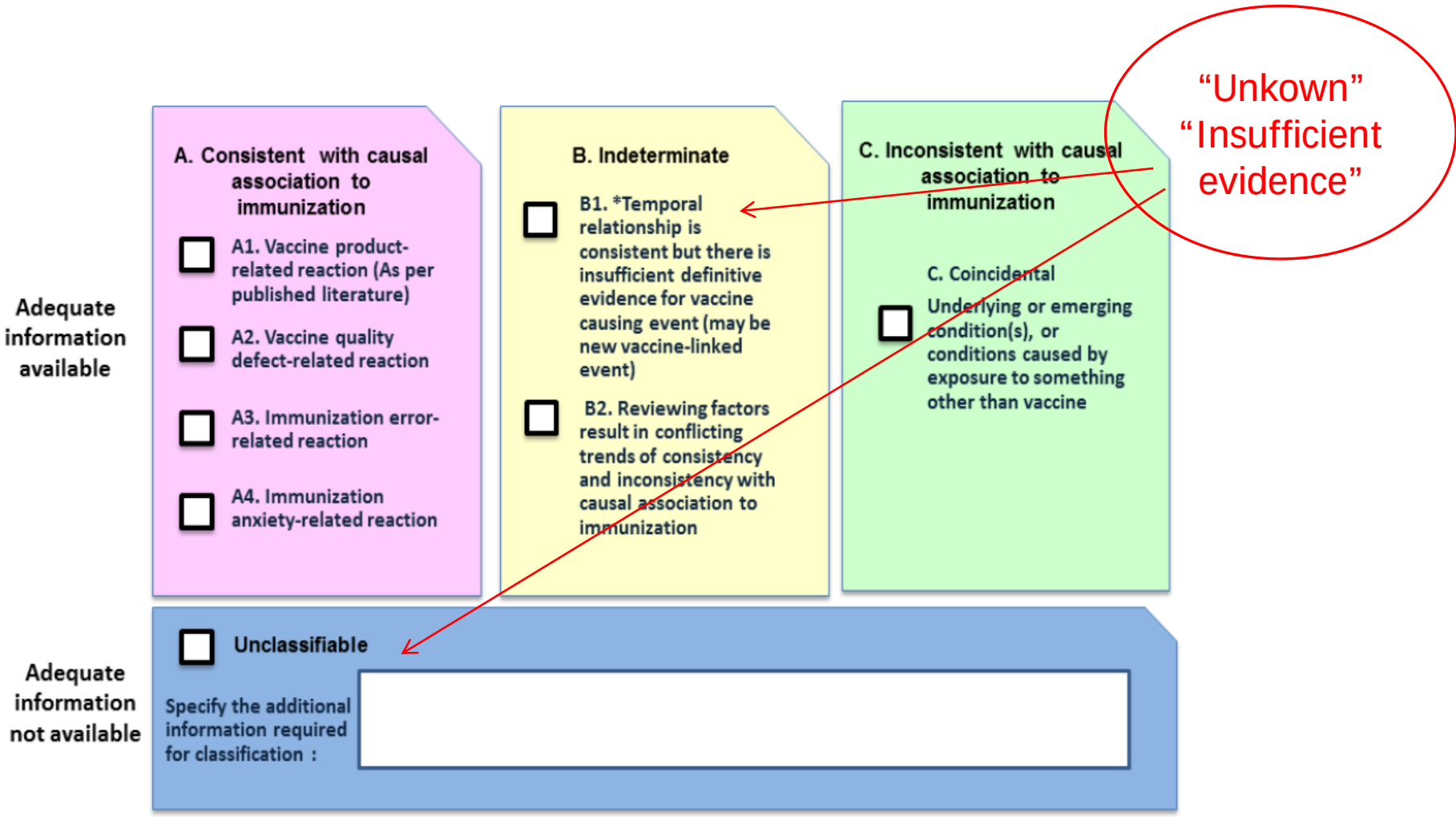
Causality Assessment
WHO Algorithm



The first step in causality assessment is to establish a firm diagnosis of the AEFI using accepted clinical case definitions (i.e. Brighton case definitions)

WHO Guideline on Causality Assessment



*B1: This is a potential signal and maybe considered for investigation

The causality assessment checklist.

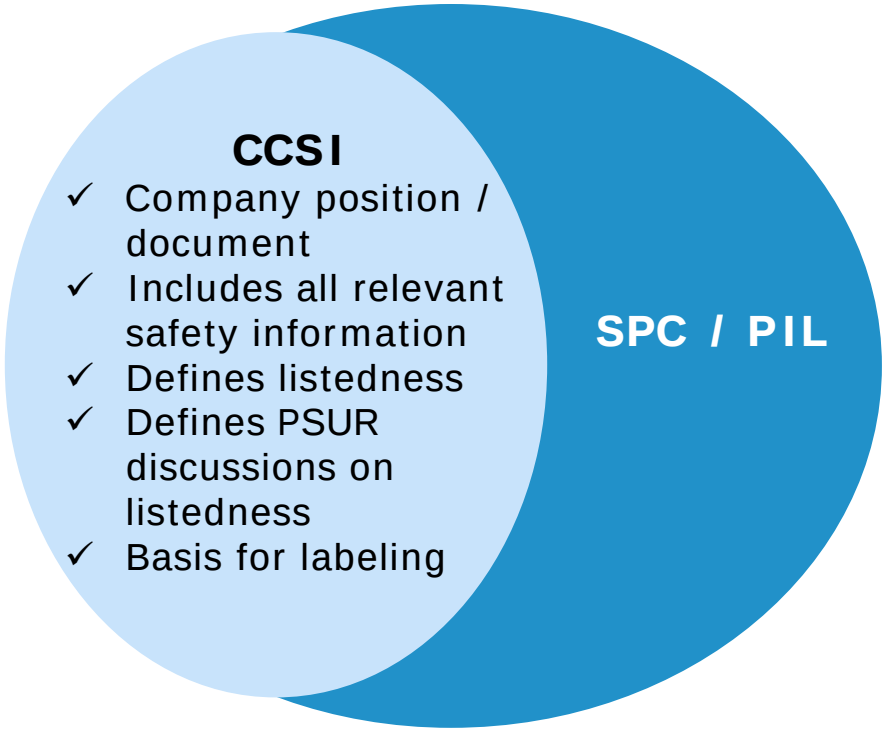
	Y N UK NA	Remarks
I. Is there strong evidence for other causes?		
Does a clinical examination or laboratory tests on the patient confirm another cause?	☐☐☐☐	
II. Is there a known causal association with the vaccine or vaccination?		
Vaccine product(s)		
Is there evidence in the literature that this vaccine(s) may cause the reported event even if administered correctly?	☐☐☐☐	
Did a specific test demonstrate the causal role of the vaccine or any of the ingredients?	☐☐☐☐	
Immunization error		
Was there an error in prescribing or non-adherence to recommendations for use of the vaccine (e.g. use beyond the expiry date, wrong recipient etc.)?	☐☐☐☐	
Was the vaccine (or any of its ingredients) administered unsterile?	☐☐☐☐	
Was the vaccine's physical condition (e.g. color, turbidity, presence of foreign substances etc.) abnormal at the time of administration?	☐☐☐☐	
Was there an error in vaccine constitution/preparation by the vaccinator (e.g. wrong product, wrong diluent, improper mixing, improper syringe filling etc.)?	☐☐☐☐	
Was there an error in vaccine handling (e.g. a break in the cold chain during transport, storage and/or immunization session etc.)?	☐☐☐☐	
Was the vaccine administered incorrectly (e.g. wrong dose, site or route of administration; wrong needle size etc.)?	☐☐☐☐	
Immunization anxiety		
Could the event have been caused by anxiety about the immunization (e.g. vasovagal, hyperventilation or stress-related disorder)?	☐☐☐☐	
II (time). If "yes" to any question in II, was the event within the time window of increased risk?		
Did the event occur within an appropriate time window after vaccine administration?	☐☐☐☐	
III. Is there strong evidence against a causal association?		
Is there strong evidence against a causal association?	☐☐☐☐	
IV. Other qualifying factors for classification		
Could the event occur independently of vaccination (background rate)?	☐☐☐☐	
Could the event be a manifestation of another health condition?	☐☐☐☐	
Did a comparable event occur after a previous dose of a similar vaccine?	☐☐☐☐	
Was there exposure to a potential risk factor or toxin prior to the event?	☐☐☐☐	
Was there acute illness prior to the event?	☐☐☐☐	
Did the event occur in the past independently of vaccination?	☐☐☐☐	
Was the patient taking any medication prior to vaccination?	☐☐☐☐	
Is there a biological plausibility that the vaccine could cause the event?	☐☐☐☐	

Note: Y, Yes; N, No; UK, Unknown; NA, Not applicable.

Tozzi et al., Vaccine 2013

Expectedness in regulatory reporting

Expectedness of an AEFI depends on the Relevant Safety Information (RSI)
ICH E2A / ICHE2D

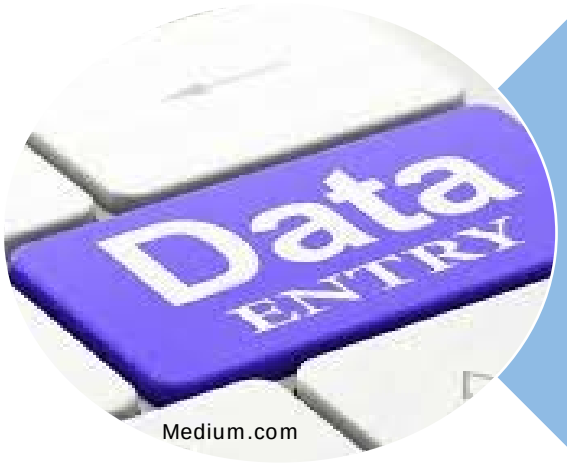


SPC - Summary of Product Characteristics
PIL - Patient Information Leaflet:

- ✓ Medico-legal document
- ✓ Safety information approved by Regulatory Authority for health professionals and patients
- ✓ Defines expectedness
- ✓ Basis for expedited regulatory reporting

CCSI: Company Core Safety Information

Data entry



Medium.com

Major actions:

- Assign case identification number*
- Perform data entry
- Medical Coding:
  - AEFI terms
  - Medical history
  - Vaccine
- Generate narrative
- Analysis of similar events

* depending on the PV database system (manual or electronic)

Medical Coding

MedDRA® -Medical Dictionary for Regulatory Activities

Medical dictionary for all activities in the frame of Regulatory Activities

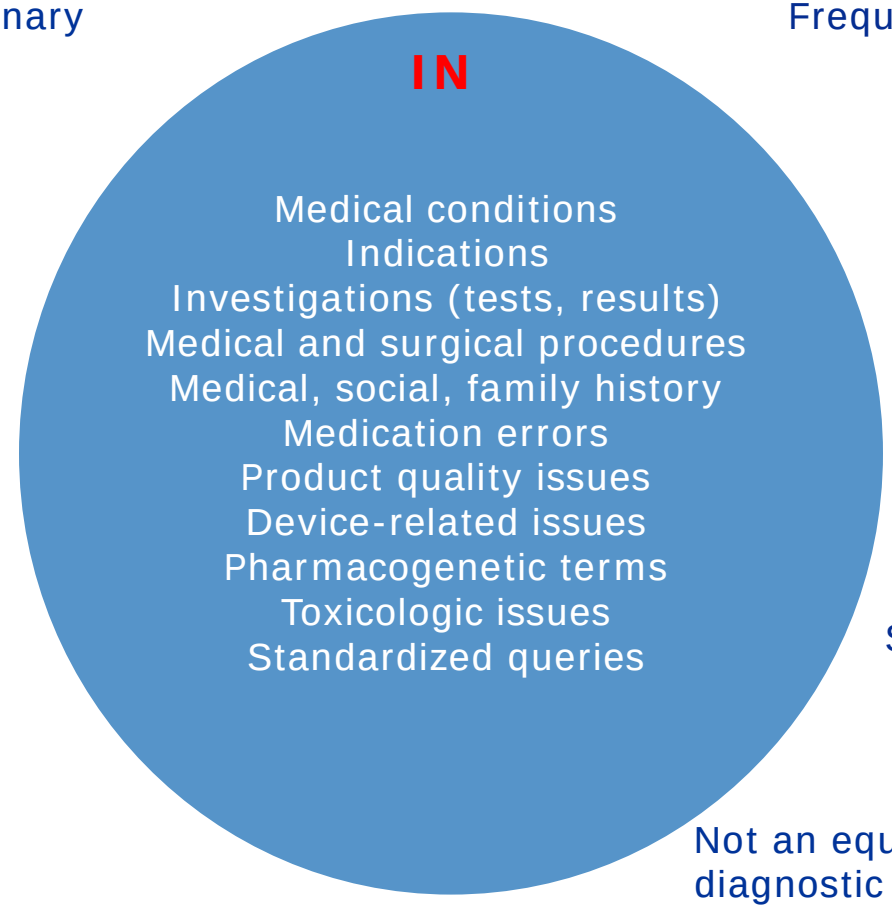
- The terminology is used through the entire regulatory process, from pre-marketing to post-marketing, and for data entry, retrieval, evaluation, and presentation
  - To standardize the communication during the whole life-cycle of a product
- Supports electronic reporting of ICSRs and eCTD
- Annual updates (version 23.0 March 2020)

Requires license

Price depends on the annual revenue of the company

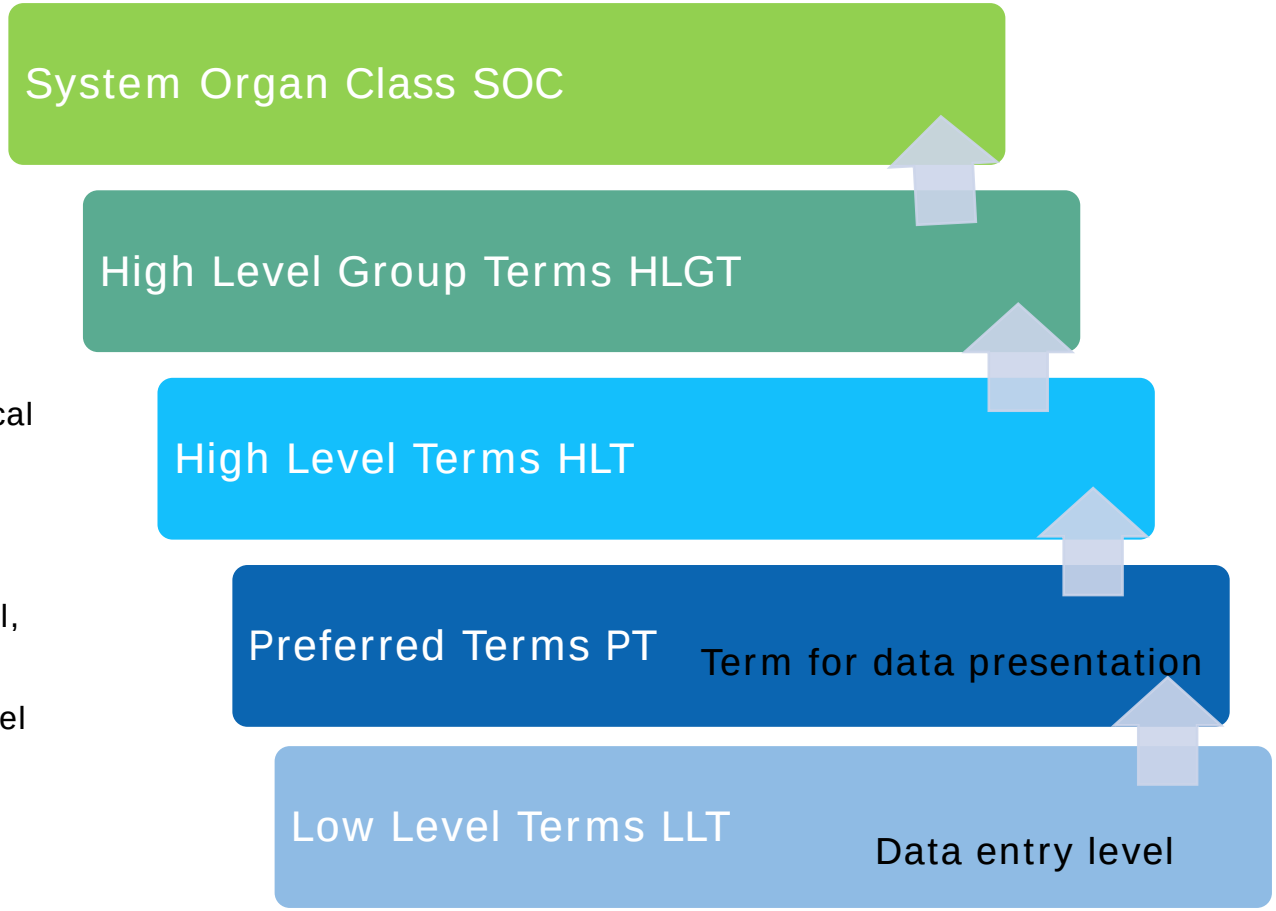
Fee waiver for SMEs using EVWEB to fulfill reporting obligations in the EU

Scope of MedDRA

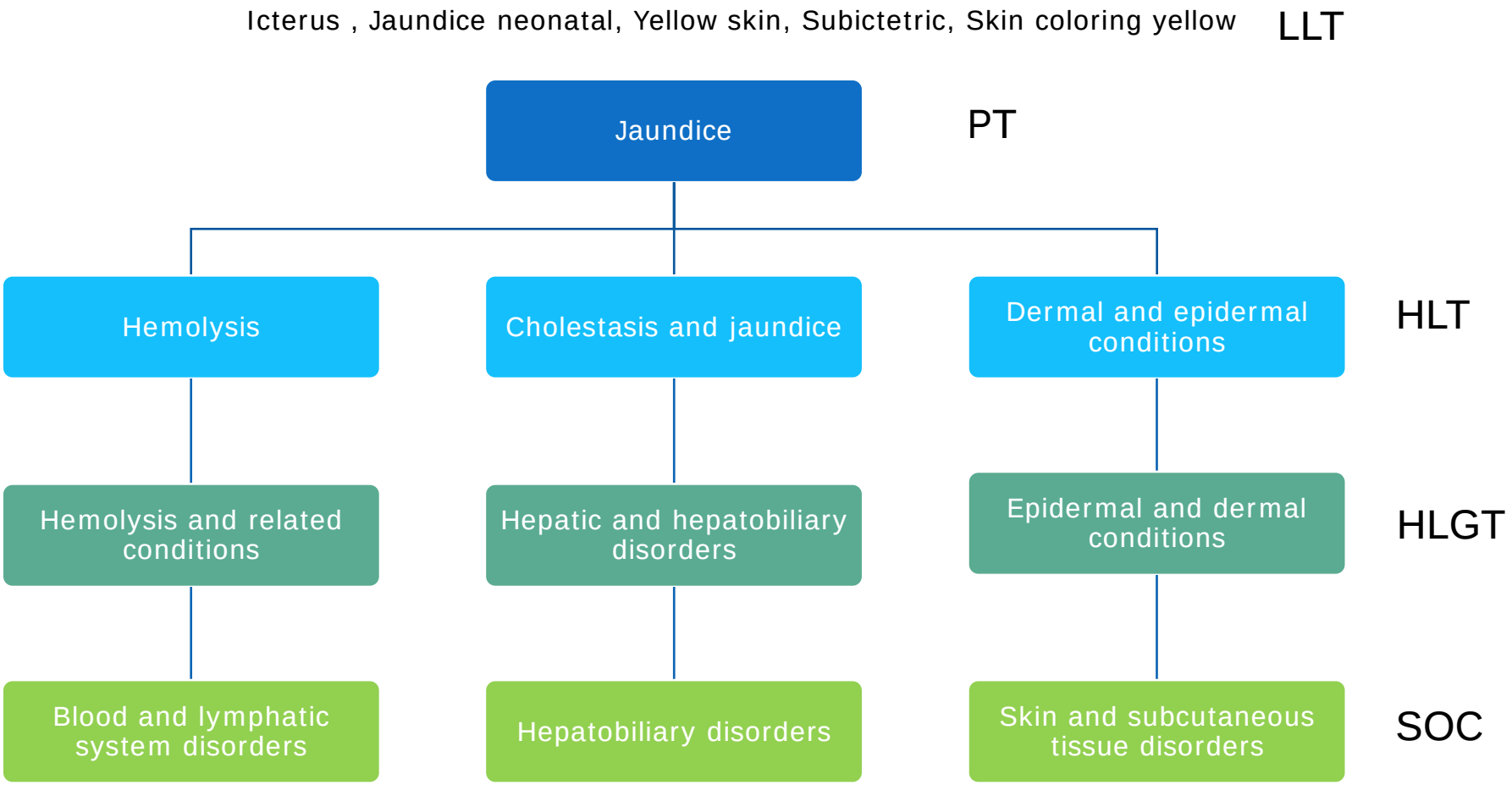


The five levels of MedDRA hierarchy

- International standardized terminology
- Enables electronic data transfer
- Data consistency of medical terms
- Multiaxiality:
  Anatomical, patho-physiological, etiological, functional
- High specificity on LLT level – spontaneously reported data often not specific enough



Multiaxial Structure - Example



Coding issues

Cascade or indirect codes

- Provide the key terms:
  - direct AE coding (e.g., dizziness) or indirect AE coding (fall and subsequent hip fracture due to dizziness)

How many codes

- Limit number of codes to understand the major issues and not get lost in lesser issues (or secondary cascade)

Lumping versus splitting

- Use diagnosis or symptoms instead of individual single events, whenever possible

Specificity

- May vary depending on case; e.g. edema may have a different medical meaning (pulmonary edema versus leg edema)

Consistency

- Many synonyms in MedDRA

Cultural, language and national differences

Points to consider

- MSSO gives tips and suggestions on coding; excellent document

Coding specificities - Examples

Medical interpretation

- Example: Reported “nausea, vomiting, diarrhea, **cramps”**
  - LLT cramps – PT Muscle spasms - SOC Musculoskeletal and connective tissue disorders
  - LLT abdominal cramps – PT abdominal pain - SOC Gastrointestinal disorders

Diagnosis versus signs and symptoms

- Example: Reported “abdominal pain, amylase and lipase elevated”
  Verbatim coding (symptoms) or pancreatitis (diagnosis)?
- Example: Reported “anaphylactic reaction with dyspnea, hypotension and laryngospasm”
  Verbatim coding diagnosis with symptoms or diagnosis and reported symptoms as co-manifestations?

Site of manifestation versus specificity

- Example: Reported “skin rash on face and neck”
  Verbatim coding of symptom only (without site of manifestation)

Data retrieval for signaling and presentation

MedDRA to retrieve and present data:

- Summary tabulations for scientific and signal detection analyses:
  - List similar events in groups to identify clusters
  - Use of SMQs (Standardized MedDRA Queries) for signal detection and monitoring
  - Present Preferred Terms PT in connection with their System Organ Class SOC

Strengths / Weaknesses of MedDRA

Strengths

- International standardized terminology
- Electronic data transfer is made easier
- Data consistency (AEFI, product information etc.)
- Multiaxiality
  - Anatomical, pathophysiological, etiological, functional

Weaknesses

- Multiaxiality
  - Primary versus secondary SOCs
  - Data consistency
- Weak coding system for post-marketing: high specificity on LLT level - reported data are often not specific enough

MedDRA big and complex in practice
Difficult to use in a paper-based system

MedDRA training required

Quality review

Major actions:

- Quality review (QC) 100%
- Check case for accuracy
- Check case for completeness
- Check case for consistency
- Ensure correct coding (AEFI, medical history and product
- Check seriousness and labeling (expectedness)

Medical review

Major actions:

- Confirm triage (prioritization)
- Check case for medical sense
- Check and confirm medical coding
- Check and confirm seriousness and labeling (expectedness)
- Make company causality assessment from medical point of view and / or upgrade reporter causality
- Request non-routine follow-up, if appropriate
- Review the data for potential signals

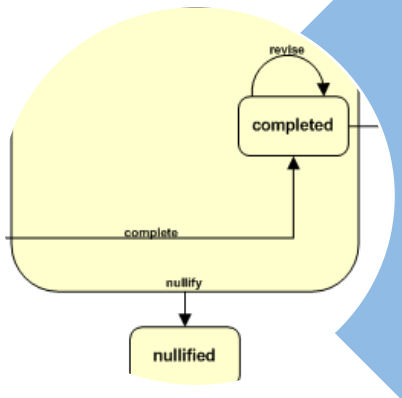
There is no actual regulation (FDA, EMA, MHRA) that requires a physician to review ICSRs, however medically qualified personnel should review all cases.

Distribution of ICSR Reconciliation

Major actions:

- Submission of expedited report (e.g., 15 day report) according to regulatory requirements (i.e., national / global)
- Distribution to business partner as per Safety Data Exchange Agreement (SDEA)
- Distribution to Safety Monitoring Committee (SMC), if applicable
- Confirm receipt of acknowledgement
- Reconciliation with external data collection partners
- Reconciliation with product quality complaints and medical information queries

Case completion - Case closure (locking)



Major actions:

- Ensure all data are corrected
- Incorporate any request changes
- Ensure that all follow-up action are completed
- Ensure that no changes can be made after locking in the case*

* depending on the PV database system (manual or electronic)

Vaccination Failure (Lack of Effect)
Causes of vaccination failures

Type of failure	Causes
Failure to vaccinate	
Usage-related	- Administration error (wrong route, dose, diluent) - Vaccination schedule not adhered to - Wrong storage (out of cold chain) - Expired vaccine used
Program-related	- Suboptimal recommendation (number and time points of doses - primary and booster) - Vaccine shortage
Vaccine failure	
Host-related	- Immunodeficiency, immunosuppressive therapy, health status - Waning immunity, age-related decrease in immune response - Low/Non-responders - Interference (antibodies or infection)
Vaccine-related	- Vaccine not 100% efficacious - Incomplete coverage of strains, variants, mutants - Vaccine-vaccine interactions (co-administered vaccines) - Manufacturing related (batch variation, quality defect)

Report of WHO/CIOMS WG on Vaccine PV (2013):Definitions and Application of Terms for Vaccine Pharmacovigilance.

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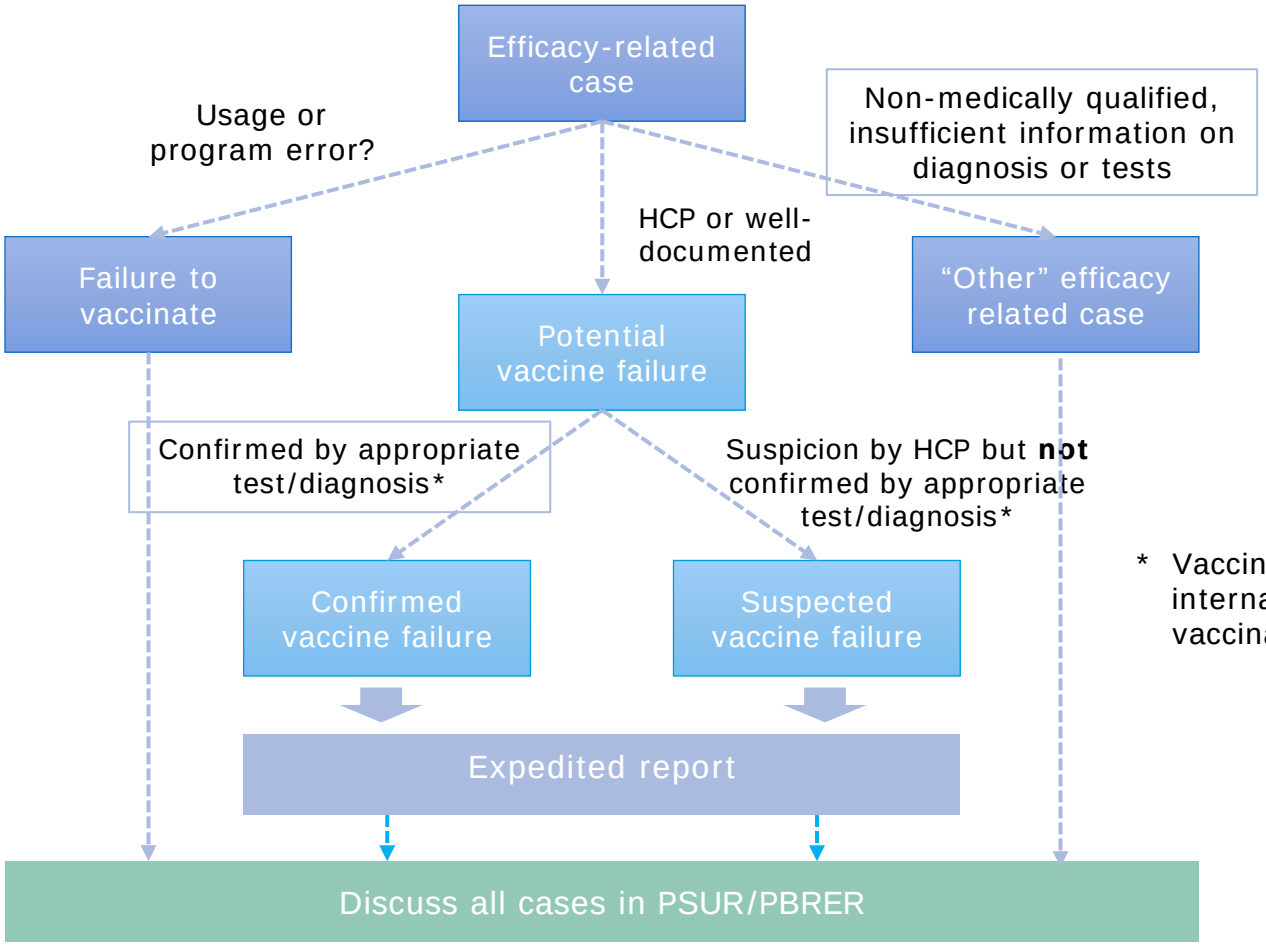
Vaccination Failure (Lack of Effect)
Assessment of efficacy related cases



Vaccines are not 100% effective. Vaccination failure is not an event, but an assessment based on vaccine specific guidelines.

* Vaccine-specific, as per internal guideline on vaccination failures

Report of WHO/CIOMS WG on Vaccine PV (2013):Definitions and Application of Terms for Vaccine Pharmacovigilance.

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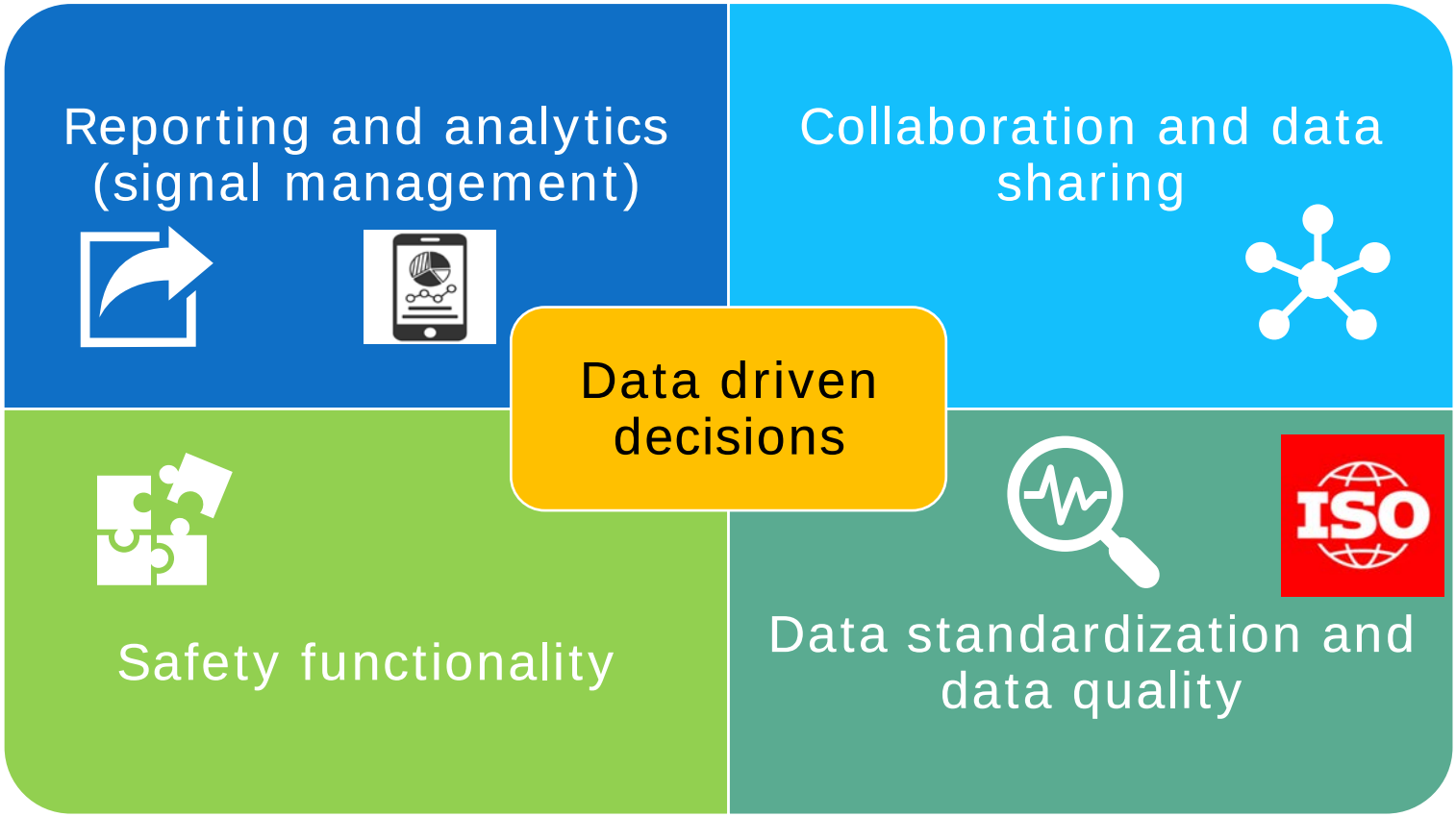
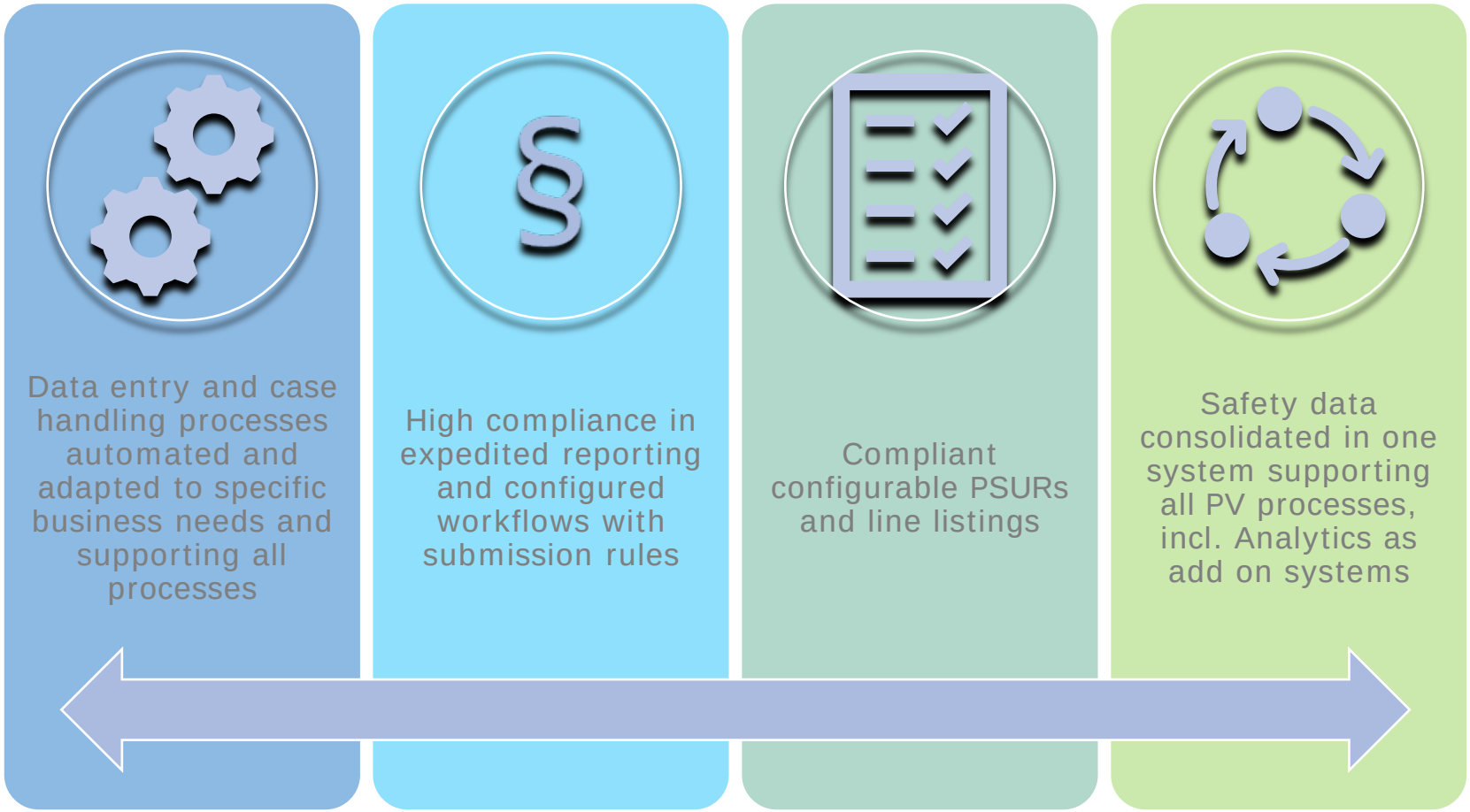
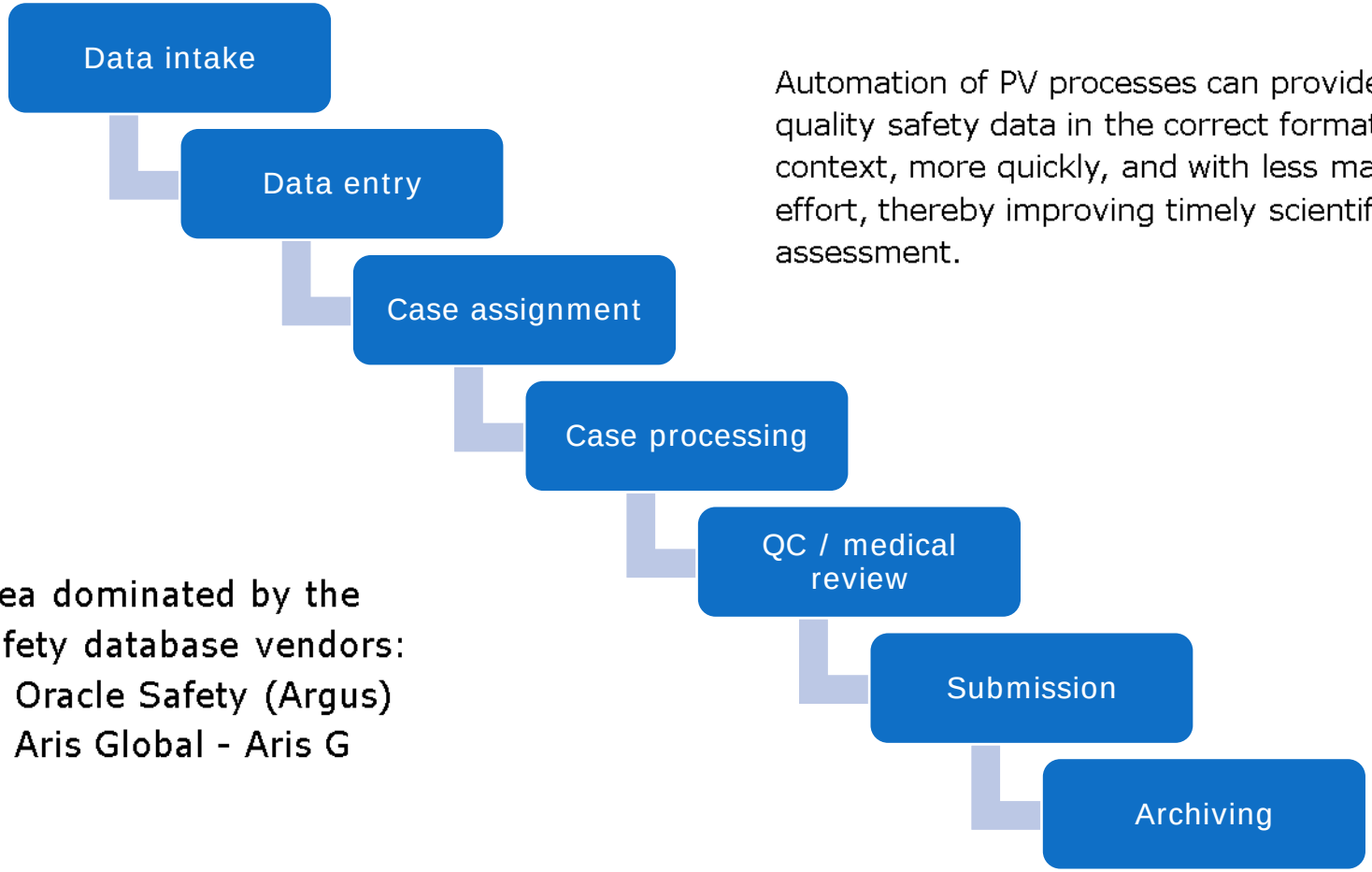
Benefits of Safety Databases



Benefits of a system-based Pharmacovigilance setup



Typical case handling workflow of a safety database system

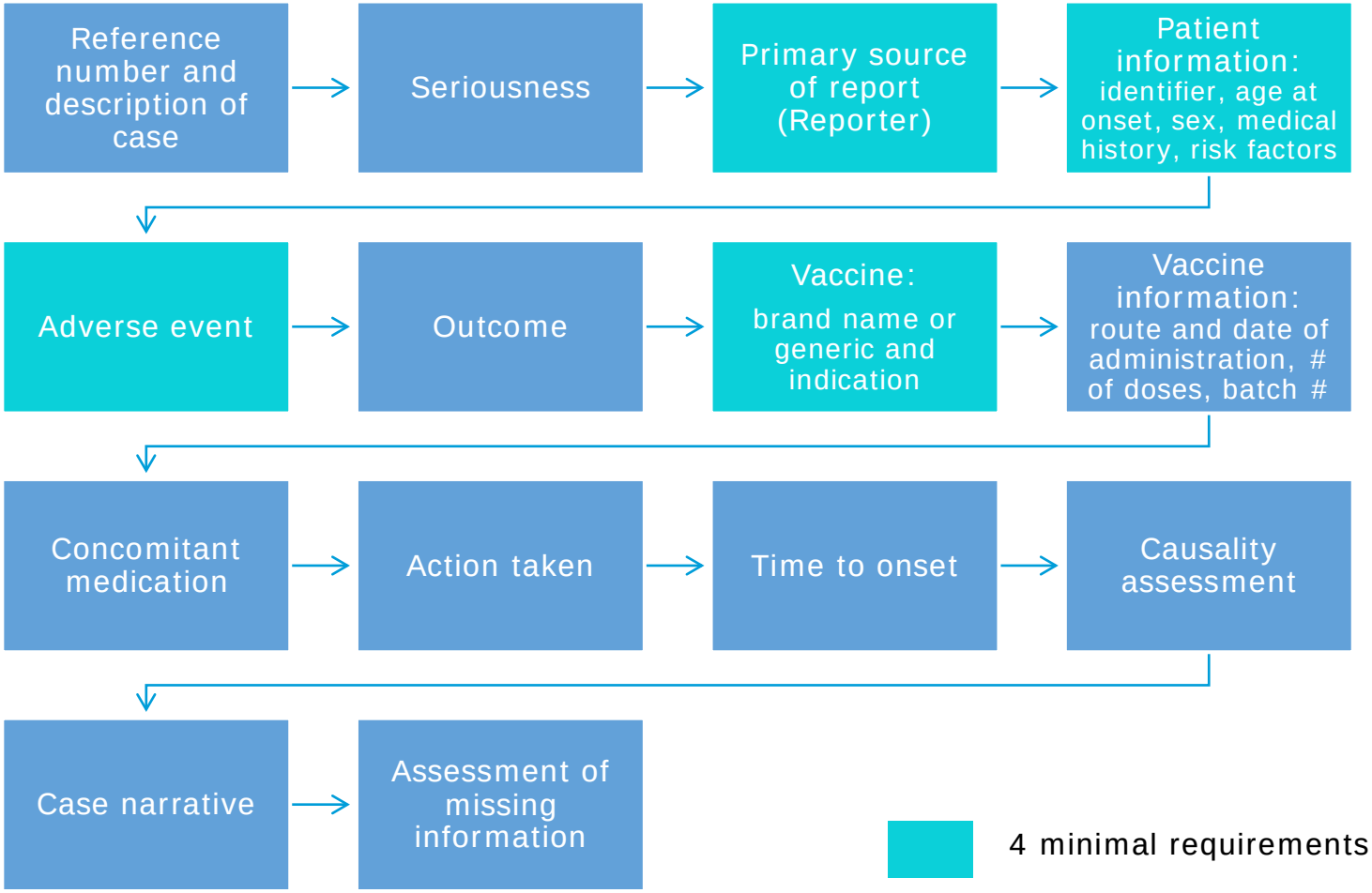


Automation of PV processes can provide high quality safety data in the correct format, in context, more quickly, and with less manual effort, thereby improving timely scientific assessment.

Area dominated by the Safety database vendors:

- Oracle Safety (Argus)
- Aris Global - Aris G

Essential data for good case quality



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