DCVMN Pharmacovigilance Training
Workshop 6
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dcvmn
Developing Countries Vaccine Manufacturers Network

Medical assessment of ICSRs Brighton case definitions

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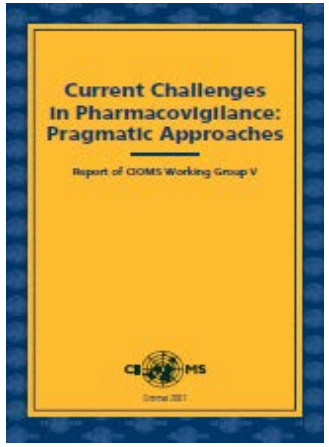
Setting the Scene
Medical Evaluation of ICSRs

- The purpose of medical review is to ensure correct interpretation of medical information.
- Information must be
  - accurate
  - complete
  - trustworthy
  - verifiable



INTERNATIONAL CONFERENCE ON HARMONISATION OF TECHNICAL REQUIREMENTS FOR REGISTRATION OF PHARMACEUTICALS FOR HUMAN USE

ICH HARMONISED TRIPARTITE GUIDELINE

POST-APPROVAL SAFETY DATA MANAGEMENT:
DEFINITIONS AND STANDARDS FOR EXPEDITED REPORTING
E2D

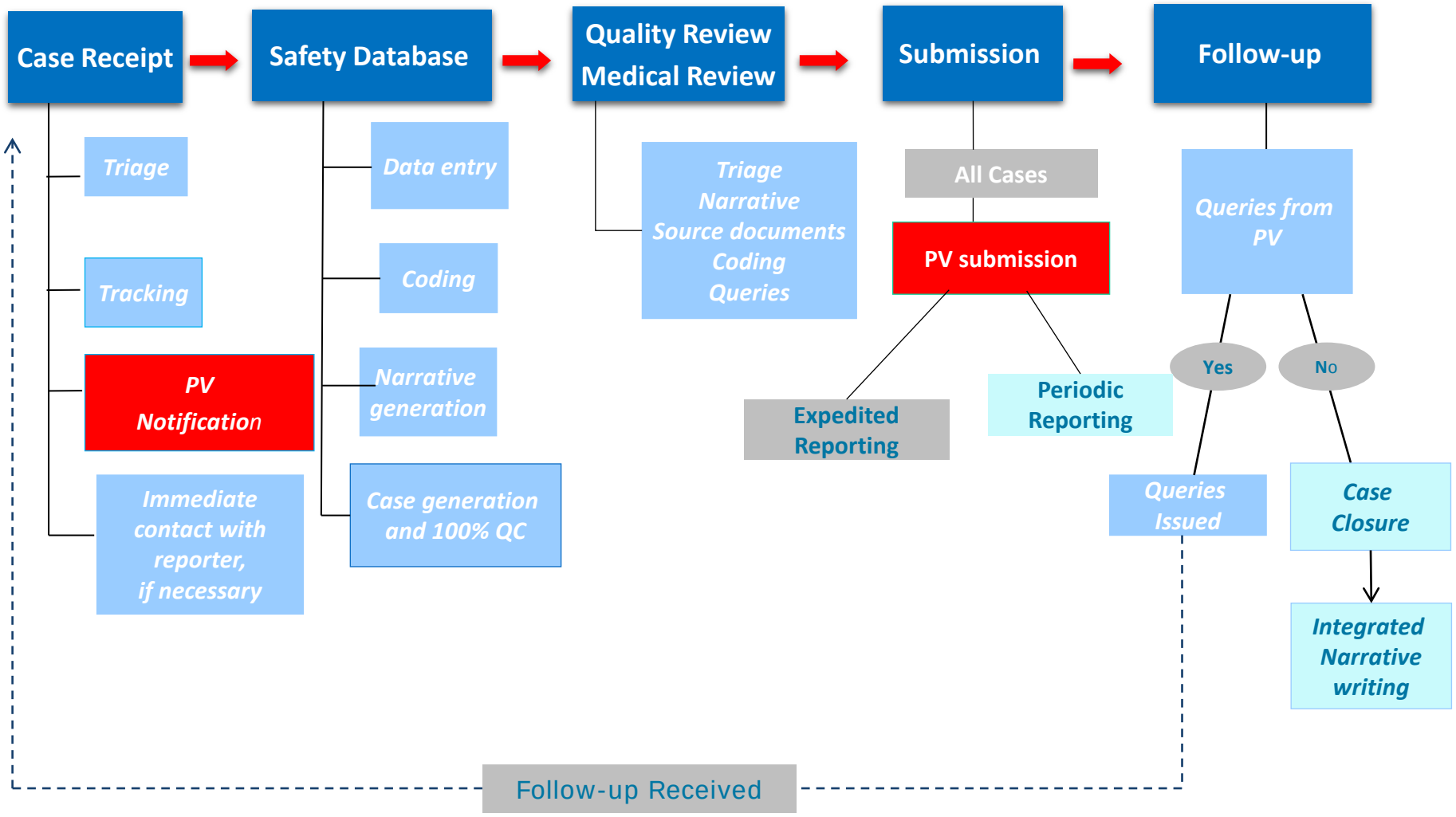
HMA
Heads of Medicines Agencies

EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

28 July 2017
EMA/873138/2011 Rev 2*

Guideline on good pharmacovigilance practices (GVP)
Module VI – Collection, management and submission of reports of suspected adverse reactions to medicinal products (Rev 2)

Safety data processing
Case handling workflow



Medical Review Process
Overview

- Verification of the reported data entered
- Review for F/U information
- Assessment of AEFI / ICSR
- Assessment of causality
- Assessment of expectedness
- MAH's comment
- Narrative

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.

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Verification of the reported data

- General information: Report type, source, receipt date, F/U status
- Patient information: initials / subject ID, age, sex, risk information etc.
- Vaccine information: suspect vaccine, vax date, primary/booster vax, # dose, single/multidose, lot #, injection site, co-medication
- Event information / assessment: description of event terms, MedDRA coding, onset date, outcome, seriousness criteria
- Review coding to ensure accurate MedDRA codes of verbatim terms
- Review assessment of expectedness as per RSI
- Verify reporter causality - assess company causality
- Review case narrative

Review for Follow-up Information

- Check for missing key data elements as per ICH E2D / GVP VI
- Determine if F/U information is required for scientific evaluation
- F/U methods to be tailored to optimize the collection of important missing information; may be driven by local culture
- Priority for F/U e.g.: 1. serious unexpected; 2. serious expected, 3. non-serious unexpected – AESIs, cases potentially leading to labelling change
- Use of targeted questionnaire / specific report form for clinically relevant AEFIs / AESIs

Assessment of ICSR / AEFI

Clinical case evaluation

Evaluation of the medical information through clinical evaluation

- Is a diagnosis possible – do reported events allow for a diagnosis?
- Have relevant diagnostic procedures been performed?
- Alternative causes of event(s) considered?

Review reported information for consistency, quality, completeness

- Does the report contain ambiguous data?
- Does the case accurately reflect the medical information in the source documents?

Confirm the event term(s) as provided in the source document

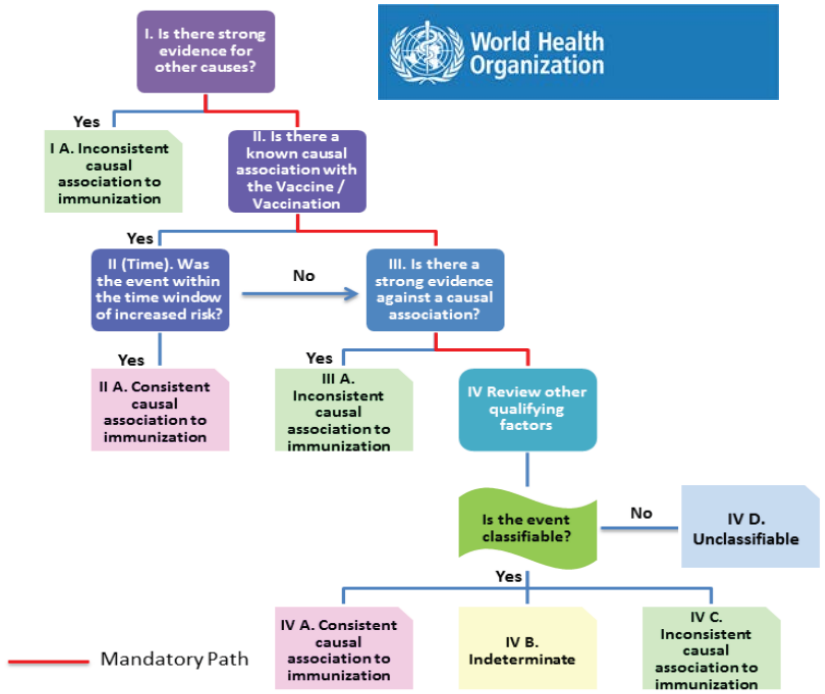
Confirm accurate transcription / selection of the verbatim events entered (as reported)

Apply Brighton Case Definition to confirm diagnosis

Assessment of causality

- Review the “as reported” causality; if no reporter causality obtained, presume case as “related”
- Determines MAH / company causality for each event and overall case assessment
- Document rationale / justification for company / MAH causality assessment
- Literature cases: “as reported” causality
- In general: For regulatory reporting causality may be upgraded, but not downgraded.

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)



Serious - Severe

- 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

Severe

Based on the **intensity** of the AE; not a factor in determining reportability (clinical description / subjective description)

Determined using grading tables, e.g.:
Mild – moderate – severe
FDA Toxicity Table

Assessment of seriousness

- Death: only serious if event caused death
- Hospitalization: only serious if inpatient stay (e.g. not emergency room / examination on an outpatient basis
- All congenital anomalies / birth defects considered serious
- 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)

Serious?

- Total blindness for 30 minutes
- „Mild“ anaphylaxis
- Suicide threat
- Spontaneous abortion
- Stomach washout in emergency room
- Lab test result above a level requiring fast tracking in protocol
- Unconsciousness for seconds

Assessment of expectedness

Expectedness defined by the Relevant Safety Information RSI

For ICSRs, assessment refers to product information (e.g., SmPC, PIL)

- Expected - Labeled
- Unexpected - Unlabeled

Determine if reported AEFI is included in the RSI

- Is the AEFI term included in the section 4.8 of the SmPC "Undesirable Effects" ?
- Is the AEFI different re its nature, severity, specificity or outcome as under 4.8 of the SmPC?

Rational for an AEFI considered «expected» if not verbatim in the SmPC

Class labelling does not count as "Expected"

SmPC - 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

MAH's Comments

Comments by Medical Reviewer to be included for all serious ICSRs at the end of the report

- Company causality (with rationale)
- Temporal association (plausible / not plausible)
- Confounding factors (underlying disease, co-medication etc.)

For non-serious cases confirm if MAH concurs with reporter's assessment

Medical reviewer may include any other important information for scientific evaluation

MAH Case Narrative

MAH's case narrative is a comprehensive stand-alone "medical story"

- All relevant clinical and related information must be included
- Key information from supplementary records included
- Clear guidance on MAH case narratives provided in CIOMS V Report

Provide Narratives for all serious and non-serious unexpected cases

Review for consistency, accuracy and quality of the narrative

Add medical evaluation comments and provide company opinion in case of alternative causes (if applicable)

Provide assessment on the influence of the ICSR on the benefit-risk relationship

Narrative components

- Lead Banner (e.g., case reference number)
- Report/Reporter Type and Patient Demographics
- Medical History, Concurrent Conditions and Concomitant Medication
- Suspect Vaccine(s)
- Timing and Onset of Event(s)
- Progression and Outcome of Event(s)
- Causality
- Closing Remarks
- Follow up Information
- Case Corrections / deletions
- Literature Information
- End of Study Unblinding for CT cases
- Reporter Comment
- Company Comment

Coded terms: Myocardial infarction. Rash. Nausea.

1. Case reference number 16041938 is a spontaneous case report sent by a hospital pharmacist which refers to a male aged 84 years.

2. The patient's past medical history included gastric ulcer, asthma, and hypertension. At the time of the event the patient had Lyme Disease and severe headache. The following drugs are known to have been taken by the patient prior to the event (start date in parentheses): cimetidine (1996), steroids (1990) and tetracycline (September 9, 1999). The patient has a history of allergy to penicillin and gin.

3. On 1 January 2000 at 1:00 PM, the patient started taking qweasytrol for vomiting. Some 12 hours later, and 10 minutes following the latest dose, the patient developed rash, dyspnea and queasiness. Over the period of the next two days, the patient also developed chest pain and later unconsciousness. Relevant laboratory test results include elevated CK-MB and relevant physical signs were hypertension, fourth heart sound and bradycardia. The patient was hospitalized. Hospital records are available on request. The eventual diagnosis made on the 10 January 2000 was myocardial infarction.

4. The patient was treated for the event with a beta-blocker; qweasytrol was discontinued on 8 January 2000.

5. The patient died on 12 January 2000 from myocardial infarction; no autopsy was done. Death occurred approximately 12 days after the treatment with qweasytrol began and 4 days after it was discontinued.

7.* The cardiologist cited in the pharmacist's report considers the myocardial infarction possibly related to qweasytrol. In his opinion, other possible etiological factors include hypertension and the patient's age.

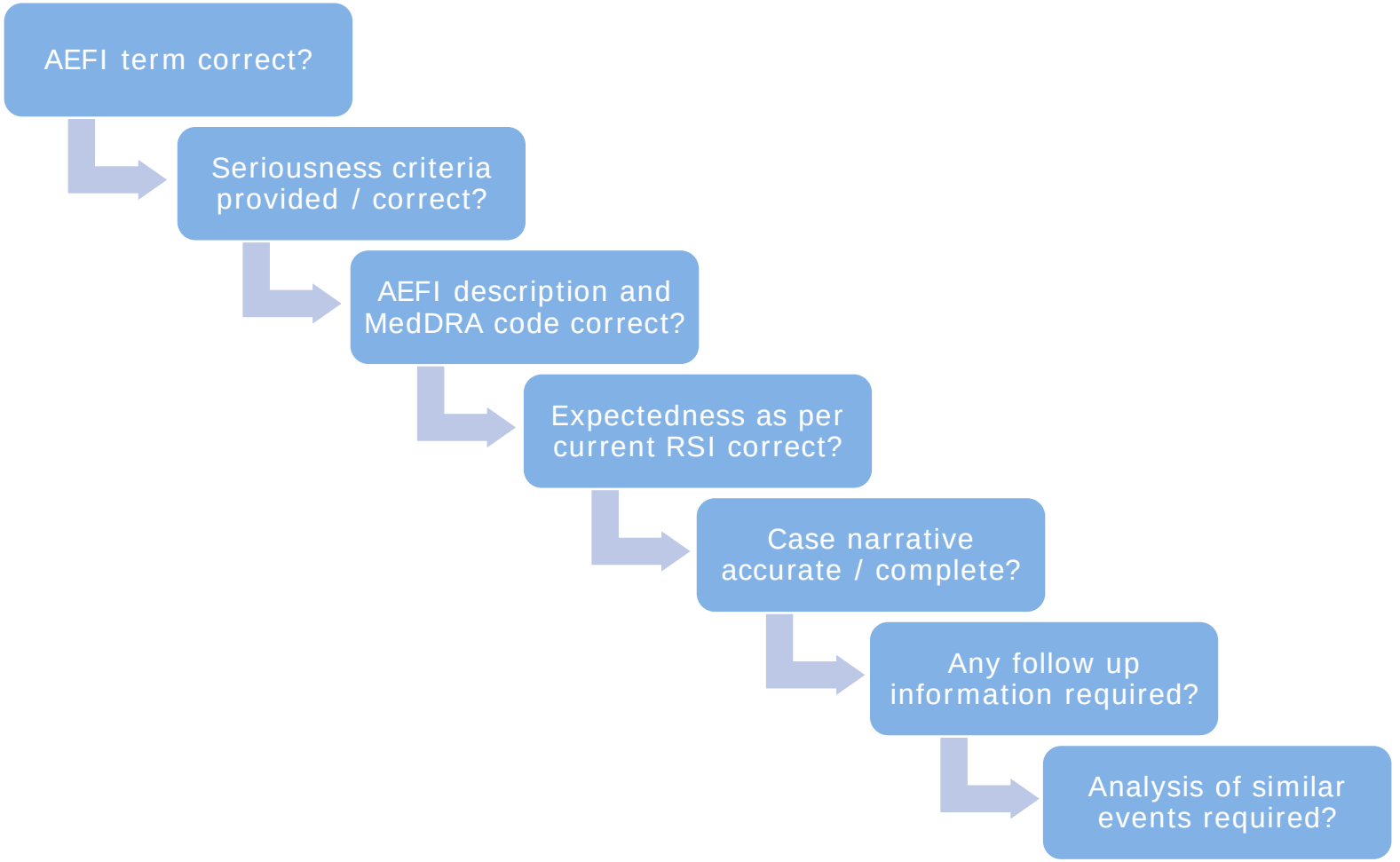
8. The company believes the following facts are also relevant in this case: as a highly selective epsilon — G2 receptor antagonist, there is no known plausible mechanism by which the drug would cause a myocardial infarction.

Example of a Standard Narrative Template

[Note: Underlining is used for illustration purposes only, to indicate information that can be extracted directly from the database on the case. Paragraph numbering is also used for demonstration purposes to highlight the order proposed for the template.]

CIOMS Working Group V: Report (Appendix 8): Current Challenges in Pharmacovigilance: Pragmatic Approaches

Medical Review Process
Summary of the Activities

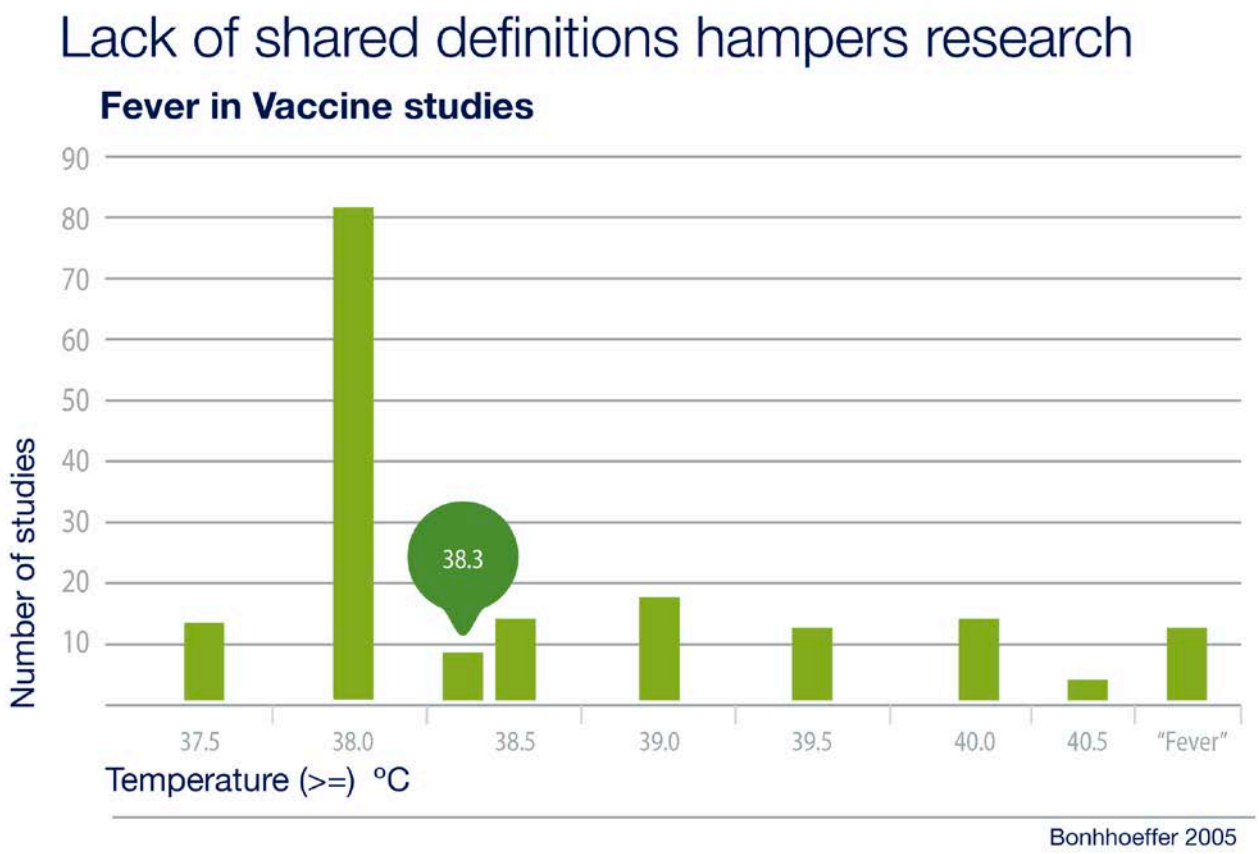


Founded in 2000

https://brightoncollaboration.us

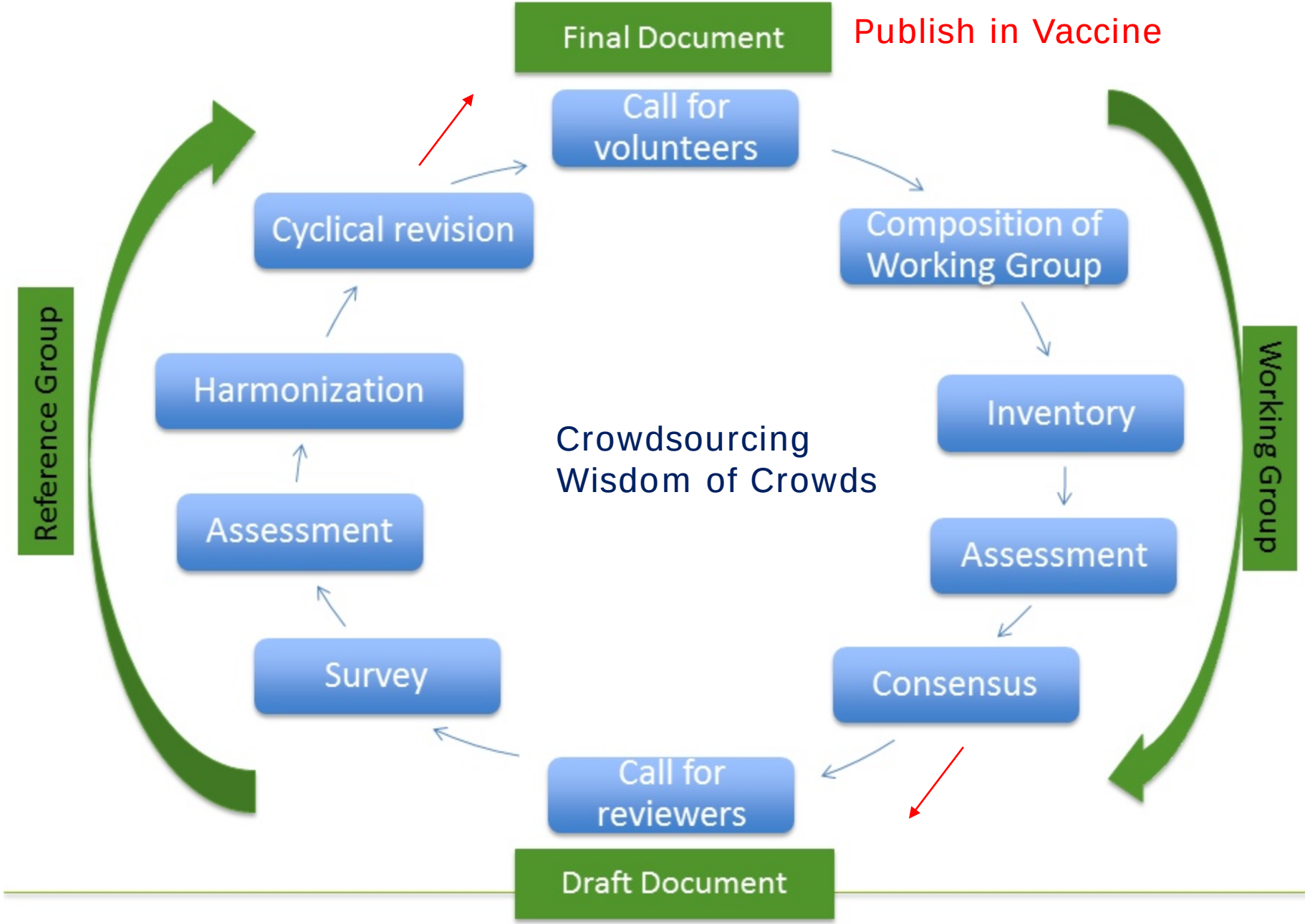
- **Goal:** to build trust in the safety of vaccines via rigorous science
- **Problem:**
  - Unlike efficacy, safety generally cannot be measured directly.
  - (Relative) safety inferred from relative absence of multiple adverse events following immunization (AEFI) studied given size of vaccinated population.
  - (Rare) AEFI easily missed unless standard case definition available.
- **Mission**: develop internationally accepted standards for monitoring vaccine safety throughout the vaccine life cycle
  - ~1000 volunteers from all stakeholders (academia, industry, government)
  - 20 years of enhancing vaccine safety research (by focusing on harmonization)

Brighton Collaboration recognized the need for harmonization



- Brighton Collaboration has delivered:
- >60 AEFI Case definitions (GAIA, GBS, seizures, intussusception etc.)
- Tiered by 3 levels of evidence
- Guidance for collection and reporting vaccine safety data
- Endorsements from major stakeholders (FDA, EMA, WHO, ….)

Brighton Collaboration Process



Basic Format of Standard Case Definitions

Level 1
- Criterion a AND
- Criterion b

→ **Definite Case, "Gold standard"**
Highest PPV
Possibly sophisticated diagnostics
(e.g., clinical trial, high income setting)

Level 2
- Criterion a OR
- Criterion b OR Criterion c

→ **Probable case**
Less sophisticated diagnostics

Level 3
- Criterion d AND
- Criterion e AND
- Criterion f

→ **Possible case**
Lowest PPV
Simple diagnostics
(e.g., passive surveillance, low income setting)

→ **Applicability during vaccine life cycle in all settings**

Aug 2021: 57 Published Brighton Case Definitions

- Abscess
- Anaphylaxis
- Aseptic Meningitis
- Bell's Palsy
- Cellulitis
- COVID-19 AESIs (ARDS, VAED, MISC/A; Pending Thrombosis, Myocarditis)
- Diarrhea
- Eczema Vaccinatum
- Encephalitis Myelitis
- Fatigue
- Fever
- Generalized Convulsive Seizure
- Generalized Vaccinia
- Guillain-Barre syndrome (GBS)
- Hypotonic-Hyporesponsive Episodes
- Inadvertent Innoculation
- Induration
- Intussusception
- Kawasaki Disease
- lgA Vasclitis (Henoch–Schönlein)
- Local reaction
- Nodule at injection site
- Pain
- Persistent crying
- Progressive Vaccinia
- Rash
- Robust Take
- Sensori-neural Hearing Loss
- Swelling
- Thrombocytopenia
- Unexplained Infant Deaths
- Vasculitic peripheral neuropathy
- Viscerotropic Disease
- Wheezing
- GAIA Obstetric x 10
- GAIA Neonatal x 11 (Microcephaly)

https://brightoncollaboration.us

Brighton collaboration | THE TASK FORCE FOR GLOBAL HEALTH

About News Publications & Tools Projects VSQ COVID-19 Get

BRIGHTON COLLABORATION CASE DEFINITIONS

To view a complete list of Brighton Collaboration (BC) publications and related tools, please click here. Publications and related tools are organized in a Google spreadsheet that is sortable and filterable by each column. Direct clickable links to publication DOIs are provided.

New BC case definitions (and associated companion guides) will be posted below and added to the spreadsheet as they become available. *To view only the companion guides, please click here.*

Case Definitions Recommended

THANK YOU

Questions ?