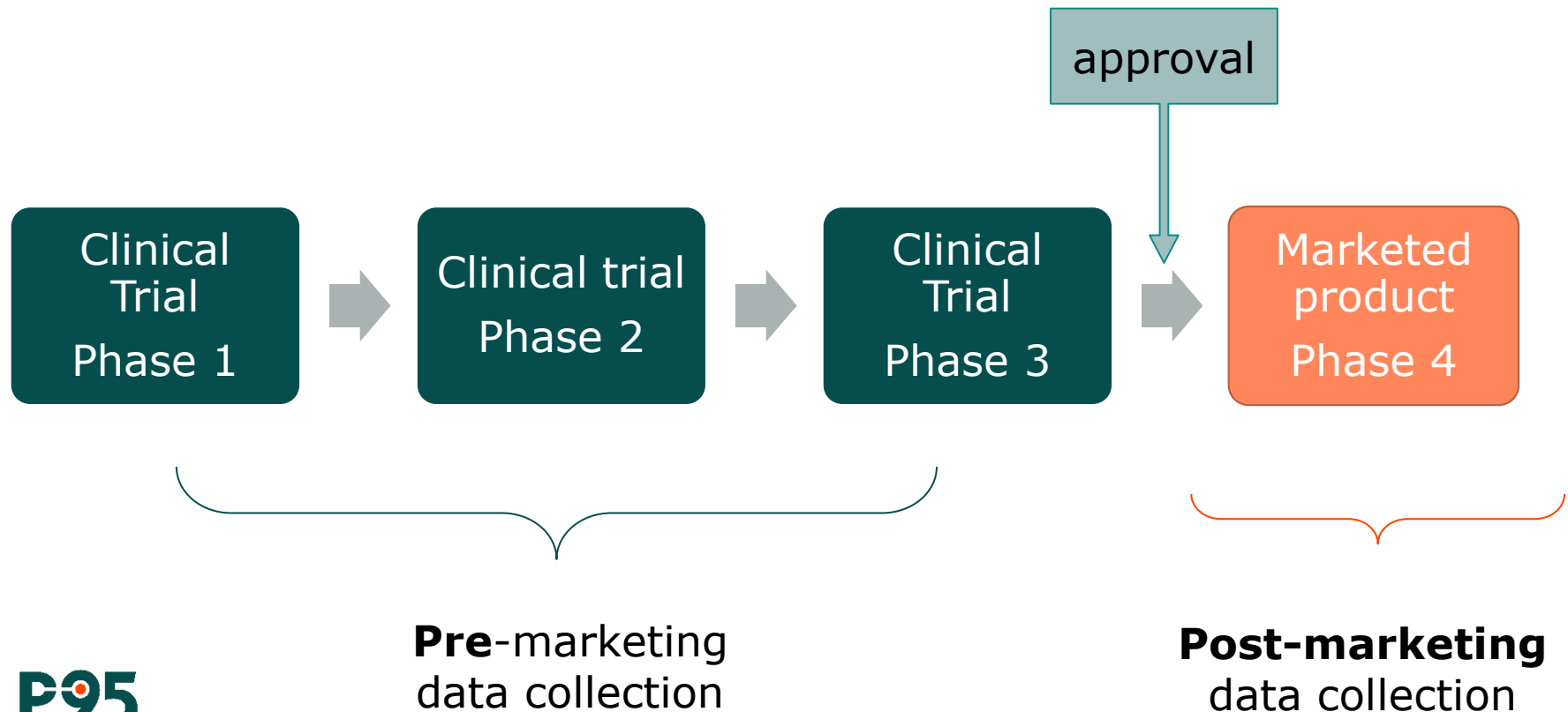# Module 3:
Safety data collection – clinical trials; passive surveillance

Module content

- Clinical trials pharmacovigilance
- Post-marketing – passive surveillance, spontaneous ADRs
- Spontaneous ADR reporting schemes
- Role of industry, regulators and public health bodies
- Vaccine-specific considerations in ADRs
- Optimising ADR reporting and data capture
- ISCR databases
- Reporting and coding standards – E2B, MedDRA
- Role of WHO – AEFI guidance, UMC/Vigibase
- Data exchange and sharing

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Safety data collection during product/ vaccine life-cycle

- Competent authorities and marketing authorisation holders should take appropriate measures to collect and collate all reports of suspected adverse reactions associated with medicinal products/ vaccines for human use originating from unsolicited or solicited sources.

approval

| Clinical Trial Phase 1 | → | Clinical trial Phase 2 | → | Clinical Trial Phase 3 | → | Marketed product Phase 4 |

Pre-marketing data collection

Post-marketing data collection

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Clinical safety

Safety in Clinical Trials (CTs)

- The general requirements, definitions and regulatory processes for the conduct of clinical trials (safety) for new vaccines are no different to medicines, notably (but not limited to):

  - ICH E2A Clinical safety data management: definitions and standards for expedited reporting | European Medicines Agency (europa.eu)

  - ICH E8 General considerations for clinical studies | European Medicines Agency (europa.eu)

  - ICH E2E Pharmacovigilance planning (Pvp) | European Medicines Agency (europa.eu)

  - E 9 Statistical Principles for Clinical Trials (europa.eu)

Specific safety requirement for vaccine CTs

- Unsolicited AEs, medically-attended AEs, serious AEs collected at designated study visits and/or reported as per protocol

- Relatedness, expectedness and seriousness – SUSARs and expedited reporting – nothing unique or specific to vaccine trials

- However, vaccines require some specific considerations in protocol design and risk management planning regarding safety:

  - Guideline on clinical evaluation of vaccines REV1 (europa.eu)

  - Guideline on good pharmacovigilance practices (GVP) - Product- or Population-Specific Considerations I Vaccines for prophylaxis against infectious diseases (europa.eu)
    - (Post-marketing GVP guidance, but principles still applicable to RMP planning in pre-authorisation phase)

  - Multidisciplinary: vaccines | European Medicines Agency (europa.eu)

Specific safety requirement for vaccine CTs

- **Reactogenicity** (i.e. the common, expected local and systemic reactions) can influence tolerability/acceptance of an intervention given to otherwise healthy populations and should be fully characterized

  - Defined local and systematic reactogenicity endpoints should be **actively solicited** within a defined period after each dose
    - Local – e.g. Pain, swelling, redness
    - Systemic – e.g. fever, headache, nausea/vomiting, myalgia/arthralgia, fatigue, chills
    - Graded by severity
    - Usually up to 7 days, but depends on type of vaccine (e.g. longer for replicating vaccines)
    - Relevant to age group (e.g. crying and irritability for infant vaccines)

- Live vaccines/replicating vectors – **viral shedding, safety in close contacts, safety in pregnancy, safety in immunocompromised**

- Adjuvants – **potential for auto-immune events, safety in early pregnancy**

- Choice of comparator – saline vs reactogenic vaccine (unintended 'unblinding'?); active comparator ('masking' safety?)

Post-marketing pharmacovigilance

Individual AE/ADR reports

- GVP module VI (Rev 2)
- Sources of ICSR information:
  - The **primary source** is the person who reports the facts about an ICSR:
    - **Healthcare professional** is defined as a medically-qualified person such as a physician, dentist, pharmacist, nurse , coroner or as otherwise specified by local regulations;
    - A **consumer** is defined as a person who is not a healthcare professional such as a patient, lawyer, friend, relative of a patient or carer.
  - Reports may be **medically confirmed** or medically unconfirmed.
  - Reports may be **unsolicited** or **solicited**.

Unsolicited safety reports

- 1. **Spontaneous reports:**

- an unsolicited communication by a healthcare professional or consumer to a company, regulatory authority or other organization (e.g. WHO, Regional Center, Poison Control Center) that describes one or more ADRs and does not derive from a study or any organized data collection scheme

- includes stimulated reports, medical info enquiries, consumer reports irrespective of medical confirmation, reports from social media

- 2. **Literature reports:**

- reports of suspected ADRs from the medical literature, including relevant published abstracts from meetings and draft manuscripts

Unsolicited safety reports

3. **Reports from non-medical sources**

- If a marketing authorisation holder becomes aware of a report of suspected adverse reactions originating from a non-medical source, for example the lay press or other media, it should be managed as a spontaneous report

4. Internet or digital media

- MAHs should regularly screen the internet or digital media under their management or responsibility, for potential reports of suspected ADRs.

- Frequency of the screening should allow for potential valid ICSRs to be submitted within the appropriate regulatory submission time frames.

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Solicited safety reports

Are derived from organised data collection systems and include the following main sources:

- Clinical trials
- Non interventional studies
- Registries
- Post-approval named patient use programmes
- Patient support & disease management programmes
- Surveys of patients and HCPs
- Compassionate use

Solicited safety reports

- these are not considered spontaneous and should be classified as study reports (unless they are an ADR from a PASS or compassionate use programme for which the protocol does not require their systematic collection)

- but require an appropriate causality assessment by a healthcare professional or an MAH to determine if they refer to a suspected ADR (and therefore whether they meet criteria for ICSR reporting)

Individual AE/ADR reports

- Reports may be **serious** or non-serious:
    - Serious if AE results in **death**, is **life-threatening**, requires **hospitalisation**, results in persistent or significant **disability** or incapacity, is a congenital **anomaly** or **birth defect**.
    - Also considered serious if medical judgement considers that intervention was required to prevent one of these seriousness criterion – in this case the AE may be considered an **important medical event (IME)**.
- Seriousness assessment should be based on the clinical history at the time of onset of the event.

Individual case safety report (ICSR)

- ICSR refers to the **format and content** for the submission of an individual report of *suspected adverse reactions* to regulatory authorities

- Four minimum criteria are required for ICSRs validation:
  - one or more identifiable reporter
  - one single identifiable patient (e.g. initials, DOB, gender…)
  - one or more suspected substance/medicinal product
  - one or more suspected *adverse reaction*
    - If the primary source has explicitly excluded a causal relationship and the notified competent authority or MAH agrees with this assessment, the report does not qualify as a valid ICSR (i.e. adverse event does not necessarily mean adverse reaction)

- The lack of any of the four elements means that the case is considered invalid and does not qualify for submission as ICSR

Post-marketing surveillance options

- Pharmacovigilance systems are used to monitor suspected adverse reactions related to all types of health medical products including vaccines

- A range of surveillance options can be used to monitor the safety post-licensure
  - **Passive surveillance**
    - Spontaneous reports
  - Active surveillance
  - Post-marketing studies

- AEFI surveillance
  - surveillance system designed to collect adverse events temporally associated with receipt of vaccines

Passive surveillance systems

- = spontaneous reporting systems
- Corner stone of most post-licensure safety monitoring systems

- **Strengths**
  - Proven to identify unrecognised reactions
  - Sensitivity is potentially high for reporting
  - Inclusive of all medicines and vaccines throughout marketing life
  - Can work rapidly
  - Can be applied widely
  - Relatively cheap to operate nationally
  - Provides information about factors which predispose patients to ADRs
  - Can be integrated into the system

- **Weaknesses**
- Cannot provide estimates of risk as
  - true number of cases is underestimated
  - total number of patients exposed is unknown
- Relies on ADR being recognised
- Not all ADRs are reported / Poor at detecting certain ADRs
  - Only 10% reactions reported; 2 to 7% serious
- May be stimulated by promotion and publicity
- Reporting high for newly marketed drugs and falls off over time
- Reports do not imply causality
- Data can be misinterpreted/abused

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What should be reported?

- Organisation of pharmacovigilance is country specific and is regulated by laws and country specific guidelines
- Different guidance on what to report

VAERS Vaccine Adverse Event Reporting System
www.vaers.hhs.gov

Healthcare providers are **required by law** to report to VAERS:

- Any adverse event listed in the VAERS Table of Reportable Events Following Vaccination that occurs within the specified time period after vaccinations
- An adverse event listed by the vaccine manufacturer as a contraindication to further doses of the vaccine

Healthcare providers are strongly **encouraged** to report to VAERS:

- Any adverse event that occurs after the administration of a vaccine licensed in the United States, whether it is or is not clear that a vaccine caused the adverse event
- Vaccine administration errors

Yellow Card
Making medicines safer

The Yellow Card Scheme relies on reporting of suspected ADRs where there is a suspicion that there is a causal relationship between the medicinal product taken and the suspected reaction experienced.

World Health Organization **VACCINE SAFETY BASICS** e-learning course

Which AEFIs should be reported?

Key point
Any AEFI that is of concern to the parents or to the healthcare worker should be reported.

In particular, health workers should report:	Serious AEFIs.
	Signals and events associated with a newly introduced vaccine.
	AEFIs that may have been caused by an immunization error.
	Significant events of unexplained cause occurring within 30 days after a vaccination.
	Events causing significant parental or community concern.
	Swelling, redness, soreness at the injection site IF it lasts for more than 3 days or swelling extends beyond nearest joint.

- **Legal vs voluntary**
- **All events vs those where there is some suspicion of causality**
- **AEs vs ADRs**

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Role of industry, regulators and public health bodies (1)

- **Marketing authorisation holder (MAH):**
  - responsible for the quality, efficacy and safety of the product
    - Pharmacovigilance activities
    - Development/implementation of the risk management plan (RMP)
    - Communication with regulatory authorities

Role of industry, regulators and public health bodies (2)

- **Regulatory authorities:**
  - Main responsibilities in
    - Guiding policy makers in developing and implementing immunization policies
    - Pharmacovigilance
    - Regulatory inspection
    - Marketing authorisation
  - Main tasks include
    - Verify submission of Risk Management Plans
    - Can mandate vaccine safety studies from the MAHs
    - Can independently investigate potential safety signals

- **(Inter)national Regulatory Authorities**
  - National, examples
    - MHRA (UK): Medicines and Healthcare products Regulatory Agency
    - PEI (Germany): Paul-Ehrlich Institut
  - International, examples
    - EMA (Europe): European Medicines Agency
    - FDA (US): Food and Drug Administration
    - AVAREF: African Vaccine Regulatory Forum

Role of industry, regulators and public health bodies (3)

- **Public Health Authorities**
  - Main responsibilities in
    - Detecting and responding to new and emerging health treats
    - Prevent disease and promote healthy behaviours
  - Main tasks include
    - Disease surveillance, including infectious and vaccine preventable diseases
    - Evaluation of public health programmes, including immunization programmes

- **(Inter)national Public Health Authorities**
  - National, examples
    - PHE (UK): Public Health England
    - RIVM (the Netherlands): National Institute for Public Health and the Environment
  - International, examples
    - ECDC (Europe): European Centre for Disease Prevention and Control
    - CDC (US): Centers for Disease Control and Prevention

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Global Safety Surveillance Reporting – Organisation

EEA: European Economic Area; USA: United States of America; ROW: Rest of the World;
MAH: Marketing Authorisation Holder; NCA: National Competent Authority; FDA: Food and Drug Administration; WHO: World Health Organisation
FAERS: FDA Adverse Event Reporting System
*countries part of the WHO Programme for international drug monitoring (PIDM) - As of October 2021, 149 members have joined the WHO PIDM.

Optimising ADR reporting and data capture

- Develop a strategy for activities to increase reporting and quality of reports from HCPs, immunisation centres, and patients including parents and carers,

- Making reporting easy and accessible (e.g., **app**, QR codes, integration, continue to enhancing forms)

- Raise understanding of the purpose and value of reporting (education modules, examinations, regional centres, developing case studies, information in trusted sources)

- Making reporters more likely to report (indicators, support from professional bodies, revalidation, networks of champions, recognise and reward reporting),

- Developing and maintaining promotion and communication strategies (develop brand, key messages, publish, distribution, social media)

Optimising ADR reporting and data capture (examples)

Data collection

Data management

Initial Data entry: App, website etc	Data review: Vigilance Hub	Database	Signal Detection

Reporting by healthcare professional or members of the public

View and updated reports, manage users and app content

Storage of reports to enable signal detection

Use of algorithms to prioritise signal detection
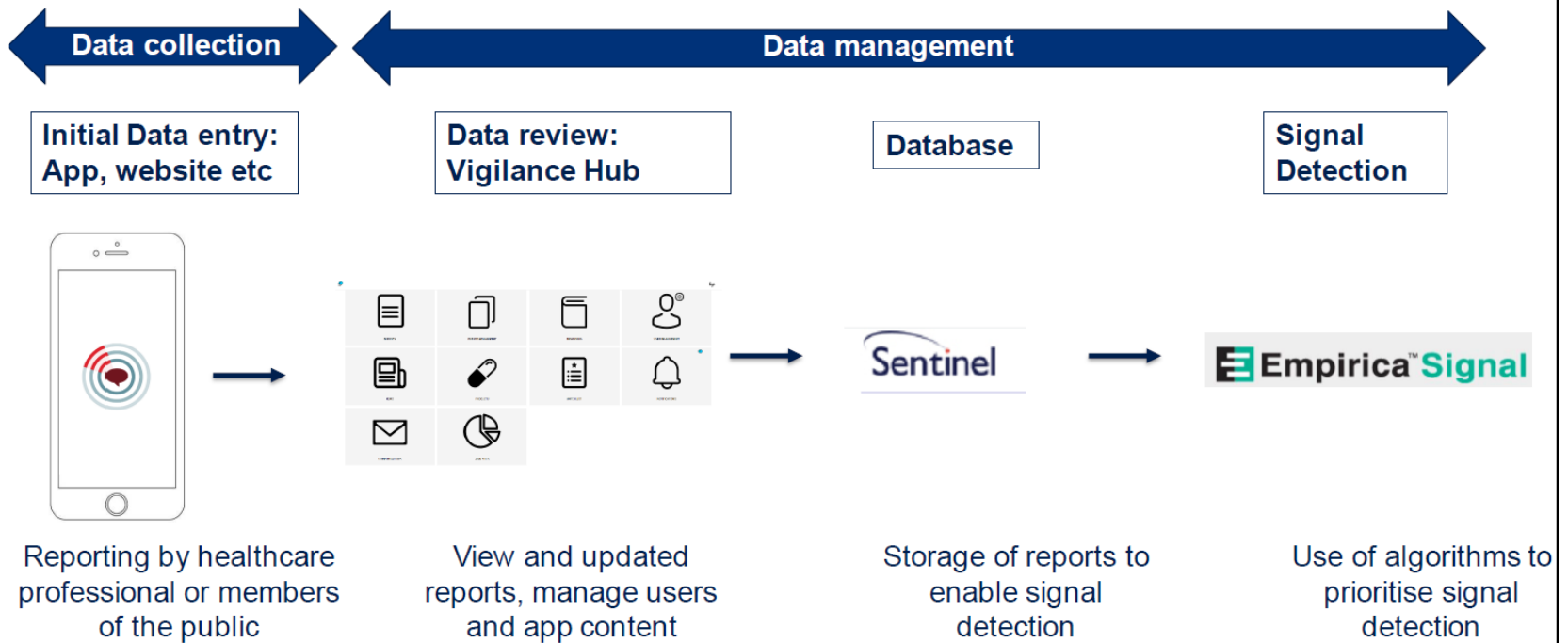
Data collection tool

- **Med Safety App**

  - Mobile application developed to engage both patients and healthcare providers on medicines safety issues
  - Pilot app initially made available in the UK, Netherlands and Croatia
  - In 2017, app rolled out in Burkina Faso and Zambia
  - Now available for wider adoption
  - Technology is made available by MHRA on behalf of the WEB-RADR project on a not-for-profit basis
  - Offers a low-cost approach for National Competent Authorities to:
    - Collect and view ADR data
    - Deliver safety messages
  - The app has potential fir pharmaceutical industry adaptation too

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Med Safety App
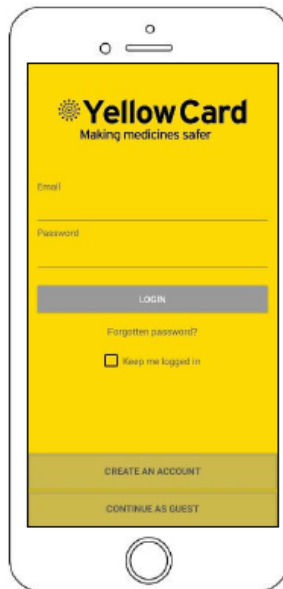
Yellow Card, UK
14/07/2015

HALMED, Croatia
18/05/2016

Burkina Faso
15/06/2017
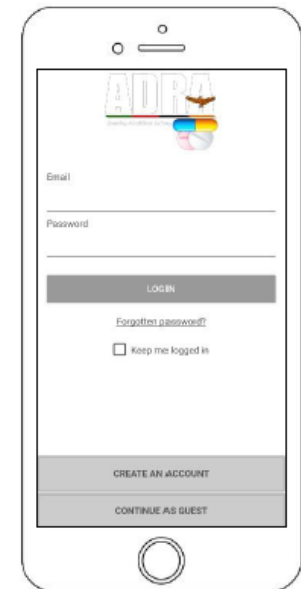
Zambia
29/06/2017

Reporting forms
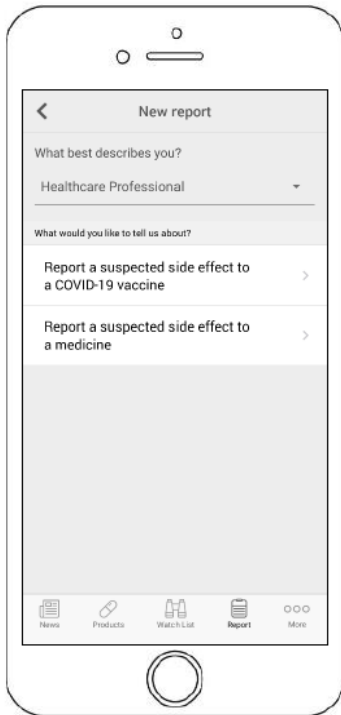
- Multiple type of form can be available for data entry
- Questions within each can be tailored
- Examples include,
  - Medicines forms
  - Vaccine forms
  - Specific disease programmes

AEFI form development
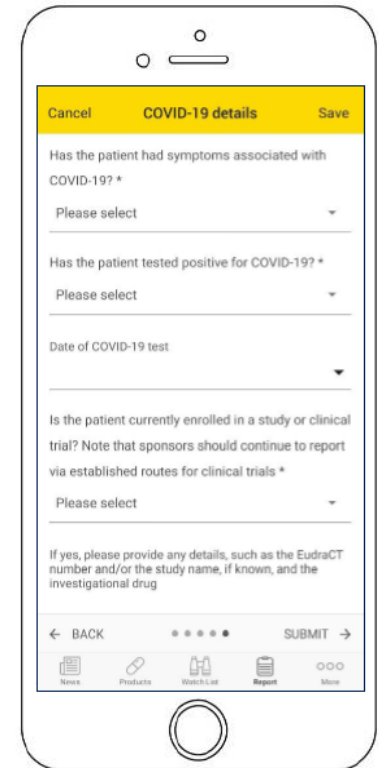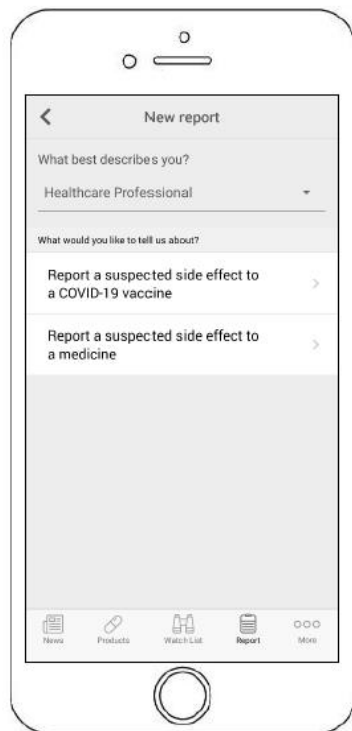
- Designed to simplify and promote the reporting of suspected adverse drug reactions (ADRs), including adverse events following immunisation (AEFIs) by both the public and healthcare providers

Forms in data collection

- Standard forms for collection of initial and follow-up information

- Forms may be designed to meet product specific requirements/specificities

- Use of simplified forms for initial collection and more elaborate forms for follow-up information

- Use of targeted follow-up questionnaires (often as part of the Risk Management Plans - RMPs)

- Use of pregnancy specific forms

Data management tool

- **Vigilance Hub**

  - Back-end system of the Med Safety App
  - Available to staff of national regulators and immunisation programmes (NRAs and EPIs) based on granted access permissions

  - Allows a user to:
    - View all submitted reports, from the Med Safety App and other linked channels
    - Edit case reports submitted (particularly relevant for updating cases with any follow-up information)
    - Manually enter paper form cases
    - Export reports of cases
    - Analyse volume and sources of cases received for specified time periods

  - Reports entered into or updated within the Vigilance Hub are automatically updated in the VigiFlow environment

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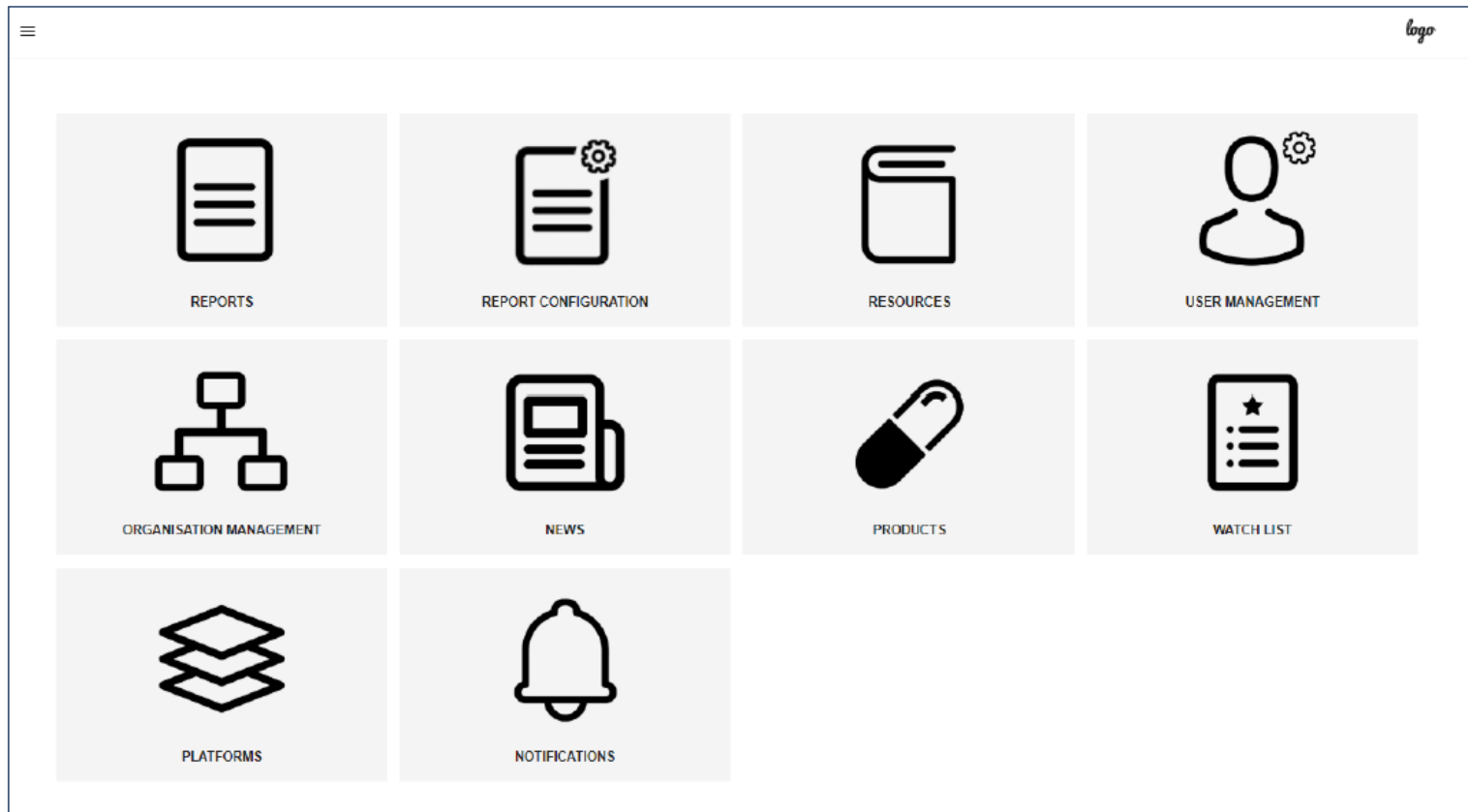
Vigilance Hub

Vigilance Hub : Case review and updates

Reporting and coding standards - Data quality

- Data quality is underpinned by international standards:
  - E2B fields
  - MedDRA
  - Drug dictionnaries
  - Quality assurance steps and audits

- Only reports of Good quality can prduce reliable signals!

Reporting and coding standards

- **E2B**

  - Standard adopted by ICH for electronic transmisión of Individual Case Safety Reports (ICSRs)
  - E2B(R3) is the current standard

  - ICSRs have increasingly shifted from paper-based to electronic reports. Therefore, electronic capturing of ADRs and its transmission have become an essential component in pharmacovigilance.
  - Electronic reporting facilitates the transfer of information and makes safety data readily available for further processing and analysis
  - Lack of harmonisation might lead to difficulties in reconciling ICSRs on the global level

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Reporting and coding standards

- **MedDRA**
  - Med = Medical
    - D = Dictionary for
      - R = Regulatory
        - A = Activities

- MedDRA is a **clinically-validated international medical terminology** used by **regulatory authorities** and the regulated **biopharmaceutical industry**. The terminology is used through the entire regulatory process, from **pre-marketing to post-marketing**, and for **data entry**, **retrieval**, **evaluation**, and **presentation**.
  - Not a drug dictionary!

- Developed by ICH (International Council for Harmonisation)

- Maintained by MedDRA-MSSO (Maintenance and Support Service Organization) and updated bi-annually with input from users

- Training materials available in multiple languages through MedDRA website (https://www.meddra.org/training-materials)

Key features of MedDRA

- Standardized terminology

- Structure facilitates data entry, analysis, reporting, and electronic communication

- Large terminology - allows great specificity

- Used to classify a wide range of information associated with the use of biopharmaceuticals and other medical products (e.g., medical devices and vaccines)

- International scope – currently available in 14 languages (incl. Spanish)

MedDRA structure

5 structural elements in the MedDRA terminology

System Organ Class (SOC) — **27**

High Level Group Term (HLGT) — **337**

High Level Term (HLT) — **1737**

Preferred Term (PT) — **24820**

Analysis level

83291

Lowest Level Term (LLT)

Coding level

SOC - represents an anatomical or physiological system
e.g., Cardiac disorders

HLGT - – a group of medical concepts
e.g., Cardiac arrythmias

HLT - a group of unique medical concepts
e.g., Rate and rhythm disorders

PT - represents a unique medical concept
e.g., Arrythmia

LLT - represents synonyms, lexical variants or quasi-synonyms of PTs
e.g., Arrhytmia, Dysarrythmia…

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MedDRA - Regulatory status (examples)

- **FDA, US**
    - Used in several databases including FAERS (drugs and biologics), VAERS (vaccines)…
    - Electronic submission required for study data and postmarketing reports (uses ICH standards)

- **EMA, EU**
    - EudraVigilance database
        - Clinical trial SUSARs (Suspected Unexpected Serious Adverse Reactions)
        - Post-authorization Individual Case Safety Reports (ICSRs)
    - Good pharmacovigilance practices (GVP) specifically mention MedDRA
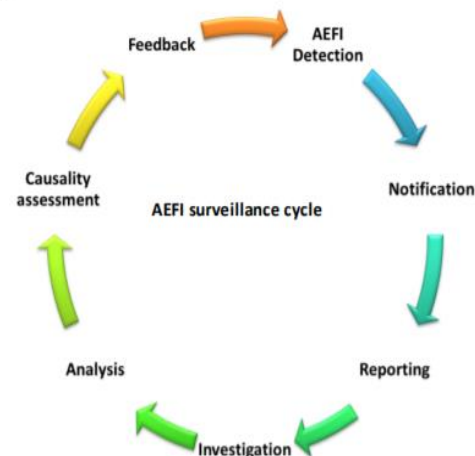   - Used throughout Summary of Product Characteristics (labeling)

Role of WHO

- Specialized agency of the United Nations responsible for international public health

- Main vaccine-related groups:
  - **WHO prequalification (PQ)** team: assesses whether a vaccine meets requirements of quality, safety and efficacy for use in immunization programmes, potentially via Emergency Use Listing (EUL) procedure
  - **Global Advisory Committee on Vaccine Safety (GACVS):** provides independent scientific advice to WHO on vaccine safety issues
  - **Strategic Advisory Group of Experts (SAGE):** advisory group to the WHO for immunization related policy

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AEFI guidance

- AEFIs are any untoward medical events that follow immunization, and that do not necessarily have a causal relationship with the immunization. The adverse event may be any unfavourable or unintended sign, abnormal laboratory finding, symptom or disease

- AEFI reporting for Covid vaccines
  - At the time of vaccine introduction, all countries should have an AEFI surveillance system in place.
  - Different steps that should be present in the surveillance model

AEFI surveillance cycle

Feedback AEFI Detection

Causality assessment

Notification

AEFI surveillance cycle

Analysis

Reporting

Investigation

Tools for AEFI

Description	Purpose	Status for COVID-19	Electronic tool
AEFI reporting form	To collect basic reports of all AEFI cases that have been notified	COVID-19 standard AEFI reporting form that includes the name of the manufacturer and brand name	Use in-country tools if available; if not WHO recommends Vigiflow
AEFI linelist	To collate the details in the reporting form	COVID-19 standard linelist that includes the name of the manufacturer and brand name	WHO recommends Vigiflow
AEFI investigation form	To collect detailed information when serious AEFI cases are investigated	Adapted to include COVID-19 specific questions	WHO AEFI investigation assistance software
AEFI causality assessment (available here)	To determine case classification of serious AEFI cases	Remains unchanged	Global Vaccine Safety on-line causality assessment tool

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VigiBase

- **VigiBase**
  - unique WHO global database of reported potential side effects of medicinal products
  - largest database of its kind in the world, with over 28 million reports of suspected adverse effects of medicines, submitted, since 1968, by member countries of the WHO Programme for International Drug Monitoring (WHO PIDM)
  - continuously updated with incoming reports

- **VigiFlow**
  - web-based individual case safety report (ICSR) management system that is available for use by national pharmacovigilance centres of the WHO PIDM
  - supports the collection, processing and sharing of data of ICSRs

- **Vaccine Adverse Event Information Management System (VAEIMS)**
  - software that has been developed to allow the transfer of AEFI data from each national database to Vigibase
  - web-based version or off-line version of VAEIMS is available to all countries free of charge

Thank you!

Muchas gracias !

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Questions & Answers session (in Spanish)