COVID-19 Vaccines: Safety Surveillance Manual

Module: Engaging with the pharmaceutical industry for COVID-19 vaccine safety surveillance

Contents

Abbreviations

AACVS	African Advisory Committee on Vaccine Safety
ACE	Angiotensin-converting enzyme
ADEM	Acute disseminated encephalomyelitis
ADRs	Adverse drug reactions
AEFI	Adverse event following immunization
AESI	Adverse event of special interest
ARDS	Acute respiratory distress syndrome
AVSS	Active vaccine safety surveillance
CEM	Cohort event monitoring
CEPI	Coalition for Epidemic Preparedness Innovations
CIOMS	Council for International Organizations of Medical Sciences
COVID-19	Coronavirus disease 2019
DCVMN	Developing Countries Vaccine Manufactures Network
DL	Data linkage
DNA	Deoxyribonucleic acid
EH	e-Health
EPI	Expanded programme on immunization
GACVS	Global Advisory Committee on Vaccine Safety
GBS	Guillain-Barré syndrome
GVAP	Global vaccine action plan
HCW	Health care worker
ICD	International classification of diseases
IFPMA	International Federation of Pharmaceutical Manufacturers and Associations
ISoP	International Society of Pharmacovigilance
ISRR	Immunization stress-related response
MAH	Marketing authorization holder
MedDRA	Medical dictionary for regulatory activities
MH	m-Health
MoH	Ministry of Health
mRNA	Messenger RNA
NIP	National Immunization Programme
NITAG	National Immunization Technical Advisory Group
NRA	National regulatory authority
PBRER	Periodic benefit-risk evaluation report
PHEIC	Public health emergency of international concern
PLSS	Post-licensure safety studies
PSUR	Product safety update report
PV	Pharmacovigilance
QPPV	Qualified person responsible for pharmacovigilance
RITAG	Regional Immunization Technical Advisory Groups
RMP	Risk management plan
RNA	Ribonucleic acid
SAGE	Strategic Advisory Group of Experts (for immunization)
SARS-CoV-2	Severe acute respiratory syndrome coronavirus 2
SKG	Significant knowledge gap
SIA	Supplementary immunization activities
SS	Sentinel surveillance
TGA	Therapeutic Goods Administration (Australian Ministry of Health)
VAED	Vaccine-associated enhanced disease
VLP	Virus-like particles
VPD	Vaccine preventable disease
WHO	World Health Organization

Glossary

Adjuvant	A pharmacological or immunological agent added to a vaccine to improve its immune response.
Adverse event following immunization (AEFI): general definition	Any untoward medical event that follows immunization and that does not necessarily have a causal relationship with the usage of the vaccine. The adverse event may be any unfavourable or unintended sign, abnormal laboratory finding, symptom or disease.
• AEFI by cause: coincidental events	• An AEFI that is caused by something other than the vaccine product, immunization error or immunization anxiety.
• AEFI by cause: immunization anxiety-related reaction	• An AEFI arising from anxiety about the immunization (see immunization stress related responses).
• AEFI by cause: immunization error-related reaction	• An AEFI that is caused by inappropriate vaccine handling, prescribing or administration, that, therefore, is preventable.
• AEFI by cause: vaccine product-related reaction	• An AEFI that is caused or precipitated by a vaccine due to one or more of the inherent properties of the vaccine product, whether the active component or one of the other components of the vaccine (e.g. adjuvant, preservative or stabilizer).
• AEFI by cause: vaccine-quality defect-related reaction	• An AEFI that is caused or precipitated by a vaccine due to one or more quality defects of the vaccine product, including its administration device as provided by the manufacturer.
Adverse event of special interest (AESI)	A preidentified and predefined medically-significant event that has the potential to be causally associated with a vaccine product that needs to be carefully monitored and confirmed by further specific studies.
Causal association	A cause-and-effect relationship between a causative (risk) factor and an outcome. Causally-associated events are also temporally associated (i.e. they occur after vaccine administration), but events that are temporally associated may not necessarily be causally associated.
Causality assessment	In the context of vaccine AEFI surveillance, a systematic review of data about the AEFI case(s) to determine the likelihood of a causal association between the event and the vaccine(s) received.
Cluster	Two or more cases of the same or similar events related in time, geography (place), and/or vaccine administered. AEFI clusters are usually associated with a particular supplier/provider, health facility, and/or a vial of vaccine or a batch of vaccines.
Contraindication	A situation where a particular treatment or procedure, such as vaccination with a particular vaccine, must not be administered for safety reasons. Contraindications can be permanent (absolute), such as known severe allergies to a vaccine component, or temporary (relative), such as an acute/severe febrile illness.
Immunity	The ability of the human body to tolerate the presence of material 'indigenous' to the human 'body' (self) and to eliminate 'foreign' (non-self) material. This discriminatory ability provides protection from infectious diseases since most microbes are identified as foreign material by the immune system.
Immunization	Immunization is the process whereby a person is made immune or resistant to an infection, typically by the administration of a vaccine. Vaccines stimulate the body's own immune system to protect the person against subsequent infection

Immunization safety	The process of ensuring the safety of all aspects of immunization, including vaccine quality, adverse event surveillance, vaccine storage and handling, vaccine administration, disposal of sharps and management of waste.
Immunization safety surveillance	A system for ensuring immunization safety through detecting, reporting, investigating, and responding to AEFI.
Immunization stress related responses (ISRR)	Stress response to immunization that may manifest just prior to, during, or after immunization.
Injection safety	The public health practices and policies dealing with various aspects of the use of injections (including adequate supply, administration and waste disposal) so that the provider and recipient are not exposed to avoidable risks of adverse events (e.g. transmission of infective pathogens) and creation of dangerous waste is prevented. All injections, irrespective of their purpose, are covered by this term (see definition of safe injection practices).
Mass vaccination campaign	Mass vaccination campaigns involve administration of vaccine doses to a large population over a short period of time.
Non-serious AEFI	An event that is not 'serious' and does not pose a potential risk to the health of the recipient. Non-serious AEFIs should also be carefully monitored because they may signal a potentially larger problem with the vaccine or vaccination or have an impact on the vaccination acceptability; in general.
Risk management plan (RMP)	A risk management plan is a document that describes the current knowledge about the safety and efficacy of a medicinal product. The RMP provides key information on plans for studies and other activities to gain more knowledge about the safety and efficacy of the medicine or vaccine. It also describes measures to be undertaken to prevent or minimise risks associated with the use of the product in patients.
Safe injection practice	Practices that ensure that the process of injection carries the minimum of risk, regardless of the reason for the injection or the product injected.
Serious AEFI	An event that results in death, is life-threatening, requires in-patient hospitalization or prolongation of existing hospitalization, results in persistent or significant disability/incapacity, or is a congenital anomaly/birth defect. Any medical event that requires intervention to prevent one of the outcomes above may also be considered as serious.
Severe vaccine reaction	Vaccine reactions can be mild, moderate or severe. Severe reactions may include both serious and non-serious reactions.
Signal (safety signal)	Information (from one or more sources) that suggests a new and potentially causal association, or a new aspect of a known association, between an intervention and an adverse event or set of related adverse events, that is judged to be of sufficient likelihood to justify verification.
Surveillance	The continual, systematic collection of data that are analysed and disseminated to enable decision-making and action to protect the health of populations.
Trigger event	A medical incident following immunization that stimulates a response, usually a case investigation.
SAGE Values Framework	Values Framework, developed by WHO's SAGE, offers guidance globally on the allocation of COVID-19 vaccines between countries, and guidance nationally on the prioritization of groups for vaccination within countries while COVID-19 vaccine supply is limited
Vaccine	A biological preparation that elicits immunity to a particular disease. In addition to the antigen, it can contain multiple components, such as adjuvants, preservatives, stabilizers, each of which may have specific safety implications.

Vaccine-associated enhanced disease (VAED)	Vaccine-associated enhanced diseases are modified and severe presentations of clinical infections affecting individuals exposed to a wild-type pathogen after having received a prior vaccine against the same pathogen.
Vaccine pharmacovigilance	The science and activities relating to the detection, assessment, understanding and communication of AEFI and other vaccine- or immunization-related issues, and to the prevention of untoward effects of the vaccine or vaccination.
Vaccination failure	Vaccination failure can be defined based on clinical endpoints or immunological criteria, where correlates or surrogate markers for disease protection exist. Primary failure (e.g. lack of sero-conversion or sero-protection) needs to be distinguished from secondary failure (waning immunity). Vaccination failure can be due to (i) failure to vaccinate, i.e. an indicated vaccine was not administered appropriately for any reason or (ii) because the vaccine did not produce its intended effect
Vaccine reaction	An event caused or precipitated by the active component or one of the other components of the vaccine. It may also relate to a vaccine quality defect.
Vaccine safety	The process that maintains the highest efficacy of, and lowest adverse reaction to, a vaccine by addressing its production, storage and handling. Vaccine safety is a part of immunization safety.

1. Introduction

The private sector plays an essential role in the development and introduction of vaccines, as well as in on-going pharmacovigilance activities to ensure efficacy, quality and safety throughout the vaccines' life cycle. Under the current pandemic, it plays a critical role in accelerated development of vaccines and therapeutics. Although diverse players make up the private sector, this module will focus on the pharmaceutical industry and their role in ensuring the safety of COVID-19 vaccines through pharmacovigilance activities, as described in risk management plans and more specifically in providing periodic safety update reports (PSURs).

1.1. Legal provisions and guidelines regarding COVID-19 vaccine safety

In countries where the regulatory authority is a member[1] or an observer of the *International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use* (ICH), ICH technical guidelines and requirements will guide companies in meeting their obligations for COVID-19 vaccine registration and continued monitoring of safety when the vaccine is on the market. Two ICH guidelines set out common standards for pharmacovigilance activities to ensure the safety of new drugs and those already on the market: *ICH E2E Pharmacovigilance Planning*[2], and *ICH E2C(R2) Periodic Benefit-Risk Evaluation Report (PBRER).*[3] Post-authorization commitments for MAHs are presented in the WHO document *Considerations for the assessment of COVID-19 vaccine*.-

In countries where the national regulatory authority (NRA) is not required to follow ICH guidelines for COVID-19 vaccine authorization and continued pharmacovigilance, existing legislation governing pharmacovigilance should be interpreted under the COVID-19 pandemic situation, to provide clear guidance and directives to the marketing authorization holder (MAH) on pharmacovigilance requirements. A risk management plan (RMP) is a key document in the marketing authorization submission dossier. The RMP describes the current knowledge about the benefits and the risks of the vaccine or medicinal product, providing key information on plans for studies and other activities to gain more data on missing information, more knowledge about the safety profile of the product, and plans for risks minimization. . Low- and middle-income countries (LMICs) may find it difficult to meet the resource requirements in RMP implementation in the light of the many competing priorities they have to manage. Hence there is a need to coordinate efforts by stakeholders and partners at national, regional, and global levels and the following key considerations should be included in specific directives and guidelines for COVID-19 vaccine safety:

- contribution to a regional RMP that includes a regional annex which considers local situations, such as epidemiological characteristics, medical practice, logistic limitations, ethnicity, and regional health and regulatory systems;
- requirements for PSURs/periodic benefit risk evaluation reports (PBRERs) under different scenarios. For example:

[1] ICH Members & Observers. Available at: https://www.ich.org/page/members-observers. Accessed 25 October 2020
[2] ICH E2E Guideline: Pharmacovigilance Planning 2004. Available at: https://database.ich.org/sites/default/files/E2E_Guideline.pdf. Accessed 25 October 2020.
[3] ICH E2C(R2) Guideline: Periodic Benefit-Risk Evaluation Report (PBRER) 2012. Available from: https://database.ich.org/sites/default/files/E2C_R2_Guideline.pdf. Accessed 25 October 2020.

    - PSUR/PBRER requirements for COVID-19 vaccines introduced in LMICs through the COVAX Facility/WHO's emergency use listing (EUL);[4]
    - COVID-19 vaccines introduced into LMICs that are outside of COVAX Facility or WHO's EUL.
- specification of routine and additional pharmacovigilance activities to be carried out during the pandemic as well as the periodicity for updating safety information. These activities may include:
    - an interim simplified PSUR (iS-PSUR) submitted more frequently;
    - post-licensure safety studies to obtain missing information on potential risks for the relevant COVID19 vaccines (as identified in the RMP), and other issues such as programmatic errors, and safety among pregnant women, paediatric populations, seniors, and individuals with co-morbidities;
    - the establishment of sentinel sites as part of an active surveillance system for COVID-19 vaccine safety.
- requirement for the vaccine manufacturer or MAH launching the COVID-19 vaccine in a country to designate a qualified person responsible for pharmacovigilance (QPPV) for monitoring its safety; the contact information and qualification of the QPPV should be clearly presented.

1.2. Risk management plans

The short timelines under which COVID-19 vaccines are being developed and ultimately deployed present challenges for guaranteeing their safety. Lessons learnt and best practices from past pandemics, such as those from 2009 H1N1 pandemic[5], should be used to guide current procedures for the safety of COVID-19 vaccines.

As with the H1N1 vaccines, more information about the immunogenicity, effectiveness, and safety of COVID-19 vaccines will only become available during their use in the field. Hence, the risk management plan for COVID-19 vaccines will be an evolving document and should be amended when new significant information becomes available, such as a change in the profile of adverse events, results from safety studies, changes in benefit-risk balance.

1.2.1. Format and components of RMPs for COVID-19 vaccines

The vaccine manufacturer or MAH is encouraged to adopt existing formats, such as the EU RMP format, which contain essential elements such as a safety specification section, pharmacovigilance activities, risk minimization activities, and evaluation of the effectiveness of the risk minimization measures[6]. RMPs in alternative formats, such as a global or core RMP, are also acceptable provided they contain the essential elements mentioned above.

[4] WHO Emergency use listing procedure. Available at: https://www.who.int/immunization_standards/vaccine_quality/EUL/en/. Accessed 25 October 2020.

[5] CHMP Recommendations for the pharmacovigilance plan as part of the risk management plan to be submitted with the marketing authorisation application for a pandemic influenza vaccine adopted by CHMP in November 2006. Revision 1. 1 adopted by CHMP on 24 September 2009 (EMEA/359381/2009).

[6] Guideline on good pharmacovigilance practices (GVP) Module V – risk management systems (Rev 2). Available from: https://www.ema.europa.eu/en/documents/scientific-guideline/guideline-good-pharmacovigilance-practices-module-v-risk-management-systems-rev-2_en.pdf. Accessed 25 October 2020.

In addition, the RMP should be accompanied by a region-specific annex (referred to as a regional annex hereafter) that takes into consideration additional context specific to the region where the vaccines are being deployed. Similar annexes are routinely implemented by certain regulatory authorities to ensure adaptation to local context, e.g. Australia-specific annex required by the Australian Government Therapeutic Goods Administration (TGA)[7]. Given the current pandemic setting, a regional annex to the RMP is a more feasible approach, taking into consideration the considerable resources required for RMP implementation and the limited resources available in LMICs. However, if there are significant differences among the local populations that could have an impact the safety profile of the vaccines, the national regulatory authority (NRA) should request that the vaccine manufacturer or MAH also submits specific pharmacovigilance (PV) plans for the local context. In general, the regional annex for COVID-19 vaccines in the RMPs should:

- highlight any differences in safety concerns between the regions where the COVID-19 vaccines are being launched, e.g., differences in the frequency, severity or nature of safety concerns, resulting from differences in the epidemiology of the COVID-19 and the target population;
- confirm that the PV and risk minimization activities are compatible with specific safety concerns specified.

1.2.2. Routine pharmacovigilance plan as part of RMP

Both routine and additional PV activities contribute to the maintenance of a positive benefit-risk balance for a vaccine. They form part of the RMP, along with further PV measures that are appropriate for the evaluation of efficacy and safety of vaccines.

For COVID-19 vaccines, as part of routine PV activities the vaccine manufacturer or MAH should describe in the RMP:

- specific activities for the collection, compilation, assessment, and reporting of adverse reactions to NRA
- format, content and periodicity of the PSUR/PBRERs
- other requirements defined in the regional annex.

During the pandemic, the usual 6-month reporting cycle may be too long for the assessment of COVID-19 vaccine safety because it is expected that there will be high levels of exposure within a short period of time. Therefore, it is recommended that an iS-PSURs be submitted on a monthly basis[5], or more frequently as the situation requires, in place of the regular PSUR for COVID-19 vaccines during the pandemic period. The iS-PSUR should include at least:

- a summary of vaccine distribution (number doses, locality of distribution, etc.);

[7] Risk management plan for medicines and biologicals–Australia-Specific Annex. Available from: https://www.tga.gov.au/book-page/risk-management-plan-australia-specific-annex. Accessed on 04 October 2020.

- analyses and documentation of spontaneously reported cases, including a classification of adverse events following immunization (AEFIs) and adverse events of special interest (AESIs) reported in individuals following immunization, following the Brighton Collaboration recommendations for COVID-19 vaccines[8];
- a description of methods for signal detection and investigation;
- analyses of safety and effectiveness data from post-marketing studies; and
- literature review of safety data.

In addition to the monthly iS-PSUR, a 6-month cumulative PSUR/PBRER should be submitted following the PBRER ICH E2C (R2) format3. This provides a cumulative overview of all available information which provides the vaccine's overall benefit-risk profile. Following the first 6-month report, the periodicity of the PSURs/PBRERs should be reviewed by the regulator.

1.2.3. Additional pharmacovigilance activities[5,6]

Additional PV activities, such as post-licensure safety studies (PLSS) should be considered to assess important identified and potential risks, and to provide important missing information. For COVID-19 vaccines, it is recommended to include, as part of the additional PV activities, a summary of the protocols and milestones for:

- PLSSs to confirm the COVID-19 vaccine safety profile(s);
- Safety studies in healthy individuals aged 6 months to <18 years;
- Safety studies in individuals with chronic disease(s), elderly, or individuals with comorbidities;
- Safety studies in pregnant women or pregnancy registry; and
- establishment of sentinel sites as part of an active surveillance system for COVID-19 vaccine safety assessment.

The pandemic COVID-19 pharmacovigilance plan will terminate when national competent authorities decide that it is no longer necessary.

1.2.4. Specific considerations under different scenarios

The NRA should provide clear guidance on PV requirements for different scenarios, as many different COVID-19 vaccines are likely to be introduced to the market, through different channels. The NRA should specify conditions when an iS-PSUR should be submitted and indicate what types of AEFIs and AESIs are to be covered in the iS-PSUR. Penalties and sanctions for non-compliance should also be clearly defined and communicated. Two possible scenarios are described below.

Scenario 1: COVID-19 vaccines submitted for WHO Prequalification Emergency Use Listing

Vaccines submitted for WHO Prequalification or Emergency Use Listing are developed by established companies who have submitted well defined RMPs for stringent review by regulatory authorities. However, the vaccines can be introduced outside of the country where they were originally authorized, in countries that may not have the resources to implement the RMP. In this case it will be important to ensure that a regional annex is included in the RMP, that will describe PV activities in the country where the vaccine is introduced that will be feasible and adapted to the local context.

[8] Brighton Collaboration Safety Platform for Emergency vACcines (SPEAC) Project (WHO slide deck presentation by Robert T Chen, Scientific Director Brighton Collaboration). Available from: https://www.dcvmn.net/IMG/pdf/8._cepi_speac_presentation_bob_chen.pdf (accessed on 07 October 2020).

In this situation, the vaccine MAH will be required to submit an RMP with a regional annex for the country where the COVID-19 vaccine(s) are to be introduced, to address safety concerns specific to the local population. When the vaccine is launched, the MAH should submit the iS-PSUR with the components and at the periodicity defined by the authority that authorized the vaccine (NRA or WHO prequalification programme). The MAH is responsible for compiling and submitting the iS-PSURs to the competent authority, while collaborating with its local representatives or distributors for implementing the iS-PSURs.

Specifically-focused safety studies and active surveillance (e.g. establishment of sentinel sites) should be carried out by the MAH or its local representatives or distributors, with oversight from country's authority for clinical trials and pharmacovigilance, with through close collaboration between all parties, particularly with the original authority that authorized the vaccine. Taking into consideration the limited resources available, PLSSs in LMICs should, at a minimum, be implemented in a few selected sites, ideally in countries with strong regulatory processes and standards, such as maturity level 3 countries identified by the WHO Global Benchmarking Tool.[9]

The PLSSs should aim to provide missing information, as identified in the RMP, and compare safety profiles in children, pregnant women, and special populations, e.g. ethnic groups, vulnerable populations and to highlight differences. The MAH in the LMICs involved, in consultation with the original authorizing authority, should provide the criteria that will be applied for PLSS site selection.

This scenario could be applied to other similar situations, for example, where a vaccine has not been approved by the local NRA but had been by another stringent NRA/WHO PQ. To ensure vaccine safety surveillance in this situation, the NRA where vaccine is deployed should consider the local context and ensure safety surveillance and reporting, as well as taking into consideration the review and decisions made by the authorising NRA/WHO PQ.

Scenario 2: COVID-19 vaccines non submitted for WHO Prequalification Emergency Use Listing

This scenario may include smaller companies that implement COVID-19 vaccines in LMICs. In this case, the vaccines may not have undergone stringent review for authorization by a regulatory authority and the MAH may have limited resources and only limited PV systems in place. Regional and coordinated approaches will be critical in this scenario to ensure the safety monitoring of these COVID-19 vaccines. Additional considerations in this scenario include:

- the smaller MAHs may consider collaborating with other MAHs to prepare a common RMP for the region where the vaccine will be introduced, similar to the agreement that was established between all European influenza vaccine manufacturers in 2005;
- regional cooperation and coordination should be adopted wherever feasible, and may include:
    - joint regional review of RMPs through regulatory reliance or task-sharing wherever feasible, with oversight from a regional review committee
        - existing regional networks, such as, the African Vaccine Regulatory Forum (AVAREF), the Western Pacific Regional Alliance of NRAs (WPRA) and the

[9] WHO Global Benchmarking Tool (GBT) for evaluation of national regulatory systems. Available from: http://www.who.int/medicines/regulation/benchmarking_tool/en/. Accessed 25 October 2020.

Pan American Network for Drug Regulatory Harmonization (PANDRH) should be leveraged;

- multi-country safety studies to evaluate the real-world safety profile of the vaccines, especially in populations not represented in clinical trials, such as children and pregnant women
  - the model used for the large-scale pilot implementation of the malaria vaccine, RTS,S, in sub-Sahara Africa should be considered[10], where the vaccine, after its efficacy was established in a phase III clinical trial, was introduced in a pilot programme in three countries to assess outstanding questions related to the public health use of the vaccine
  - a master protocol was developed by the MAH as part of the RMP, along with country specific-protocols for in-country evaluation.

- training should be provided to the smaller MAHs on:
  - common core RMP components and region-specific requirements, especially the regional annex;
  - regulatory obligations for vaccine PV for the region, including review of PSURs and analysis of AEFIs.

1.3. Oversight

Oversight should be at different levels:

- at the national level, the NRA is responsible for providing clear guidance on requirements for the PV of COVID-19 vaccines as described previously and in addition:
  - the NRA should contribute to a regional annex for the RMP and to the establishment of criteria for study site selection;
  - the NRA should provide oversight for study implementation, including inspection of study sites;
  - the NRA should provide clear guidance to the MAH on requirements for routine communication of study findings, and ad hoc communications for any urgent emerging issues, as well as implement a coordinated routine communication plan with stakeholders such as NIP/EPI and the MAH;
  - in countries where national AEFI review committees are established, the committee should be ready to review the PLSS data as they become available
- at the regional level, a regional review committee with scientific and regulatory expertise should be established to:
  - advise on the establishment of elements for a common RMP for the region, including a regional annex;
  - develop and communicate clear guidance to MAHs on criteria for study site selection in the region;
  - periodically review regional RMPs, PSURs/PBRERs, including outcome from PLSSs, if local NRAs do not have the necessary resources;
- at the international level, an international review committee should be established to

[10] WHO Q&A on the malaria vaccine implementation programme (MVIP). Available from: https://www.who.int/malaria/media/malaria-vaccine-implementation-qa/en/. Accessed 25 October 2020.

- review the study protocols;
- review and analyse multi-country study data;
- evaluate the performance of MAHs in LMICs through mechanisms such as PV inspections.

1.4. Data sharing

Data sharing is essential for generating reliable evidence on the safety of COVID-19 vaccines which will facilitate timely regulatory actions and effective public health interventions. Information collected from AEFI systems, active surveillance of AESIs, spontaneous reporting of adverse events, and PLSSs are all important sources of data. To be successful at sharing data in a timely manner, while respecting data security and patient privacy, close collaboration among in-country stakeholders, such as the authority overseeing the clinical trials and PV activities, the NRA, the expanded or programme on immunization or national immunization programme (EPI or NIP), and the WHO prequalified programme (for vaccines introduced through the WHO's EUL) is critical. More specifically, effective data flow needs to be established between the NRA or the WHO prequalified programme and the MAH. The NRAs and the WHO prequalified programme should consider making data sharing a condition of marketing authorization or inclusion on the EUL for COVID-19 vaccines during the pandemic, particularly in countries where current legislation does not make data sharing mandatory. Periodic PV inspection should be conducted to verify its compliance, and corrective measures taken, when necessary. Alternatively, a data sharing agreement or memorandum of understanding can be established between the MAH and the NRA or WHO prequalified programme before the vaccine is introduced.

Data sharing and data sharing platforms are discussed in detail in Module: data sharing (Link to Module XXX will be added). In the context of coordinated regional review of RMPs and evaluation of multi-country safety studies, a data sharing platform is critical for:

- enabling data pooling from multi-country sites to facilitate meaningful interpretation
- enabling review committees to review PLSS outcomes
- identification of patterns and safety issues of regional importance.

1.5. Training

A number of training needs to enhance pharmacovigilance competencies and to enable regional coordination have been identified:

Training needs	Training Target				Training providers
	NRA/PV review staff	National AEFI Committee	Regional Review Committee	MAH / subsidiary	
Legislation and legal obligations for pharmacovigilance	✓			✓	DCVMN, IFPMA, ISoP, NRA
RMP review: common core elements, regional annex, iS-PSUR core elements	✓		✓		WHO, NRA
Ethics review of study protocols	✓	✓	✓		CIOMS, WHO
Review of safety study outcomes		✓	✓		WHO, GACVS, AACVS
Pharmacovigilance for vaccine safety	(✓)			✓*	DCVMN, IFPMA

* Qualified person responsible for pharmacovigilance (QPPV)

AACVS: African Advisory Committee on Vaccine Safety; CIOMS: Council for International Organizations of Medical Sciences; DCVMN: Developing Countries Vaccine Manufactures Network; GACVS: Global Advisory Committee on Vaccine Safety; IFPMA: International Federation of Pharmaceutical Manufacturers and Associations; ISoP: International Society of Pharmacovigilance; NRA: national regulatory authority; WHO: World Health Organization

In LMICs, MAH may also require training to understand NRA's requirements and how to compile, summarize and analyse data from COVID-19 vaccine safety studies.

Coordination will be critical for the efficient provision of all levels of training. Existing training materials and programmes should be leveraged as much as possible. Stringent regulatory authorities can contribute their technical expertise to help LMICs to strengthen their regulatory systems. It is equally critical to ensure that designated QPPVs and local subsidiaries of large vaccine manufacturers and MAHs can set up efficient in-country PV systems. To this end, existing networks, such as DCVMN (Developing Countries Vaccine Manufacturers Network) and IFPMA (International Federation of Pharmaceutical Manufacturers and Associations) can play a key role in coordinating and delivering training to the private sector in anticipation of the introduction of COVID-19 vaccines, as they have a good understanding of the needs and capacity of these companies.[11]

[11]Hartmann K, Pagliusi S, Precioso A. Landscape analysis of pharmacovigilance and related practices among 34 vaccine manufacturers' from emerging countries. Vaccine. 2020;38(34):5490-7. doi: 10.1016/j.vaccine.2020.06.016.

1.6. Funding

The post-licensure safety studies, carried out by the MAH, may be supported financially through COVAX, the vaccine pillar of the ACT Accelerator. Training could be co-funded by several stakeholders. GAVI, the Vaccine Alliance, and WHO could potentially provide funding to train the NRAs, with stringent regulatory authorities potentially providing technical expertise and/or financial support. Industry networks such as DCVMN and IFPMA should support the training needs of MAHs, through funding and scientific expertise. Funding needs for monitoring systems, and platforms for data sharing between the NRAs or the WHO prequalified programme and MAH at the regional level are discussed in Module: data sharing (Link to Module XXX will be added).