COVID-19 Vaccines: Safety Surveillance Manual

Module: Stakeholders in 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

Vaccine safety monitoring, including effective reporting of adverse events following immunization (AEFIs), investigation and assessment of reported cases and taking necessary actions, requires broad and timely collaboration between national, regional and international stakeholders. These stakeholders include:

- vaccine developers, manufacturers and marketing authorization holders (MAHs);
- regulatory authorities who initially approve vaccine clinical trial protocols, assess their results and, if shown to be safe and efficacious, grant marketing authorizations, and withdraw marketing authorization if the vaccine is found to be unsafe;
- policy makers who recommend the use of vaccines, and specify the relevant vaccine target groups;
- vaccine providers who deliver vaccines and report possible AEFIs; and
- the public health institutes that investigate and assess adverse events.

Since the vaccines that will be used for protection against COVID-19 will be produced and used in many different countries and administered to large numbers of people in a short period of time, international collaboration to ensure their safety and effectiveness will be essential. Therefore, mapping national, regional and global stakeholders and their responsibilities is key for ensuring appropriate vaccine safety monitoring of these newly developed vaccines.

2. Identification of stakeholders and their roles

At the core of this collaboration are the immunization service providers who can be public or private, or both, depending on the organization of the country's health care system. It is possible that the role of country's immunization service providers will be extended to offer COVID-19 vaccines to selected target population groups for COVID-19 vaccination campaigns.

Here we provide comprehensive list of national, regional and global stakeholders and describe their routine roles in vaccination and their roles in safety monitoring and assessment for COVID-19 vaccines.

3. National stakeholders

3.1. Ministries of Health

The routine roles of Ministries of Health (MoHs) are to:

- increase support for national immunization programmes and ensure financial sustainability;
- develop and introduce laws, regulations, and policies that support immunization programmes;
- ensure a secure, high-quality supply base of vaccines;
- develop region- and country-specific plans, in collaboration with other regional and national stakeholders, when necessary;
- prioritize and assume full ownership of national immunization programmes and to create equity-driven programmes that reach all members of the community.

In the context of COVID-19 vaccine safety monitoring, MoHs are expected to:

- ensure availability of funding for national stakeholders to conduct key activities to strengthen safety monitoring for COVID-19 vaccines;
- establish a national coordination task force or working group consisting of multi-disciplinary and multi-agency representatives to ensure inter-stakeholder coordination and cooperation;
- generate vaccine demand and ensure acceptability;
- establish efficient communication mechanisms for COVID-19 vaccines between regulatory authorities, immunization programmes, Ministry of Education and other authorities, so that the population is informed about vaccine safety issues and can report any concerns; and
- be prepared to respond to rumours and media and community concerns.

3.2. National regulatory authorities

The national regulatory authorities (NRA) are responsible for ensuring that any pharmaceutical product, including vaccines, used within the country is (i) of good quality, (ii) effective, and (iii) safe for the purpose or purposes for which it is proposed.

The core functions of the NRA are:

- marketing authorization and licensing activities;
- pharmacovigilance, including surveillance of AEFIs;
- NRA lot release, with a system for lot release of vaccines;
- laboratory access, with use of laboratories when needed;
- regulatory inspection, with regular inspection of vaccine manufacturers for GMP compliance; and
- regulatory oversight of clinical trials, with evaluation of clinical performance through authorized clinical trials.

In the context of COVID-19 vaccine safety monitoring, NRAs are expected to:

- oversee preparations for emergency use listing (EUL);
- verify submission and review of risk management plans prior to marketing authorization and making risk-based recommendations for post-licensure safety surveillance;
- oversee communication and information sharing with immunization programmes, pharmacovigilance centres and other key institutions on COVID-19 vaccines safety updates to enhance the NRA's ability to make science-based decisions to protect public health;
- have authority to mandate COVID-19 vaccine safety studies by the vaccine manufacturers, MAHs and importers of vaccines, as required;
- have the independent authority to investigate potential safety signals and assure the continued post-authorization safety of COVID-19 vaccines;
- oversee the monitoring of COVID-19 vaccine safety;
- share safety information generated with national, regional, international decision-makers vaccine manufacturers and MAHs.

3.3. Expanded programmes on immunization and national immunization programmes

Their routine roles of expanded programmes on immunization (EPIs) and national immunization programmes (NIPs) are to:

- protect the population against vaccine-preventable diseases (principal role);
- respond with timely information, when public concerns about safety and efficacy of vaccines are raised to sustain public trust in vaccines and vaccination;
- be responsible for safe storage, handling including maintenance of the cold chain (continuous refrigeration), delivery and administration of vaccines released by the NRA;
- ensure that health care staff respond to adverse events;
- ensure that sufficient training and capacity is provided so that AEFIs are minimized;
- provide feedback to all levels on the findings of the investigation and causality assessment;
- provide guidance on monitoring, supervising and training to all stakeholders,
- if there are no pharmacovigilance centres in the country:
    - oversee monitoring, information collection, assessment of serious AEFIs;
    - ensure that causality assessments for AEFIs are conducted as per guidelines; and
    - search for and analyse safety signals.
- provide expert support for field investigations; and
- recommend decisions for vaccination policies.

The roles of the EPIs and NIPs for COVID-19 vaccine safety monitoring, in collaboration with NRAs, are expected to include:

- when recommended, conducting specific active surveillance studies for COVID-19 vaccines, similar to those for other new vaccines i.e., typhoid conjugate, malaria, Ebola, and dengue vaccines, with active surveillance and sentinel sites to identifying signals and establish causality;
- regularly reviewing reports submitted to passive safety surveillance systems to identify rates and unexpected patterns, with special attention to serious outcomes, such as death, disabilities, life-threatening events, and programmatic errors;
- identifying and quantifying public concerns surrounding vaccines through cross-sectional surveys and monitoring of social media;
- developing a national framework to process vaccine safety signals and determine which should be prioritized for more rigorous evaluation and risk assessment;
- measuring and characterizing background rates of medical outcomes that may become temporally associated with COVID-19 vaccines; and
- measuring and characterizing other AEFIs identified in active surveillance and sentinel systems; and
- coordinating existing active and sentinel surveillance nationally, regionally and globally to ensure harmonization, avoid duplication, increase power to detect rare events and take advantage of variability in vaccination practices and target population.

3.4. National pharmacovigilance centres

The routine roles for national pharmacovigilance centres, when they exist, include:

- collecting and analysing case reports for AEFIs;
- supporting AEFI committees in performing causality assessment for AEFIs;
- detecting and analysing vaccine safety signals;
- alerting prescribers, vaccine manufacturers and MAHs and the public if new risks for adverse reactions are observed; and
- overseeing vaccine safety and risk communication.

The roles of the national pharmacovigilance centres for COVID-19 vaccine safety monitoring are expected to include:

- ensuring timely submission of Covid-19 AEFIs and adverse events of special interest (AESIs) data from EPIs, NIPs and pharmacovigilance centres across the country for data compilation, analysis and signal detection; and
- sharing information with key national stakeholders on COVID-19 vaccine safety and with the global community by uploading the information on the global pharmacovigilance database; Vigibase maintained at UMC Sweden under the WHO International Drug Monitoring Programme.

3.5. AEFI review committees

The main responsibilities of AEFI review committees are to:

- Provide guidance for AEFI investigation so that the correct cause can be determined;
- assess potential causal links between AEFIs and vaccines, using standard procedures;[1]
- monitor reported AEFI data for potential signals of previously unrecognized vaccine-related adverse events and support further investigations to establish if causality exists;
- make the necessary recommendations to rectify problems, communicate with national stakeholders and other national and international experts, when required.

The terms of reference for the AEFI review committees for COVID-19 vaccine safety monitoring are expected to include:

- assessing potential causal links between AEFIs and AESIs and COVID-19 vaccines;
- monitoring AEFI data for identification of potential signals of previously unidentified COVID-19 vaccine related adverse events;
- reviewing all serious AEFIs presented for expert opinion and arranging further investigation to establish causality, if required;
- communicating with other national and international experts, when required, to establish causality and resolve vaccine quality issues;

[1] WHO. Causality assessment of an adverse event following immunization (AEFI) User manual for the revised WHO AEFI causality assessment classification (Second edition). Available from; https://www.who.int/vaccine_safety/publications/gvs_aefi/en/. Accessed 30 October 2020.

- advising NRAs, EPIs and NIPs on COVID-19 vaccines AEFI- and AESI-related issues when requested;
- advising the Ministry of Health (MoH) on COVID-19 vaccines and Immunization safety-related matters when requested; and

The committee should be independent of the NRAs, NIPs/EPIs, MoHs and MAHs, with no conflicts of interest.

3.6. National immunization technical advisory groups

The main roles of national immunization technical advisory groups (NITAGs) are to:

- guide national governments and policymakers for the development and implementation of evidence-based, locally relevant immunization policies and strategies that reflect national priorities;
- support NIPs/EPIs and NRAs and empower them to address issues associated with vaccine quality and safety and the introduction of new vaccines and immunization technologies; and
- help governments and NIPs/EPIs to address public concerns

The roles of NITAGs (or of a COVID-19 working group within the NITAG) for COVID-19 vaccine safety monitoring are expected to include:

- providing the latest information on different COVID-19 vaccine platforms, risk/benefit analyses, COVID-19 EUL status, etc.; and
- reviewing the available evidence to be considered for recommendations for COVID-19 vaccine introduction, include identification of priority target groups for COVID-19 introduction.

3.7. Vaccine manufacturers

The routine roles of the vaccine manufacturers are to:

- continue to develop, produce and supply innovative and high-quality vaccines that meet countries' needs;
- support research and vaccine specific training needs for immunization;
- establish a risk minimization plan for new vaccines;
- participate in open dialogues with countries and the public sector to ensure sustainable access to current and new vaccines; and
- to continue to innovate manufacturing processes and pricing structures.

The roles of vaccine manufacturers for COVID-19 vaccine safety monitoring are expected to include:

- sharing risk management plans for COVID-19 vaccines with NRAs;
- conducting phase IV studies on COVID-19 vaccines and submitting product safety update reports (PSURs) on a regular basis to help policy decisions; the frequency of PSUR submissions may be increased to bi-monthly/monthly to guide quick corrective actions and decisions;
- responding to national requests to share additional and updated information on product information and clinical trial data; and

- keeping the countries updated on safety and efficacy findings from phase IV studies in other countries.

3.8. Academia

The main routine roles of academia are:

- to promote innovation to accelerate the development of new and improved vaccines;
- to pursue a multidisciplinary research agenda that focuses on transformational impact and is based on the needs of end users;
- to embrace new ways of working that speed up and improve dialogue with other researchers, regulators and manufacturers; and
- to align actions and increase effectiveness in responding to local and global immunization challenges.

The roles of academia for COVID-19 vaccine safety monitoring are expected to include advising and facilitating research activities concerning COVID-19 vaccines, including sentinel-site based and specific studies related to AESIs.

3.9. Health care providers

The routine roles of health care providers are to:

- provide vaccine and vaccination information prior to providing high-quality immunization services;
- identify areas where immunization services could be improved and innovations implemented;
- serve as proactive, credible advocates to promote the value of vaccines and vaccination and recruit other advocates:
- use existing and emerging technologies to improve information delivery and capture;
- dialogue with communities and the media and use effective communications techniques to convey messages about vaccines; and
- address clinical case management for adverse events.

The roles for health care providers for COVID-19 vaccine safety monitoring are expected to include:

- ensuring staff training on detection, management and reporting of Covid-19 vaccine AEFIs identified through active and passive surveillance;
- properly supervising to ensure both serious and non-serious AEFIs are captured and that serious AEFIs are adequately investigated; and
- developing a communication protocol, including the use of a trusted spokesperson, to promptly inform the public about any investigation or rumours.

3.10. Beneficiaries

The roles of beneficiaries are the same in the context of COVID-19 vaccine safety monitoring as for routine vaccine safety monitorin, and include to:

- understand the risk and benefits of vaccines and immunization, viewing this as part of being a responsible citizen;
- differentiate between genuine and false information and ensure that correct information is communicated, and prevent the circulation of false information;
- demand safe and effective immunization programmes as a right from their leaders and government and hold leaders and government accountable for providing them;
- participate in public-health discussions;
- be involved in key decisions about immunization processes;
- participate and contribute to the immunization delivery process; and
- convey the needs and perspectives of their communities to policymakers.

3.11. Media

The routine roles of the media are to:

- understand the benefits of, and concerns about, immunization in order to accurately report on and effectively promote immunization programmes;
- engage in country, regional and global advocacy beyond the immunization community to ensure vaccines and immunization are understood as a right for all; and
- use effective communications techniques to convey messages about vaccines and to address safety concerns.

The roles for media for COVID-19 vaccine safety monitoring are expected to include:

- keeping up-to-date with media releases, press information packages, briefing papers, web materials, talking points disseminated by MoHs on COVID-19 vaccines and vaccination;
- proactively identifying, filtering out and preventing the spread of misinformation;
- participation in media workshops and training sessions to learn about the rationale for COVID-19 vaccine introduction and understand the key messages; and
- ensuring the dissemination of factual, clear messages to the public prior to introduction of COVID-19 vaccines.

3.12. Non-governmental organizations and professional societies

Non-governmental organizations and professional societies do get involved in the promotion and implementation of routine immunization programmes at both the country and global levels, follow national guidelines and regulations for the design and delivery of immunization programmes that fulfil the duty of accountability to national authorities, contribute to improved evaluation and monitoring systems within countries.

Non-governmental organizations and professional societies should participate in the development and testing of innovative approaches for the delivery of COVID -19 immunization services that reach the most vulnerable people.

4. Regional stakeholders

4.1. Regional regulatory networks

Regional regulatory networks such as the African Vaccine Regulatory Forum (AVAREF), the South-East Asia Regulatory Network (SEARN), the European Medicines Agency (EMA) play an essential role in routine pharmacovigilance. For example, EMA's large Eudravigilance database is a system for managing and analyzing information on suspected adverse reactions to medicines, including vaccines, that have been authorized or are being studied in clinical trials in the European Economic Area and also those authorized for use outside the European Union, the Article 58 authorized vaccines. These latter include vaccines for protection against a WHO public health priority disease, such as COVID-19. These networks play a key role in implementing regulatory reliance for pharmacovigilance of COVID-19 vaccines as described in Module on regulatory reliance [link will be added]

4.2. Regional Technical advisory committees on vaccine safety

The roles of regional advisory committees on vaccine safety vary between regions. All WHO regions have established Regional Technical Advisory Groups (RTAGs) on immunization but play different roles to those played by the NITAGs as they provide recommendations on regional immunization priorities and strategies in the light of regional epidemiological and social issues to the WHO regional directors as well as the countries in their respective regions.

The roles for RTAGS for COVID-19 vaccine safety monitoring are expected to include rapid, real-time exchange of information and joint assessment of routine safety data, should there be a safety signal

5. Global stakeholders, their routine roles and responsibilities and their role in the COVID-19 vaccine safety monitoring

5.1. International Coalition of Medicines Regulatory Authorities

The International Coalition of Medicines Regulatory Authorities (ICMRA) is a voluntary, executive-level entity of worldwide medicines regulatory authorities set up to provide strategic coordination, advocacy and leadership. ICMRA acts as a forum to support international cooperation among medicines regulatory authorities. The coalition aims to identify ways to better use existing initiatives and resources, develop strategies to address current and emerging challenges in global human medicine regulation, such as the growing complexity of globalized supply chains and provide direction for common activities and areas of work.

ICMRA aims to expedite and streamline the development of COVID-19 vaccines and treatments. In April 2020, ICMRA members pledged to strengthen global collaborative efforts to align the facilitation of rapid development, approval and global roll-out of safe and effective medicines and vaccines to prevent and treat COVID-19. Collective statements and efforts including describing the key characteristics of clinical trials that are most likely to generate the conclusive evidence needed to enable the accelerated approval of potential treatments and vaccines against COVID-19.

5.2. The Council for International Organizations of Medical Sciences

The Council for International Organizations of Medical Sciences (CIOMS) is an international, non-governmental, non-profit organization established jointly by WHO and UNESCO in 1949. Its mission is to advance public health through guidance on health research and policy including ethics, medical product development and safety. CIOMS is in official relations with WHO and is an associate partner of UNESCO. The CIOMS pharmacovigilance guidelines have been used as the basis for International Council on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH) Guidelines (see Section 5.3). The longest running of the CIOMS Working Groups, since 2002, is dedicated to standardized MEDDRA Queries (SMQs). This implementation working group has produced the 'Red Books' on the Development and Rational Use of Standardised MedDRA Queries (SMQs), updated in 2016. The CIOMS Guide to Active Vaccine Safety Surveillance, published in 2017 will be used for guidance for COVID-19 vaccine safety monitoring. The 2012 report of the CIOMS WHO working group on the Definitions and Applications of Terms for Vaccine Pharmacovigilance is used as the reference document for AEFI surveillance and causality assessment.

5.3. International Council on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use

The International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use (ICH) is unique in bringing together the regulatory authorities and pharmaceutical industry to discuss scientific and technical aspects of pharmaceuticals and develop ICH guidelines. Since its inception in 1990, ICH has gradually evolved, to respond to increasingly global developments in the pharmaceutical sector and these ICH guidelines are applied by a growing number of regulatory authorities. ICH's mission is to achieve greater harmonisation worldwide to ensure that safe, effective and high-quality medicines are developed, and registered and maintained in the most resource efficient manner whilst meeting high standards. Since its announcement of organisational changes in October 2015, ICH has grown as an organisation and now includes 17 Members and 32 Observers.

The COVID-19 pandemic has prompted an urgent need for a harmonized, standardized approach for coding and reporting COVID-19 infections as a global health issue. ICH has defined E2B[2] as the international standard for transmitting adverse event reports that includes message standards required for effective transmission of individual case safety reports (ICSR). The ICH M1 Points to Consider Working Group and the medical dictionary for regulatory activities (MedDRA) maintenance and support services organization (MSSO), with the approval of the MedDRA Management Committee, are issuing Notifications for MedDRA users regarding existing and new terms for COVID-19 concepts. These notifications are available on the MedDRA website. The latest Version 23.1 notifies the addition of new terms to MedDRA.

5.4. WHO prequalification

The WHO prequalification (PQ) office verifies that vaccines used in immunization programmes are safe and effective. It provides Member States and procurement agencies, such as Gavi, the Vaccine Alliance,

[2] https://ich.org/page/e2br3-individual-case-safety-report-icsr-specification-and-related-files

the Global Fund and UN organizations like UNICEF, with the information required to purchase vaccines matching the specific needs of the programme. WHO prequalification of vaccines is a comprehensive assessment that takes place through a standardized procedure aimed at determining whether the product meets requirements for safety and efficacy in immunization programmes. The full prequalification assessment process includes the following components:

- review of production process and quality control procedures
- laboratory testing
- WHO site audit to manufacturing facilities with the responsible NRA.

Once a vaccine is prequalified and introduced to the market, WHO ensures it continues to meet standards by, for example investigating complaints from the field and reports of AEFIs.

The WHO PQ office is playing a major role in prequalification of new COVID-19 vaccines and for possible EUL of COVID-19 vaccines.

5.5. WHO Global Advisory Committee on Vaccine Safety

The Global Advisory Committee on Vaccine Safety (GACVS) provides independent, authoritative, scientific advice to WHO on vaccine safety issues of global or regional concern with the potential to affect in the short- or long-term national immunization programmes. This includes providing advice on urgent matters as needed, such as COVID-19 vaccine safety monitoring.

Issues to be considered by the Committee are jointly decided by the WHO Secretariat and the Committee. More specifically, the role of the GACVS is expected to include:

- rigorous review of the latest knowledge, in all fields ranging from basic sciences to epidemiology, concerning any aspect of vaccine safety of global or regional interest, in close collaboration with all parties involved, including experts from national governments, academia, and industry;
- assessment of causality between vaccines and/or their components and adverse events attributed to them;
- creation of ad hoc task forces, when necessary, with a mandate to commission, monitor and evaluate appropriate methodological and empirical research on any suspected association between specific vaccines/vaccine components and adverse event(s); and
- providing scientific recommendations that are intended to assist WHO, the WHO's Strategic Advisory Group of Experts (SAGE) for vaccines and immunization, national governments and international organizations in formulating policies regarding vaccine safety issues, with particular attention to those problems that affect developing countries.

5.6. WHO Strategic advisory group of experts

SAGE serves as the principal advisory group to WHO for the development of policy related to vaccines and immunization. SAGE is charged with advising WHO on overall global policies and strategies, ranging from vaccine and technology research and development, to delivery of immunization and linkages between immunization and other health interventions. The mandate of SAGE is to provide strategic advice rather than technical input, and it is not restricted to childhood vaccines and immunization but

extends to the control of all vaccine-preventable diseases. SAGE advises the WHO Director-General specifically on:

- adequacy of progress towards the achievement of the goals of the Global Immunization Vision and Strategy (GIVS);
- major issues and challenges to be addressed with respect to achieving the goals of GIVS;
- immunization programme response to current public health priorities;
- major general policies, goals and targets, including those related to vaccine research and development;
- adequacy of WHO's strategic plan and priority activities to achieve the GIVS goals consistent with its mandate and considering the comparative advantages and the respective roles of partner organizations;
- cross-departmental activities and initiatives related to vaccine and immunization technologies and strategies and linkages with other health interventions; and
- engagement of WHO in partnerships that will enhance achievement of global immunization goals.

In the context of COVID-19 vaccine safety monitoring, a WHO SAGE working group has been formed to:

- provide continuous review of the available evidence on the progress of candidate vaccines against COVID-19, and provide regular updates to SAGE;
- provide guidance for the development of prediction models to determine the optimal age groups and target populations for vaccine introduction and guide vaccine introduction for optimal impact, and contribute to updates of target population profiles of COVID-19 vaccines for outbreak and endemic use;
- provide policy advice to SAGE on the accelerated use of COVID-19 vaccines (pre-licensure and post-licensure) to mitigate the public health impact of COVID-19, to possibly curtail the ongoing pandemic, as well as to prevent or reduce the risk of spread of disease in the future; this will include recommendations for early allocation of vaccines when vaccine supplies are still limited; and
- provide guidance to ensure equitable access to vaccination, and guidance on the safety of vaccines when safety data from wider population use become available, in close collaboration with GACVS.

The following Covid 19 documents have been endorsed by WHO SAGE:

- WHO SAGE Values framework for the allocation and prioritization of COVID-19 vaccination; and
- Roadmap for prioritizating population groups for vaccines against COVID-19.

5.7. WHO Immunization, Vaccines and Biologicals

The Immunization, Vaccines and Biologicals (IVB) Department is responsible for targeting vaccine-preventable diseases, vaccines, immunization policy and research. IVB is involved in addressing immunization challenges in the context of accelerating urbanization, migration and displacement, conflict and political instability, unaffordability of newer vaccines in middle-income countries,

unexpected vaccine supply shortages both locally and globally, and rising vaccine hesitancy. Strategies for the continued vaccine preventable infectious disease outbreaks, and disease elimination goals that have not yet been achieved are being developed and pursued.

In the context of COVID-19 vaccine safety monitoring, guidance on national deployment and vaccination plans for COVID-19 vaccines and checklists for immunization programmes preparing for COVID-19 vaccination programmes are being prepared but are not yet available.

5.8. UNICEF

UNICEF and its partners support immunization programmes in over 100 countries. Their activities include logistics, monitoring and advocacy for immunization and acting on infodemics, and documenting vaccine coverage through the WHO/UNICEF Joint Reporting Form.

In the context of COVID-19 vaccine safety monitoring, UNICEF is providing support to the immunization programmes in countries with current activities and distribution of COVID-19 vaccines.

5.9. Uppsala Monitoring Centre

The Uppsala Monitoring Centre (UMC) is a WHO Collaborating Centre, located in Uppsala, Sweden that provides training, guidance and support to countries in the WHO Programme for International Drug Monitoring. They manage VigiBase, WHO's database of individual case safety reports and the world's largest repository of adverse effects from medicines, including vaccines. Member countries submit reports of suspected adverse drug reactions to the database VigiBase. In 2019 VigiBase contained more than 20 million reports, and is used to analyse global patterns of suspected harm caused by medicines. In the context of COVID-19 vaccine safety monitoring, UMC will proceed with safety signal detection.

5.10. Brighton Collaboration

The Brighton Collaboration develops case definitions for adverse events and guidelines for investigations and assessment of adverse events in formal pharmacoepidemiological studies. In the context of COVID-19 vaccine safety monitoring, a list of possible AESIs have been developed under contract with CEPI (See Section 5.13). Case definitions to be used for investigating possible AESIs including background rates are under development. Study protocols are being developed for background incidence studies and association studies initiated for confirmatory studies should a safety signal arise.

5.11. COVID-19 Vaccines Global Access Facility

GAVI co-leading the COVID-19 Vaccines Global Access (COVAX) facility the vaccines pillar of the Access to COVID-19 Tools (ACT) Accelerator. Gavi's impact draws on the strengths of its core partners, the World Health Organization, UNICEF, the World Bank and the Bill & Melinda Gates Foundation. This is a global risk-sharing mechanism for pooled procurement and equitable access to COVID-19 vaccines when they become available. COVAX aims to end the acute phase of the pandemic by the end of 2021.

5.12. Vaccine Safety Net

The Vaccine Safety Net (VSN)[3] established by WHO, is a network of a diverse group of digital information resources (websites and social media), VSN members, located in countries around the world and providing scientifically based information on vaccine safety in various languages. The mission of the VSN is to help internet users find reliable vaccine safety information tailored to their needs. A key player in the project is the GACVS (see Section 5.5). who developed three categories of criteria for good information practices - regarding credibility, content and accessibility/design to which sites providing information on vaccine safety should comply. VSN evaluates websites for their adherence to these criteria. This will be an invaluable resource for information on COVID-19 vaccines and vaccination for all stakeholders.

5.13. The Coalition for Epidemic Preparedness Innovations

The Coalition for Epidemic Preparedness Innovations (CEPI) is a global partnership launched in 2017 to develop new vaccines for emerging infectious diseases and bring them through to phase I and II vaccine trials. In the context of COVID-19 vaccine safety monitoring, CEPI has signed contracts with 10 vaccine developers and have established partnerships with 5 clinical sample testing laboratories to create a centralised global network to reliably assess and compare the immunological responses generated by COVID-19 vaccine candidates. This approach will ensure uniformity in assessment and informed identification of the most promising vaccine candidates. Through this specific network, up to the limit of programme funding, eligible COVID-19 vaccine developers (both CEPI-funded and non-CEPI funded developers) can use the laboratories, without per sample charges, to analyse the immune response elicited by their COVID-19 vaccine candidates in preclinical, Phase I and Phase IIa vaccine trials. CEPI has partnered with the Brighton Collaboration in funding the Safety Platform for Emergency vACcines (SPEAC) project in 2019 through the Task Force for Global Health. SPEAC aims to create capacity and solutions for harmonized safety assessment of CEPI vaccines.

5.14. International Federation of Pharmaceutical Manufacturers and Associations

The International Federation of Pharmaceutical Manufacturers and Associations (IFPMA) represents the research-based pharmaceutical companies and associations across the globe. In the context of COVID-19 vaccine safety monitoring, IFPMA members, which include the leading innovative biopharmaceutical companies in the vaccine field, are aiming to develop safe and effective COVID-19 vaccines.

5.15. Developing Countries Vaccine Manufactures Network

The members of the Developing Countries Vaccine Manufactures Network (DCVMN) are vaccine manufacturers from developing countries that aim to provide a consistent and sustainable supply of quality vaccines at an affordable price that are accessible to developing countries. DCVMN is an alliance of over 40 public and private vaccine manufacturing companies from 14 emerging countries/territories engaged in supply of vaccines for local and international use.

[3] https://www.vaccinesafetynet.org/

To provide DCVMN members and the Executive Committee with all the information required to make high-level policy decisions, they have set up a COVID-19 committee whose objective is to assess the evolving situation of the pandemic and to:

- evaluate prime COVID-19 vaccine candidates;
- evaluate technical information (research roadmaps, animal models, clinical trial protocols, formulation (e.g. adjuvant effects) etc.);
- evaluate solutions provided by organizations such as, but not limited to, WHO, CEPI, Gavi, PAHO, UNICEF (e.g., COVID-19 AMC, ACT-accelerator, COVAX Facility)
- develop and support solid bases for statements to support DCVMN dialogue with global stakeholders and in public meetings; and
- assess and share technologies important for COVID-19 vaccine development, through surveys and reports.