CIOMS Guide to Active Vaccine Safety Surveillance:

Report of CIOMS Working Group on Vaccine Safety

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- What is CIOMS?
- Recent publications, pipeline
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Acronym & Logo

Council for

International

Organizations of

Medical

Sciences

- ***Mission Statement***

  CIOMS mission is to advance public health through guidance on health research including ethics, medical product development and safety

CIOMS in short

- Organization located in Geneva :
  A. International
  B. Nongovernmental
  C. Not-for-Profit

- In official relations with WHO + Associate Partner of UNESCO

- ... for WHO, health authorities, academic organizations, pharmaceutical industry and other concerned stakeholders
  ➢ an organization of medical science organizations

- *Forum for discussion and neutral platform to elaborate new ideas in medical product development, pharmacovigilance and research ethics (bioethics)*

Organization

Executive committee

President: Prof. Hervé Le Louet - since Nov. 29, 2016 (member of PRAC)

Vice president: Prof. Samia Hurst (Swiss academy of sciences)

Secretary-General: Dr Lembit Rägo (CIOMS secretariat, former WHO Regulatory Unit Head)

<= 12 representatives (mostly from national and international members)

Secretariat

Secretary-General Dr. Lembit Rägo (since April 18, 2016) and team; located in Geneva (close to WHO und UN Palais des Nations)

Mandate: „day to day management in conformity with statutes and directions of executive committee“

CIOMS

Members - General Assembly

International Organizations (12)

National Organizations, Associate Members (11)

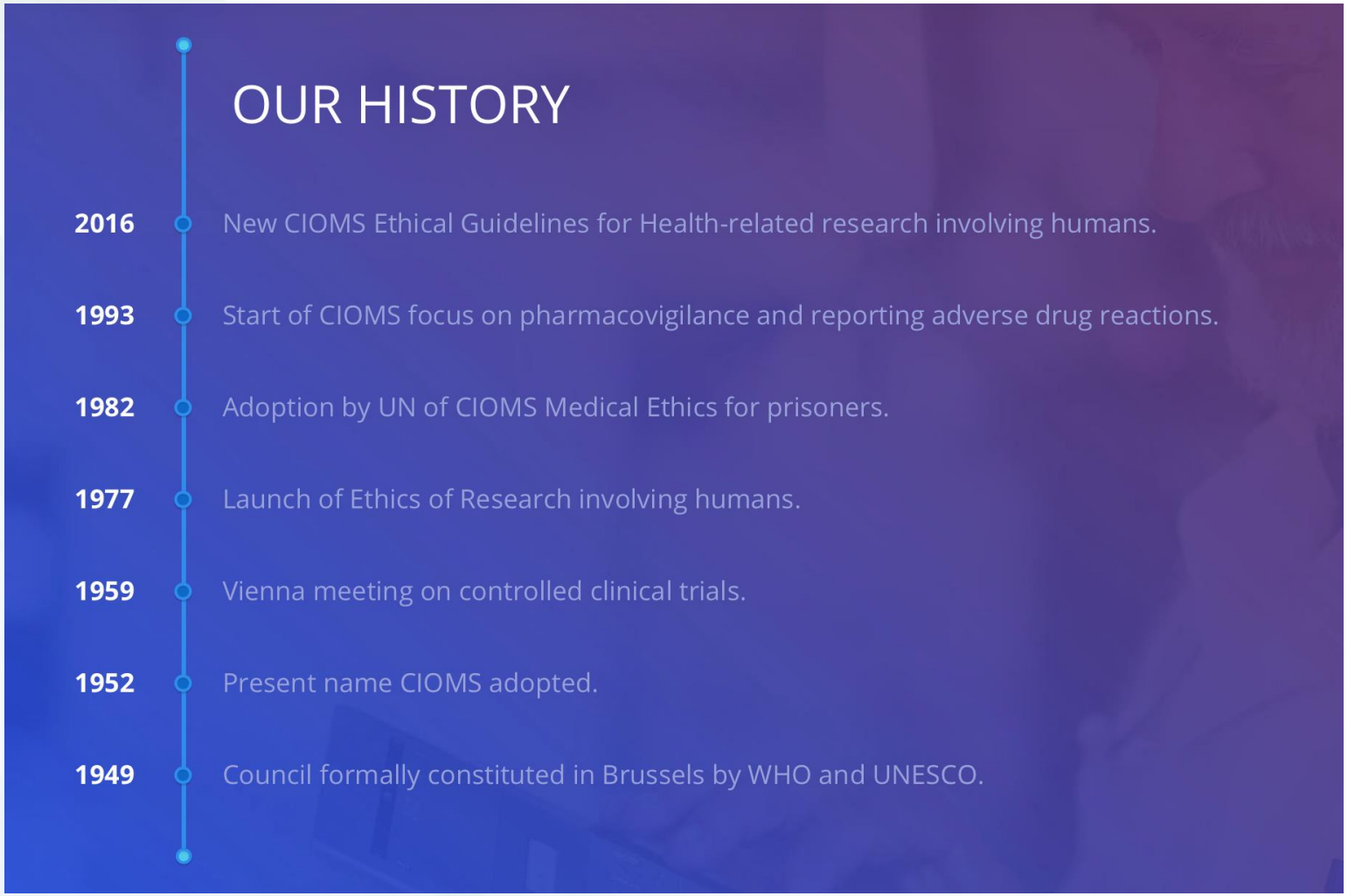
Associate Members (19)

Collaborations

Partners: Authoritative, international organizations dealing with related topics

e.g. WHO, PAHO/AMRO, ICH, IFPMA

Historic landmarks



Programs, Activities

Bioethics

Since 1967; 1. CIOMS Round Table Conference "Biomedical Science and the dilemma of Human Experimentation") Issuance of significant guidelines; latest revision 2016

Focus on "low and middle income countries"; translation into various languages

Pharmaco-vigilance

1986 first PV Working Group, 13 more working group reports until today

Several ICH Guidelines are based on results of CIOMS Working Groups

Product Develop-ment

Trends and Prospects in Drug Research and Development, Proceedings of the 11th CIOMS Round Table Conference, Geneva, Switzerland, 8-9 December 1977. Ed. Z. Bankowski, J.F. Dunne, published by Scrip World Pharmaceutical News, London, 1978.

Core of activities: Technical Working Groups

Run-time:Mostly 2-4 years, or even more than 10 years (SMQs)

Impact: legally not binding, yet significant influence on healthcare community (including decision makers and other organizations with impact); can also be transformed to be legally binding when embodied in regional/national legislation

Pharmacovigilance: Working Groups

Working Group	Period (some examples)	Report / Year
CIOMS I	-	International Reporting of Adverse Drug Reactions (1990)
CIOMS II	-	International Reporting of Periodic Drug Safety Update Summaries (1992)
CIOMS III	-	Guidelines for Preparing Core Clinical Safety Information on Drugs (1995)
CIOMS IV	01/1995 – 07/1997	Benefit-risk balance for marketed drugs (1998)
CIOMS V	04/1997 – 08/2000	Current Challenges in Pharmacovigilance: Pragmatic Approaches (1999)
CIOMS WG on SMQs	05/2002 -	Development and Rational Use of Standardized MedDRA Queries (SMQs): Retrieving Adverse Drug Reactions with MedDRA (2004)
CIOMS VI	03/2001 -10/2004	Management of Safety Information from Clinical Trials (2005)
CIOMS VII	-	Development Safety Update Reports (DSUR): Harmonizing the Format and Content for Periodic Safety Report during Clinical Trials (2006)
CIOMS VIII	-	Practical Aspects of Signal Detection in Pharmacovigilance (2010)
CIOMS/WHO WG	11/2005 – 10/2010	Definition and Application of Terms for Vaccine Pharmacovigilance (2012)
CIOMS IX	-	Practical Approaches to Risk Minimisation for Medicinal Products (2014)
CIOMS X	06/2011 – 07/2015	Evidence Synthesis and Meta-Analysis for Drug Safety (2016)
CIOMS SMQ Implementation WG	(05/2002) – 2018/19	Development and Rational Use of Standardised MedDRA Queries (SMQs): Retrieving Adverse Drug Reactions with MedDRA (2016)
CIOMS WG to Vaccine Safety	2013 -2016	**CIOMS Guide to Active Vaccine Safety Surveillance (2017)** CIOMS Guide to Vaccine Safety Communication (2017/2018?)

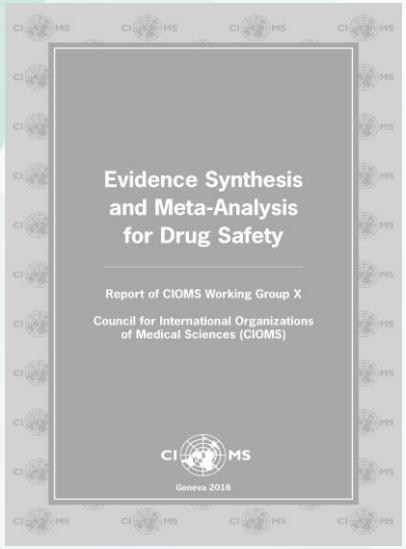
Impact on ICH Guidelines

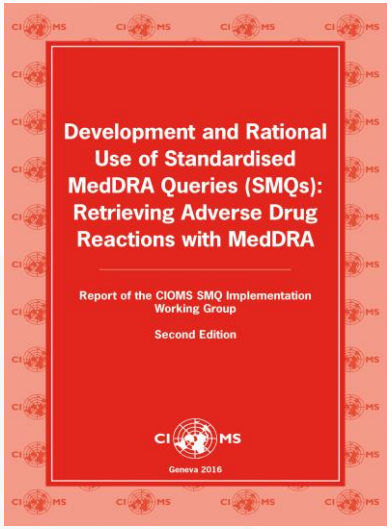
CIOMS pharmacovigilance guidelines served as a basis for several ICH guidelines. Some examples:

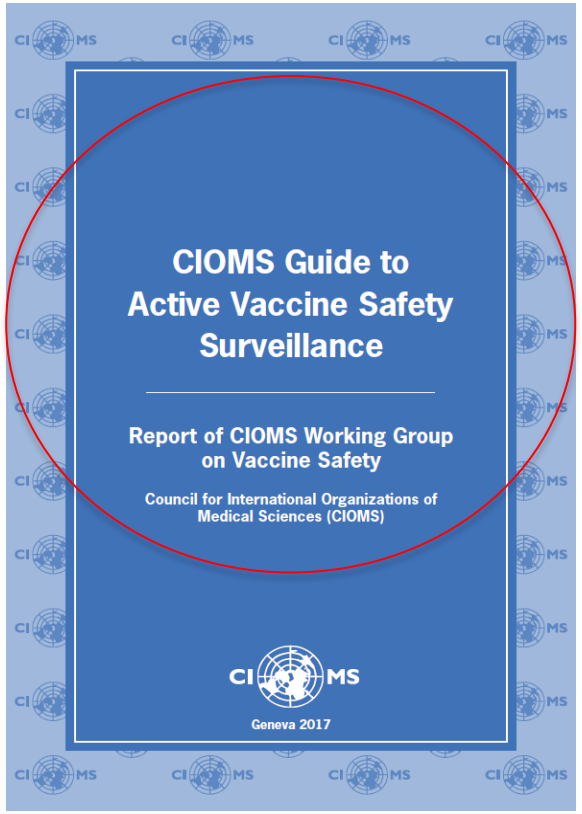
Working Group	ICH Guideline
CIOMS WG I und II Reports (1990, 1992)	ICH-E2A (1994): Clinical Safety Data Management – Definitions and Standards for Expedited Reporting
CIOMS IA (1992)	ICH E2B: Clinical Safety Data Management – Data elements for transmission of individual case safety reports
CIOMS WGs II und III (1992, 1995)	ICH-E2C (1996): Clinical Safety Data Management – Periodic Benefit-Risk Evaluation Reports (PBRER)
CIOMS WG V (2001)	ICH-E2D (2003): Post-Approval Safety Management – Definitions and Standards for Expedited
CIOMS WG VIII Report (2006)	ICH-E2F (2010): Development Safety Update Reports

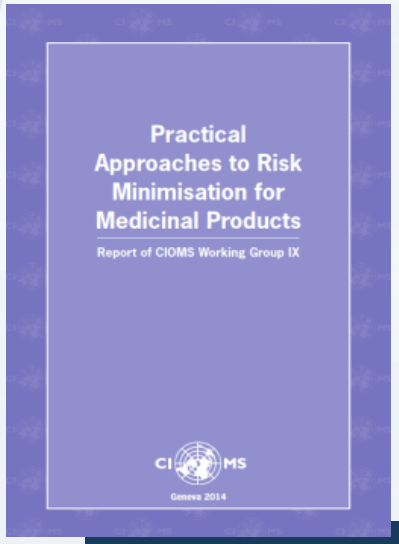
Pharmacovigilance: Recent Publications

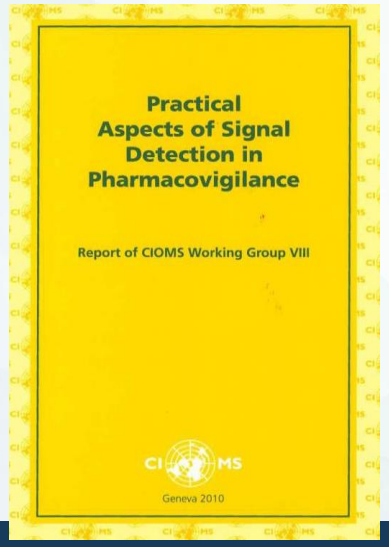
https://cioms.ch/shop/product-category/recently-published/

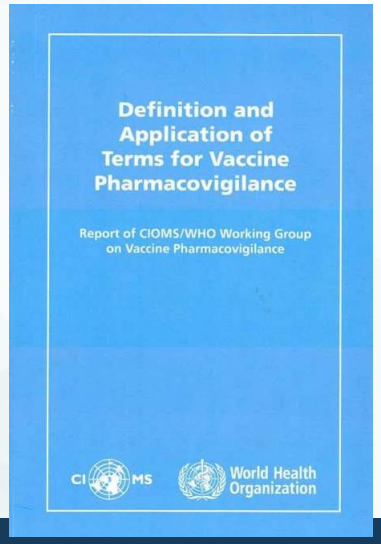












Background to CIOMS Guide on AVSS

In 2013, CIOMS created a Working Group on Vaccine Safety (WG) to address unmet needs in the area of vaccine pharmacovigilance with a specific focus on resource-limited countries (RLCs). The development of the Blueprint identified the need for enhancement of the performance of both active and passive surveillance and for development of harmonized tools and methods, which would lead to facilitating the exchange of information between stakeholders. The WG decided to support decision-makers at country-level by creating a Guide to Active Vaccine Safety Surveillance (AVSS) that:

- Aids decision-makers in determining the best course of action when confronted with a launch of a new vaccine or a vaccine that is new to their country,
- Complements WHO's guidance on surveillance of adverse events following immunization as well as previous CIOMS guidance on other aspects of pharmacovigilance.
- Helps generating reliable data about specific safety concerns is becoming a priority for all countries.

The Guide (1)

The Guide provides:

- A structured process for determining if AVSS is warranted
- If warranted, the analytical approaches that can be used depending on the types of data that is available on vaccinations, health events, and population demographic and medical characteristics.
- An essential vaccine information source list for evaluating the extent of data resources, and several case studies for review.

The Guide (2)

A Two part Guide:

Part 1 includes an introduction to core principles and concepts, especially the need to identify a specific gap and confirm its existence before proceeding to AVSS. It also reviews alternatives to AVSS for closing SKGs

Part 2 is a shift, both in subject and tone. It assumes the user has gone through all the steps and determined that AVSS is indeed the right tool and appropriate. It then provides a high level overview of the types and key issues related to AVSS

Part I

- Acknowledgements/Acronyms/Foreword
- Chapter 1: Key Background Concepts And Introduction
- Chapter 2: Identification Of Significant Knowledge Gaps/The Appropriate Tools To Close Them

Part II

- Chapter 3: Active Vaccine Safety Surveillance – Principles And Methods
- Chapter 4: Practical Aspects Of Conducting AVSS Studies
- Appendix I: Essential Vaccine Information (EVI)
- Appendix II. Membership And Meetings Of The CIOMS Working Group On Vaccine Safety
- Glossary/Bibliographic References

Active Vaccine Safety Surveillance (AVSS)

The WG used the following AVSS working definition for the scope of this guide:

"*AVSS is a data collection system that seeks to ascertain as completely as possible the number of AEFIs in a given population via a continuous organized process.*

In AVSS the information is collected with defined objectives to investigate one or several AEFIs which are often pre-specified adverse events of specific interest (AESIs), e.g. intussusception following rotavirus immunization. In an active public health surveillance system, the health department, the national regulatory authority (NRA), or other responsible entity initiates and maintains regular contact with health care providers or other relevant reporting sources (e.g. hospitals, laboratories or patients) to identify cases of the health condition(s) of interest."

A Significant Knowledge Gap (1)

A Knowledge Gap is a lack of information, a research gap or question on some aspect of vaccine safety that has not been answered sufficiently.

- If the knowledge gap has the potential to negatively influence the benefit-risk profile of the vaccine to such a degree that it could *significantly* effect the safety of those receiving vaccinations, it can be described as a "significant knowledge gap" (SKG).
  - A SKG may be specific to a particular country, region, or population subset (e.g. the elderly, pregnant women, etc.)
- Knowledge Gaps may occur at any point in the lifecycle/in various circumstances
  - AVSS may be indicated in circumstances that include introduction into a country of a vaccine that has been well-characterized elsewhere, but in which local introduction may represent new issues (e.g.. new population, new indication, new multivalent form).
  - A new vaccine without significant prior global experience, such as a novel vaccine aimed primarily at diseases of resource-limited countries.
  - Following vaccine introduction in a country, there may be a need for AVSS because a concern has arisen on account of a safety signal detected through passive surveillance.

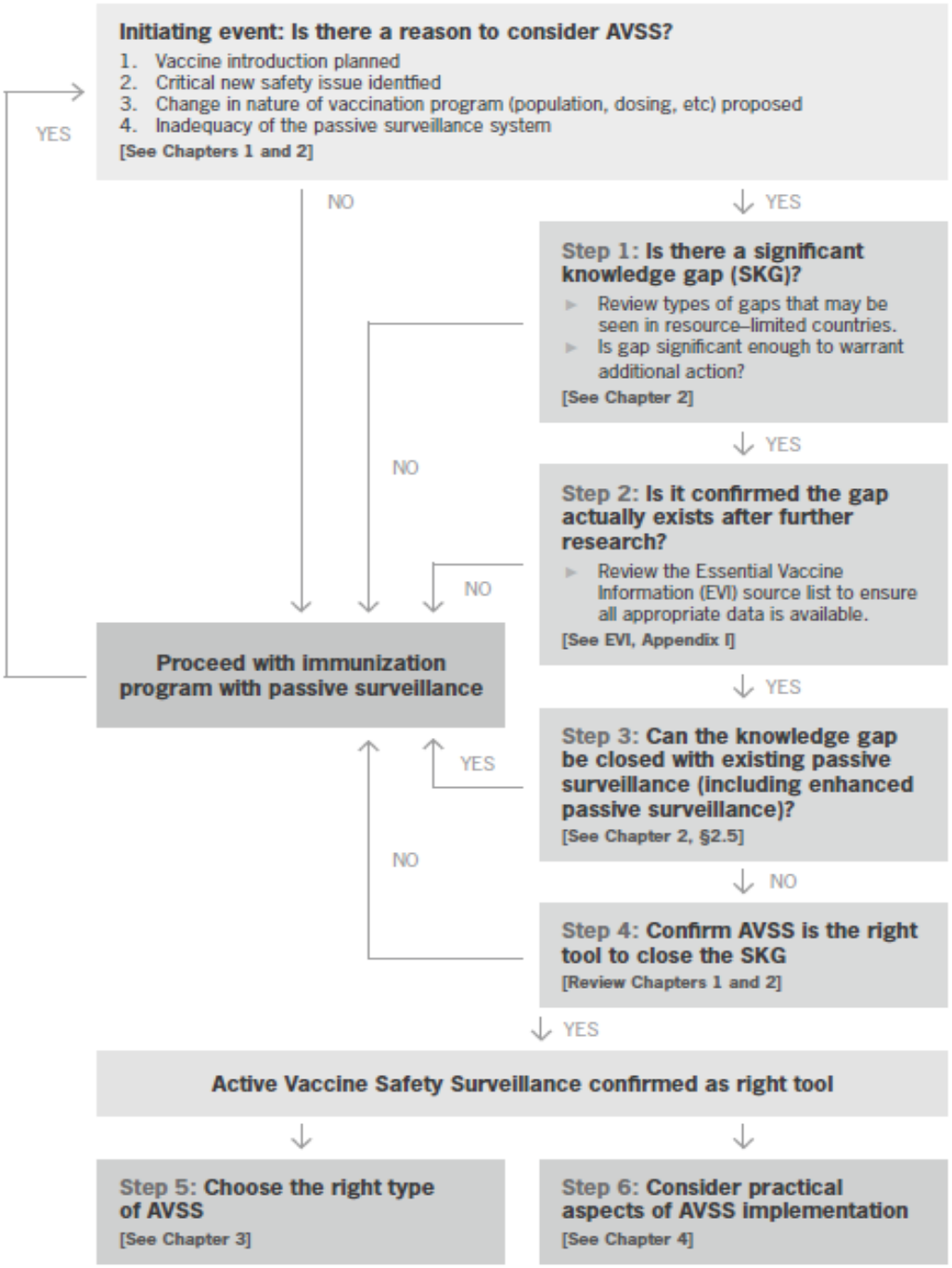
A Significant Knowledge Gap (2)

- Chapter 2 of the Guide describes in detail why SKGs for vaccines may exist, including: The novelty of the vaccine, factors related to use in a new region, planned populations for vaccination, changes to the vaccine schedule, formulation, or dose, how the vaccine will be used and the local disease burden and epidemiology of disease in a specific country or region may also create an SKG

- A SKG Does Not Necessarily Mean AVSS is required. If a significant knowledge gap does exist, in many (even most) cases it can be addressed through passive surveillance

Algorithm

Figure 2. Algorithm: six-step process for considering AVSS



The Essential Vaccine Information (EVI)

For the purpose of determining what basic safety data is needed and whether a knowledge gap truly exists, the WG developed an instrument, the Essential Vaccine Information (EVI), a source which lists the types of information that are most helpful in determining outstanding safety data needs.

- The use of EVI depends on the history and circumstances of the vaccine under review, and provides a set of resources that can be consulted to determine the available safety data
- The EVI process includes a step by step approach to gathering data, obtaining additional data, and reviewing the data to confirm an SKG exists.
- The EVI is meant to be use in most approval scenarios, and specifically provides guidance for Local Registration and WHO prequalification

Collaboration

Step	Steps in determining if there is a gap and how to close it	Responsible and/ or accountable	Consulted and/ or informed of decision
Pre	Is there a reason to consider AVSS?	WHO, NRA/NIP, MAH	PvC, medical communities, appropriate expert advisory and other relevant organizations.
1	Is there a significant knowledge gap?	WHO, NRA/NIP, MAH	PvC, MAH, other NRAs, WHO, NGO, MO, payers, academia
2	Is it confirmed the gap actually exists after further research?	WHO, NRA/NIP, MAH	PvC, MAH, other NRAs, WHO, NGO, MO, payers, academia
3	Can the knowledge gap be closed with existing passive surveillance (including enhanced passive surveillance)?	NRA/NIP, MOH MAH	PvC, MAH, other NRAs, WHO, NGO, MO, academia
4	Confirm: is AVSS the right tool to close the significant knowledge gap?	NRA/NIP, MOH MAH	PvC, MAH, other NRAs, WHO, academia
5	Choose the right type of AVSS.	NRA/NIP, MAH	PvC, MAH, other NRAs, WHO, NGO, MO, academia
6	Consider practical aspects of implementation.	NRA/NIP	NECs, PvC, MAH, other NRAs, WHO, NGO, MO
Post	Who determines action based on results?	NRA/NIP	MAH, donors, PvC, other NRAs, WHO, NGO, MO

Active collaboration is paramount to success pharmacovigilance and AVSS in particular.

- Stakeholders include all parties responsible for vaccine development and manufacture, licensure, administration and implementation of the vaccine campaign, funding, policy-making and assessment, and communication of the plan and results.

- Though all parties share a common interest in disease prevention through vaccination, they differ with respect to their responsibilities, their accountability, and their perspectives on who should be consulted, and who should be informed.

NRA – national regulatory authority,; NIP – national immunization programme; MAH – marketing authorization holder;
MOH – Ministry of Health ; PvC – pharmacovigilance centre; MO – multilateral organization

Discussion

This CIOMS guide provides an important tool for key stakeholder to use in considering if they have a SKG related to the safety of vaccine, and ensuring that they choose the appropriate tool for closing that SKG to ensure public health.

The step by step approach proposed by the CIOMS Working Group will be of great interest and practical use to those working in the emerging field of *maternal immunization*.

With the expanded vaccination of pregnant women, SKGs are to be expected in the post approval setting. Performing the appropriate AVSS for this important new public health tool will be critical to the successful launch and acceptance of these new vaccines.

Conclusion

The Guide can be particularly important for decision-makers faced with

(1) potential new vaccines to be introduced rapidly into disease-endemic regions,
(2) expanded vaccine coverage into new populations, and/or
(3) vaccines that may have limited baseline safety data.

While not intended to be comprehensive, especially when complementary guidance is readily available from other sources, the CIOMS Guide to Active Vaccine Safety Surveillance can serve as *a framework to assess when active vaccine safety surveillance might be needed and how it might be conducted*, and provides a valuable list of practical aspects requiring consideration before undertaking such studies.

Acknowledgement: This presentation was prepared based on some elements of PowerPoint presentation of Dr Franz Gruber about CIOMS and the poster by Steven R. Bailey[a], Lembit Rägo, Ulrich Heininger[c], Irina Caplanusi[d] presented at INMIS conference in Brussels September 10th to the 12th , 2017

[a]Pfizer, Collegeville, PA, [c]University of Basel Children's Hospital, PO Box CH-4031 Basel, Switzerland and [d]European Medicines Agency, 30 Churchill Place, Canary Wharf, London E14 5EU, UK

Where to learn more?

The Guide Itself: CIOMS Guide to active vaccine safety surveillance. Report of CIOMS Working Group on Vaccine Safety. Geneva, Switzerland: Council for International Organizations of Medical Sciences (CIOMS); 2017 (available at https://cioms.ch/shop/)

In *Vaccine* journal: Heininger U, Holm K, Caplanusi I, Bailey SR, on behalf of the CIOMS Working Group on Vaccine Safety. Guide to active vaccine safety surveillance: Report of CIOMS working group on vaccine safety – executive summary. Vaccine 2017, 35(32):3917-3921

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