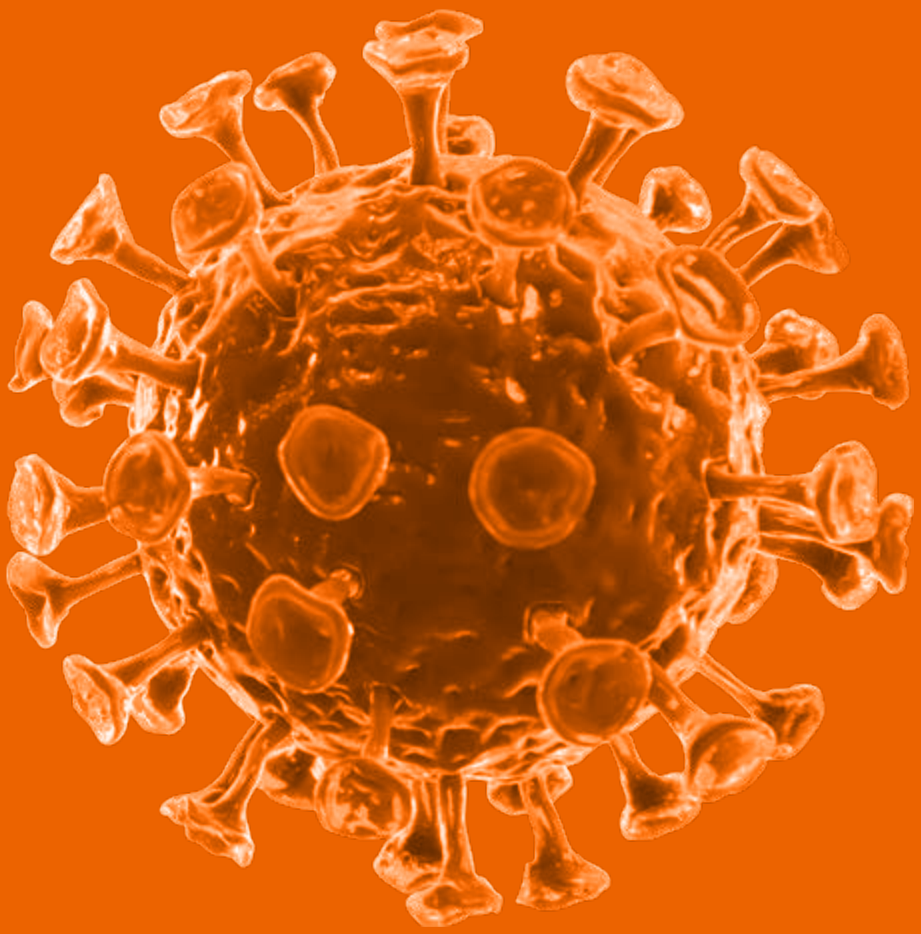
PROTOCOL TEMPLATE

TO BE USED AS A TEMPLATE FOR OBSERVATIONAL STUDY PROTOCOLS

SENTINEL SURVEILLANCE OF ADVERSE EVENTS OF SPECIAL INTEREST (AESIS) AFTER VACCINATION WITH COVID-19 VACCINES



ADDENDUM

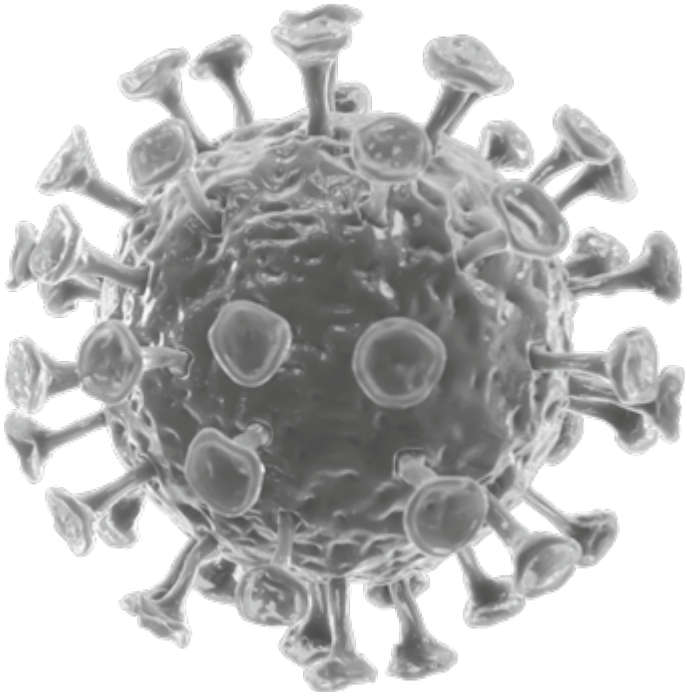
TO COVID-19 VACCINES: SAFETY SURVEILLANCE MANUAL – MODULE ON MONITORING AND RESPONDING TO ADVERSE EVENTS OF SPECIAL INTEREST (AESI)

World Health Organization

PROTOCOL TEMPLATE

TO BE USED AS A TEMPLATE FOR OBSERVATIONAL STUDY PROTOCOLS

SENTINEL SURVEILLANCE OF ADVERSE EVENTS OF SPECIAL INTEREST (AESIS) AFTER VACCINATION WITH COVID-19 VACCINES



ADDENDUM

TO COVID-19 VACCINES: SAFETY SURVEILLANCE MANUAL – MODULE ON MONITORING AND RESPONDING TO ADVERSE EVENTS OF SPECIAL INTEREST (AESI)

World Health Organization

Protocol template to be used as template for observational study protocols for sentinel surveillance of adverse events of special interest (AESIs) after vaccination with COVID-19 vaccines.

ISBN 978-92-4-002950-7 (electronic version)
ISBN 978-92-4-002951-4 (print version)

Suggested citation. Protocol template to be used as template for observational study protocols for sentinel surveillance of adverse events of special interest (AESIs) after vaccination with COVID-19 vaccines. Geneva: World Health Organization; 2021. Licence: CC BY-NC-SA 3.0 IGO.

Cataloguing-in-Publication (CIP) data. CIP data are available at http://apps.who.int/iris.

Acknowledgements

The preparation of this protocol was commissioned by World Health Organization (WHO), coordinated by Christine Guillard with the support of Noha Iessa, in the pharmacovigilance (PVG) team, within the Regulation and Prequalification department at WHO Headquarters, Geneva, Switzerland. This document is based on the principles described in the WHO COVID-19 vaccines: safety surveillance manual.[1] It was developed under the guidance of the WHO Global Advisory Committee on Vaccine Safety (GACVS). Active surveillance protocols developed by United States Centers for Disease Control and Prevention (US CDC)[2] and European Medicines Agency vACcine Covid-19 monitoring readinESS (EMA-ACCESS)[3] projects were reviewed. Key aspects of these protocols were adapted to low- and middle-income country (LMIC) settings.

Special acknowledgements to Steven Anderson, Barbara Law and Saad B. Omer, members of the Scientific Committee, who provided expert advice throughout the project. The protocol was written by Kaatje Bollaerts and Anke Stuurman with technical input from Wendy Hartig-Merkel, Omar Okasha, Elodie Sole, Anirudh Tomer, Thao Mai Phuong Tran from the P95 Excellence in Pharmacovigilance and Epidemiology team.

The significant contributions of Bartholomew Dicky Akanmori, Don Ananda Chandralal Amarasinghe, Madhav Ram Balakrishnan, Oleg Benes, Jose Luis Castro, Amavi Edinam, Sujeet Jain, Houda Langar, Jayantha Bandula L. Liyanage, Helvert Felipe Molina Leon, Diadié Maiga, Sergio Raul Munoz Navarro, Irma Desiree Pastor, Jinho Shin from WHO regional offices and the PVG team in WHO headquarters, Geneva, Switzerland is gratefully acknowledged. Sarah D. Bennett, Laura Conklin, Jane Gidudu and Zunera Gilani from the US CDC provided useful comments and advice.

1 Covid-19 vaccines: safety surveillance manual. (https://www.who.int/publications/i/item/10665338400, accessed 9 March 2021).

2 Reddy et al. Safety monitoring of ROTAVAC vaccine and etiological investigation of intussusception in India: study protocol. BMC Public Health. 2018; 18:898. doi:10.1186/s 12889-018-5809-7.

3 ACCESS (vACCinecovid-19 monitoring readinESS). Kawai A, Arana A et al. Safety Protocol for Hospital Case–Based Monitoring of Specific Adverse Events Following COVID-19 Vaccines: A Protocol Template from the ACCESS project. (https://vac4eu.org/wp-content/uploads/2021/02/3d.Safety-Protocol-for-Hospital-Case%E2%80%93Based-Monitoring-of-Specific-Adverse-Events-Following-COVID-19-Vaccines-A-Protocol-Template-from-the-ACCESS-project.pdf, accessed 9 March 2021)

Introduction

WHO has published the COVID-19 vaccines: safety surveillance manual to guide the processes for collecting, analysing and sharing safety data and information on COVID-19 vaccines within and across countries.[4] To accompany this manual and facilitate the conduct of active safety surveillance studies using harmonized tools and methods, a protocol template for hospital case-based sentinel surveillance studies is proposed. Sentinel surveillance is an active safety surveillance study design that can be used for signal detection and evaluation. **The present template is for sentinel surveillance studies of COVID-19 vaccines for the purpose of safety signal detection**. Sentinel surveillance is based on an active safety surveillance study design that can be used for signal detection and evaluation. The present protocol template describes study designs for hospital case-based monitoring of pre-defined adverse events of special interest (AESIs) following COVID-19 vaccination in all age groups.

This protocol template was developed in addition to the cohort event monitoring (CEM) for COVID-19 vaccines protocol template, under the guidance of a scientific committee including former and current Global Advisory Committee on Vaccine Safety (GACVS) committee members, and reviewed by the GACVS during its meeting held on 1-3 December 2020.[5] The CEM protocol template describes a single arm cohort design that can be used to detected signals for multiple AESIs and serious adverse events (SAEs) within the same cohort. The sentinel surveillance protocol template describes case-control and self-controlled risk interval study designs. These designs are particularly valuable when investigating a potential association between one specific rare and serious adverse event and a vaccine. Although this method can be used for signal detection, it is more suitable to be used to test the hypothesis of an association, following detection of a strong or serious signal that has been generated through passive or other surveillance processes.

Two study designs are described; a self-controlled risk interval (SCRI) design, and a case-control design, depending on the AESI studied. For AESIs with acute onset and a short period of increased risk following vaccination, a SCRI design should be used. Only vaccinated cases are included in this design. The date of vaccination is the index date. For each AESI, a post-vaccination risk interval and a post-vaccination control interval are defined and the incidence of the AESI in the two intervals is compared. For outcomes with unpredictable or late onset, a case-control design should be used. Patients with the AESI are defined as cases. Control patients i.e., without the AESI, will be selected among patients hospitalized for other specified causes not related to the AESI, other AESIs associated with the COVID-19 vaccine or COVID-19 disease. The COVID-19 vaccination status (exposure) is documented and the proportion of patients exposed among cases and controls is compared.

4 World Health Organization. Covid-19 vaccines: safety surveillance manual. Geneva2020. Last accessed 11 March 2021; Available from: https://www.who.int/publications/i/item/10665338400.

5 GACVS. Report of the meeting of the WHO Global Advisory Committee on Vaccine Safety (GACVS), 1–3 December 2020. WER. 2021;96:13-20.

It is important to note that AESIs are predefined medically-significant events that have the potential to be causally-associated with a vaccine product and that need to be carefully monitored and confirmed by further specific studies. AESIs are considered to be serious, if they: result in death, are life-threatening, require inpatient hospitalization or prolongation of existing hospitalization, result in persistent or significant disability/incapacity, or result in a congenital anomaly/birth defect (as per WHO definition of serious adverse events). Although the AESIs investigated using this protocol will be serious (as they result in hospitalization), not all SAEs or AESIs can be monitored with this protocol as not all AESIs that are serious will be presented in an inpatient hospital setting e.g., AESIs that are diagnosed in outpatient or emergency room settings such as skin conditions or anaphylaxis will not be detected. It is critical that medical and study staff follow all national reporting requirements and other local or institutional procedures related to SAEs, including reporting and other follow up processes related to adverse events. This includes any unexpected adverse events, or any other categories of post-vaccination events that may be locally defined.

How to use this template to develop your sentinel surveillance study protocol

The sentinel surveillance protocol template should be used as a guide and adapted to country, regional or populational specificities, as necessary. To guide this adaptation, sections of the template protocol to be completed are shown within orange square brackets ([ ]), and the instructions within orange triangular brackets (<< >>).

It is important also to note that the adult informed consent form (ICF), provided in this template, and the process of obtaining informed consent, must be adapted to the local situation and language as well as to special populations (e.g., minors, pregnant women, elderly individuals lacking full capacity, migrants, prisoners) that require a tailored approach to consent. This includes possible surrogate decision-makers (e.g., parents, adult children) or study advocates for inclusion of prisoners or orphans and additional forms such as assent forms as well as tailoring the study details provided to participants during the informed consent process. For patients that are not well enough to consent (either still hospitalized or returning to hospital after being discharged home), informed consent obtained from the next of kin should be considered. This is not always possible, and depends on the medical institution, the circumstance in which the consent is obtained and followed up, and how data from these patients are used in the future. Information on relevant ethical considerations can be found in CIOMS guidelines 9-10 and 15-17[6].

All protocols developed using this template should be reviewed by a scientific committee and by relevant ethics committees and institutional review boards, at a national level, at the level of the study sites, or at the institution of the sponsor, as required by applicable laws and regulations. Protocols developed based on this template that receive technical of financial support from WHO should be submitted for formal review to the WHO Ethics Review Committee.

---

6 Council for International Organizations of Medical Sciences (CIOMS). International ethical guidelines for health-related research Involving humans (2016). Geneva: CIOMS; 2016. Last accessed 17 March 2021; Available from: https://cioms.ch/wp-content/uploads/2017/01/WEB-CIOMS-EthicalGuidelines.pdf.

Suggested process

- Step 1: Constitute a study coordination team consisting of representatives from the immunization programme, national regulatory authority, pharmacovigilance centre, chair of the national adverse events following immunization (AEFI) committee, and academia.
- Step 2: Identify the role and responsibilities of the different institutions, and nominate a focal person to lead and coordinate the process of protocol development and obtain the consensus of the study coordination team. Complete section 6 of the template protocol with this information.
- Step 3: Define the target population (age groups), identify study sites, review the list of AESIs for the COVID-19 vaccine(s) in use,[7] and complete the protocol (including informed consent forms and data collection tools). If technical assistance from WHO is required at this stage, send an email request to gvsi@who.int and the WHO country office focal person.
- Step 4: Discuss the draft protocol with the study coordination team and study site representatives to obtain their input and endorsement and then finalise the protocol.
- Step 5: The final protocol should be reviewed by an independent scientific committee to ensure that it is scientifically sound, and then reviewed by the national or local independent ethics committee (IEC) or the institutional review board (IRB) of participating institution(s).
- Step 6: Develop the study procedures, the data management plan and statistical analysis plan.

Disclaimer: WHO cannot accept any responsibility or liability for the conduct of studies by third parties that follow this protocol template. Studies conducted by third parties using this protocol template cannot be considered 'WHO studies'. The WHO logo cannot be used in studies conducted by third parties or studies that are not 'WHO studies'. Protocols developed based on this template that receive technical of financial support from WHO should be submitted for formal review to the WHO Ethics Review Committee.

Version control table for this protocol template

Version	Version date	Reason for new version
V1.0	22 December 2020	First draft