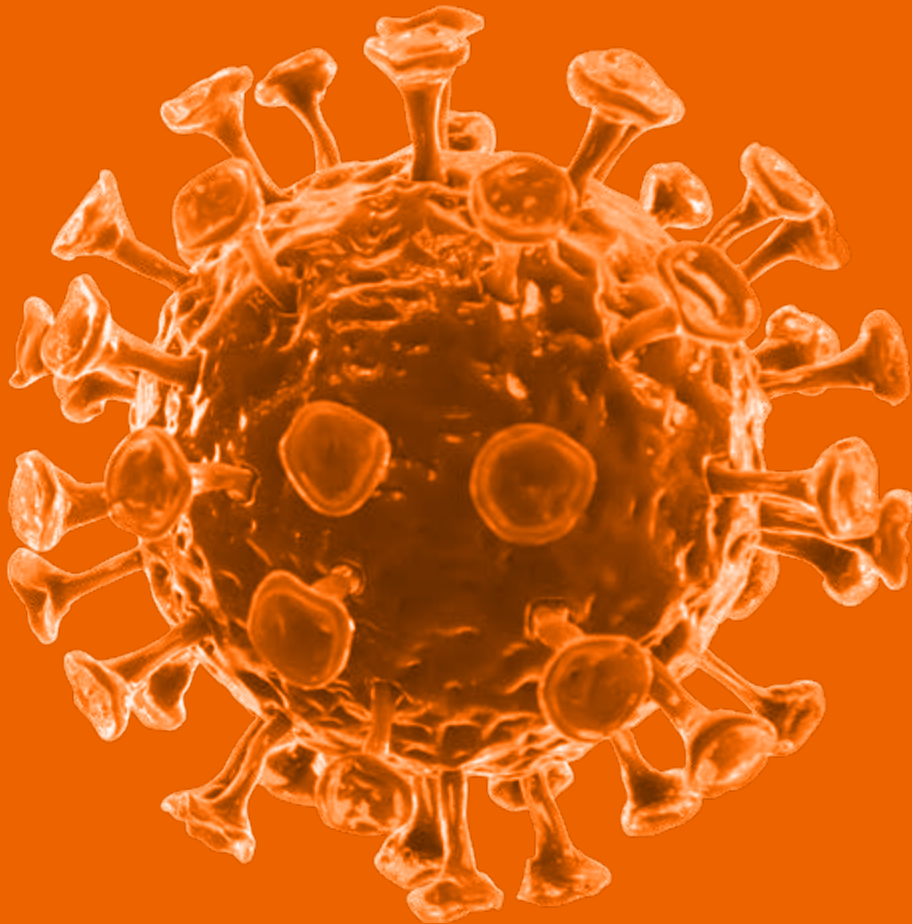


# **PROTOCOL TEMPLATE**

TO BE USED AS A TEMPLATE  
FOR OBSERVATIONAL STUDY  
PROTOCOLS

# **SENTINEL SURVEILLANCE OF ADVERSE EVENTS OF SPECIAL INTEREST (AESI) 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)



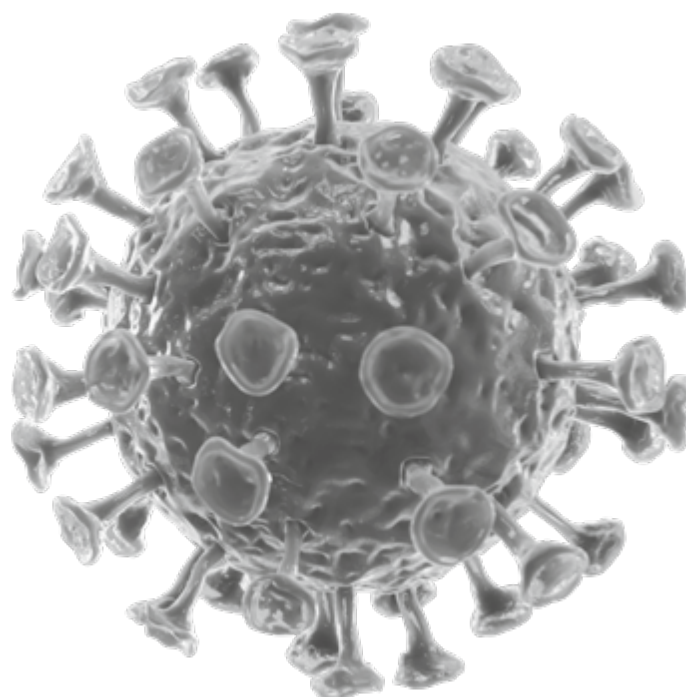
World Health  
Organization



# **PROTOCOL TEMPLATE**

TO BE USED AS A TEMPLATE  
FOR OBSERVATIONAL STUDY  
PROTOCOLS

# **SENTINEL SURVEILLANCE OF ADVERSE EVENTS OF SPECIAL INTEREST (AESI) 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)

© World Health Organization 2021

Some rights reserved. This work is available under the Creative Commons Attribution-NonCommercial-ShareAlike 3.0 IGO licence (CC BY-NC-SA 3.0 IGO; <https://creativecommons.org/licenses/by-nc-sa/3.0/igo>).

Under the terms of this licence, you may copy, redistribute and adapt the work for non-commercial purposes, provided the work is appropriately cited, as indicated below. In any use of this work, there should be no suggestion that WHO endorses any specific organization, products or services. The use of the WHO logo is not permitted. If you adapt the work, then you must license your work under the same or equivalent Creative Commons licence. If you create a translation of this work, you should add the following disclaimer along with the suggested citation: "This translation was not created by the World Health Organization (WHO). WHO is not responsible for the content or accuracy of this translation. The original English edition shall be the binding and authentic edition".

Any mediation relating to disputes arising under the licence shall be conducted in accordance with the mediation rules of the World Intellectual Property Organization (<http://www.wipo.int/amc/en/mediation/rules/>).

**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](https://creativecommons.org/licenses/by-nc-sa/3.0/igo).

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

**Sales, rights and licensing.** To purchase WHO publications, see <http://apps.who.int/bookorders>. To submit requests for commercial use and queries on rights and licensing, see <http://www.who.int/about/licensing>.

**Third-party materials.** If you wish to reuse material from this work that is attributed to a third party, such as tables, figures or images, it is your responsibility to determine whether permission is needed for that reuse and to obtain permission from the copyright holder. The risk of claims resulting from infringement of any third-party-owned component in the work rests solely with the user.

**General disclaimers.** The designations employed and the presentation of the material in this publication do not imply the expression of any opinion whatsoever on the part of WHO concerning the legal status of any country, territory, city or area or of its authorities, or concerning the delimitation of its frontiers or boundaries. Dotted and dashed lines on maps represent approximate border lines for which there may not yet be full agreement. The mention of specific companies or of certain manufacturers' products does not imply that they are endorsed or recommended by WHO in preference to others of a similar nature that are not mentioned. Errors and omissions excepted, the names of proprietary products are distinguished by initial capital letters.

All reasonable precautions have been taken by WHO to verify the information contained in this publication. However, the published material is being distributed without warranty of any kind, either expressed or implied. The responsibility for the interpretation and use of the material lies with the reader. In no event shall WHO be liable for damages arising from its use.

# Acknowledgements

---

The preparation of this protocol was commissioned by World Health Organization (WHO), coordinated by Christine Guillard with the support of Noha Ilesha, 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.<sup>1</sup> 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)<sup>2</sup> and European Medicines Agency vACCine Covid-19 monitoring readinESS (EMA-ACCESS)<sup>3</sup> 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/s12889-018-5809-7.

3 ACCESS (vACCine covid-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.<sup>4</sup> 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.<sup>5</sup> The CEM protocol template describes a single arm cohort design that can be used to detect 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.

---

<sup>4</sup> 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>.

<sup>5</sup> 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<sup>6</sup>.

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 or 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,<sup>7</sup> 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 [gvs@who.int](mailto:gvs@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 or 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
V2.0	1 February 2021	Second draft following input from WHO Headquarters and P95
V3.0	12 February 2021	Third draft following input from Scientific Committee
V3.1	5 March 2021	Draft with update on Brighton Collaboration definitions
V3.2	8 April 2021	Draft with integration of comments from external reviewers
V3.3	20 April 2021	Draft with integration of comments from ethics review committee

<sup>7</sup> Law B. SO2-D2.1.2 Priority list of COVID-19 adverse events of special interest: Quarterly update December 2020. Safety Platform for Emergency vACCines (SPEAC); 2021. Last accessed 11 March 2021; Available from: [https://brightoncollaboration.us/wp-content/uploads/2021/01/SO2\\_D2.1.2\\_V1.2\\_COVID-19\\_AESI-update\\_V1.3.pdf](https://brightoncollaboration.us/wp-content/uploads/2021/01/SO2_D2.1.2_V1.2_COVID-19_AESI-update_V1.3.pdf)





**Start of sentinel surveillance study  
protocol template**

---

**Sentinel surveillance of adverse  
events of special interest (AESIs)  
after immunization with COVID-19  
vaccines**

# Title page

---

<b>Abbreviated study title</b>	COVID-19-SENT-[COUNTRY]-[NUMBER]
<b>Full study title</b>	Sentinel surveillance of adverse events of special interest (AESIs) after vaccination with COVID-19 vaccines in [COUNTRY]
<b>Study ID</b>	
<b>Research question and objectives</b>	<ul style="list-style-type: none"><li>— To estimate the risk of pre-defined adverse events of special interest (AESIs) with acute onset and a short period of increased risk following immunization with a COVID-19 vaccine using a self-controlled risk interval (SCRI), study design;</li><li>— To compare the odds of having been vaccinated among cases with the AESI under investigation with the odds of having been vaccinated among controls for AESIs with unpredictable or late onset using a case-control study design.</li></ul>
<b>Country(ies) of study</b>	
<b>Protocol version</b>	
<b>Date of protocol version</b>	
<b>Protocol authors</b>	

# 01 Contents

<b>1. Contents</b>	<b>2</b>
<b>2. List of tables</b>	<b>4</b>
<b>3. List of figures</b>	<b>5</b>
<b>4. Protocol sign-off</b>	<b>6</b>
<b>5. Documentation of protocol amendments</b>	<b>7</b>
<b>6. Study team and responsibilities</b>	<b>8</b>
6.1 Study team	8
6.2 Responsibilities	8
<b>7. Abbreviations</b>	<b>9</b>
<b>8. Synopsis</b>	<b>10</b>
<b>9. Background and rationale</b>	<b>15</b>
<b>10. Objectives</b>	<b>16</b>
10.1 Primary objective	16
<b>11. Methods</b>	<b>17</b>
11.1 Settings	17
11.2 Study sites	17
11.3 Study design	17
11.4 Self-controlled risk interval (SCRI) study	18
11.4.1 Study population	18
11.4.2 Study period	19
11.4.3 Study variables	20
11.4.4 Data sources	23
11.4.5 Study flow and data collection	23
11.4.6 Withdrawal from the study	26
11.4.7 Pregnancy	26
11.4.8 Sample size	26
11.4.9 Data analyses	29
11.5 Case-control study	30
11.5.1 Study population	30
11.5.2 Study period	31
11.5.3 Study variables	31
11.5.4 Controls	32
11.5.5 Other variables	33
11.5.6 Data sources	34
11.5.7 Study flow and data collection	34
11.5.8 Withdrawal from the study	38
11.5.9 Pregnancy	38
11.5.10 Sample size	38
11.5.11 Data analysis	42

<b>12. Standardized analyses</b>	<b>43</b>
12.1 Multi-site recruitment	43
12.2 Different COVID-19 vaccines	43
<b>13. Data management</b>	<b>44</b>
13.1 Data entry using an electronic tool	44
13.1.1 Data security	44
13.2 Data transfer	44
13.3 Data retention and archiving	45
<b>14. Quality assurance, monitoring and reporting</b>	<b>45</b>
14.1 Monitoring	45
14.2 Periodic reporting	45
14.3 Final analyses and reporting	46
<b>15. Study management</b>	<b>46</b>
15.1 Data transfer	46
15.2 Data retention and archiving	46
15.3 National pharmacovigilance centre/AEFI committee/national immunization programme manager/dedicated scientific committee	47
15.4 Changes to the protocol	47
15.5 Management and reporting of adverse events and adverse reactions	47
<b>16. Ethical considerations</b>	<b>48</b>
16.1 Guiding principles	48
16.2 Respecting participants' autonomy	48
16.3 Participant confidentiality	49
16.4 Independent Ethics Committee/Institutional Review Board	49
<b>17. Dissemination of study results</b>	<b>49</b>
<b>18. Study limitations</b>	<b>50</b>
<b>19. References</b>	<b>51</b>
<b>20. Annexes</b>	<b>52</b>
Annex 1	52
Adverse events of special interest	52
Annex 2	54
Case definitions	54
Annex 3	57
Catchment population calculation for SCRI study design	57
Annex 4	58
Catchment population calculation for case-control study design	58
Annex 5	59
Data dictionary	59
Annex 6	64
Relationships between study tables	64
Annex 7	65
Informed consent form	65

# 02 List of tables

Table 1: Study sites with principal investigators and contact details .....	17
Table 2: Minimum number of cases required to reject the null hypothesis that the relative incidence of AESI during risk versus self-control intervals is equal to 1. Probability of type-I error is set at 5%, power at 80%, and proportion of the total observation period a patient spends in the risk interval at 25%, 33%, and 50%. .....	27
Table 3: Catchment area sizes required to detect a relative incidence of 2, 3, 4 or 5 for AESIs with annual background rates varying from 0.1-1000 per 100,000 people and a post-vaccination risk interval of 7 or 42 days, at different levels of vaccination uptake (VU) during the study period, assuming the proportion of observation period a patient spends in the risk interval is 25% (probability of type-I error is set at 5%, power at 80%).....	28
Table 4: Minimum number of cases required to detect different odds ratios (ORs) for 25%, 50% and 75% vaccination coverage, assuming a power of 80%, a probability of type-I error at 5%, and a control-to-case ratio of 1:1, 2:1, 3:1 and 4:1. ....	39
Table 5: Catchment population required to detect an odds ratio (OR) of 2 to 5 for AESIs with known annual background rates varying from 0.1 to 1,000 per 100,000 people per year at three different levels of vaccination coverage (in controls), control-to-case ratios of 1:1 and 2:1 (probability of type-I error at 5%, and power at 80%) .....	41
Table 6: Catchment population required to detect an odds ratio (OR) of 2 to 5, for AESIs with known annual background rates varying from 0.1 to 1,000 per 100,000 people per year at three different levels of vaccination coverage (in controls), and control-to-case ratios of 3:1 and 4:1 (probability of type-I error at 5%, and power at 80%).....	41
Table A1-1: Adverse events of special interest (AESI), their risk windows, and recommended study design. ....	52
Table A2-1: Adverse events of special interest (AESI), and Brighton Collaboration (BC) case definitions (if available). ....	53

# List of figures

---

Fig 1:	Schematic representation of the risk and self-control intervals for adverse events with a risk interval from d0 to d7, a washout period of one week (d8-d14), and a self-control interval three times the length of the risk interval (d15-d38), where d0 is the day of the last dose of COVID-19 vaccine received prior to the event date. Patients with an event during the a) risk interval or b) self-control interval are included in the analysis. Patients with an event c) during the washout period or, d) after the end of the self- control interval are not included. ....	22
Fig 2:	Minimum number of cases required to reject the null hypothesis that the relative incidence of the AESI during the risk versus self-control interval is equal to 1. The probability of type-I error is set at 5%, the power at 80%, and the proportion of the observation period a patient spends in the risk interval varies from 10 to 90%. The lines show the minimum number of patients needed for a relative incidence of 2, 3, 4 or 5. ....	27
Fig 3:	Summary of study flow and data collection for case-control studies .....	35
Fig 4:	Minimum number of cases required to detect odds ratios (ORs) from 2 to 5 for different levels of vaccination coverage, assuming a power of 80%, a probability of type-I error at 5%, and control-to-case ratio of 1:1, 2:1, 3:1 and 4:1. ....	40



# 04

## Protocol sign-off

---

This protocol has been discussed, reviewed and approved by the Scientific Committee consisting of the following members:

- [NAME]
- [NAME]
- [NAME]
- [NAME]
- [NAME]
- [NAME]
- [NAME]

### Protocol title:

Sentinel surveillance of adverse events of special interest (AESIs) after vaccination with COVID-19 vaccines in [COUNTRY]

**Version:** [0.1]

I have reviewed and approved the protocol.

Name of Scientific Committee member: [NAME] Date	Signature
Name of Scientific Committee member: [NAME] Date	Signature
Name of Scientific Committee member: [NAME] Date	Signature
Name of Scientific Committee member: [NAME] Date	Signature



# Documentation of protocol amendments

---

Version	Version date	Reason for new version

# Study team and responsibilities

## 6.1 Study team

	Capacity	Organisation	Role	Name
<i>Research team</i>	Principal investigator			
	Project manager			
	Data monitor			
	Other research staff			
<i>Study site(s)</i>	Investigator			
	Study coordinator			
	Other research staff			
<i>Scientific committee</i>				
<i>Data owner</i>				
<i>Sponsor</i>				

## 6.2 Responsibilities

Organisation/Capacity	Responsibilities
	Identification of potential participants
	Inform study participants and obtain signed informed consent
	Case confirmation
	Obtain vaccine exposure status (must be different to those obtaining medical information)
	Obtain medical information/history

# 07 Abbreviations

---

<b>ADEM</b>	Acute disseminated encephalomyelitis
<b>AE</b>	Adverse event
<b>AEFI</b>	Adverse event following immunization
<b>AESI</b>	Adverse event of special interest
<b>ARDS</b>	Acute respiratory distress syndrome
<b>BC</b>	Brighton Collaboration
<b>CEM</b>	Cohort event monitoring
<b>CIOMS</b>	Council for International Organizations of Medical Sciences
<b>COVID-19</b>	Coronavirus disease 2019
<b>(e)CRF</b>	(electronic) Case report form
<b>DMP</b>	Data management plan
<b>GBS</b>	Guillain-Barré syndrome
<b>GEP</b>	Good epidemiological practice
<b>ICF</b>	Informed consent form
<b>IEC</b>	Independent ethics committee
<b>IRB</b>	Institutional review board
<b>MIS-C</b>	Multisystem inflammatory syndrome in children
<b>NIP</b>	National immunization programme
<b>OR</b>	Odds ratio
<b>RI</b>	Relative incidence
<b>SAE</b>	Serious adverse event
<b>SARS-CoV-2</b>	Severe acute respiratory syndrome coronavirus 2
<b>SCCS</b>	Self-controlled case series
<b>SCRI</b>	Self-controlled risk interval
<b>VAED</b>	Vaccine-associated enhanced disease
<b>VC</b>	Vaccine coverage
<b>VU</b>	Vaccine uptake
<b>WHO</b>	World Health Organization

# Synopsis

<b>Full title of study</b>	Sentinel surveillance of adverse events of special interest (AESIs) after immunization with COVID-19 vaccines in [COUNTRY]
<b>Background and rationale</b>	<p>In December 2019, an outbreak of respiratory disease caused by a novel coronavirus strain was reported in Wuhan City, Hubei Province, China. The novel coronavirus was named 'severe acute respiratory syndrome coronavirus 2' (SARS-CoV-2), while the disease associated with it is referred to as COVID-19. The virus spread to different parts of China and an increasing number of countries worldwide and on 30 January 2020 World Health Organization (WHO) announced that the outbreak was a public health emergency of international concern (PHIC).</p> <p>The development of safe and effective vaccines is key in containing the SARS-CoV-2 pandemic. Systematic vaccine safety surveillance is indispensable for ensuring the safety of vaccines, and public trust of vaccines, in countries with differing pharmacovigilance capacities. Acknowledging that routine passive reporting systems might not be sufficient to allow the rapid assessment and appropriate public health response during COVID-19 vaccine introduction, active safety surveillance is recommended. This protocol describes hospital-based sentinel surveillance designed to detect safety signals of rare adverse events of special interest (AESIs) or to evaluate safety signals arising from other sources, following vaccination with [VACCINE/COVID-19 vaccines] in [COUNTRY].</p>
<b>Objectives</b>	<p>The overall aim of this study is to monitor the safety of COVID-19 vaccines in [COUNTRY] in real-life conditions for the purpose of safety signal detection and evaluation.</p> <p>The primary objective is:</p> <ul style="list-style-type: none"><li>— To estimate the risk of pre-defined AESIs with acute onset and a short period of increased risk following immunization with a COVID-19 vaccine using a self-controlled risk interval (SCRI), study design;</li><li>— To compare the odds of having been vaccinated among cases with the AESI under investigation with the odds of having been vaccinated among controls for AESIs with unpredictable or late onset using a case-control study design.</li></ul>

<b>Study design</b>	<p>This study will collect data through hospital case-based monitoring of pre-defined AESIs following COVID-19 immunization. All patients with these AESIs will be identified along with their COVID-19 vaccination status to determine whether COVID-19 vaccination is associated with an increased risk of these AESIs. Surveillance will be active and two study designs will be used, depending on the AESI studied:</p> <ul style="list-style-type: none"> <li>— For AESIs with acute onset and a short period of increased risk at vaccination, a <b>self-controlled risk interval (SCRI) study</b> will be used. Only patients who have been vaccinated will be included in the SCRI. For each AESI, a post-vaccination risk interval and a post-vaccination control interval will be defined, and indexed on the date of vaccination. The incidence of the AESI in the two intervals will be compared.</li> <li>— For AESIs with unpredictable or late onset, a <b>case-control study</b> will be used. Cases will be defined as patients with the AESI. Control patients, i.e., without the AESI, will be selected among patients hospitalized for causes other than the AESI or other AESIs related to COVID-19 vaccine exposure or respiratory illness. The COVID-19 vaccination status will be documented for both cases and controls and the odds of vaccination among cases and among controls will be compared.</li> </ul> <p><b>Note</b> that the data collection methods for AESI cases will be the same, irrespective of the design.</p>
<b>Study period</b>	<p>The study will start as soon as possible after the implementation of the national immunization programme (NIP), taking into consideration feasibility (including vaccine uptake).</p> <p>The study will end as soon as the required number of cases to be able to detect a pre-defined level of risk have been identified (refer to section on sample size).</p>
<b>Population</b>	<p>The source population will consist of individuals residing in the catchment area of the participating hospitals.</p> <p>Inclusion criteria - SCRI study:</p> <ul style="list-style-type: none"> <li>— potential case of AESI;</li> <li>— residence in the catchment area of the participating hospital;</li> <li>— received at least one dose (first dose) of COVID-19 vaccine;</li> <li>— informed consent given.</li> </ul> <p>Inclusion criteria - case control study:</p> <ul style="list-style-type: none"> <li>— probable case of AESI <b>OR</b> hospital control;</li> <li>— eligible for COVID-19 vaccination (as per local eligibility criteria, e.g. age-defined policy) at least four weeks prior to the date of symptom onset;</li> <li>— residence in the catchment area of the participating hospital;</li> <li>— informed consent given.</li> </ul>

## Variables

Exposure of interest (for SCRI and case-control studies):

Vaccination with at least one dose of any COVID-19 vaccine administered in routine clinical practice. The following information on vaccination will be collected for each dose, if available:

- vaccination status
- vaccine dose
- vaccine brand
- vaccination date
- vaccine batch number
- source of vaccination history (vaccination card, medical records, patient self-report).

Outcomes (SCRI and case-control studies):

The outcome of interest will be the presence of [ONE OR MORE PRE-DEFINED AESIs REQUIRING HOSPITALIZATION]. Outcomes with an acute onset and a short period of increased risk at vaccination ([LIST RELEVANT AESIs WITH ACUTE ONSET/SHORT PERIOD OF INCREASED RISK AT VACCINATION], see ANNEX 1) will be studied using a SCRI study, and those with an unpredictable or late onset ([LIST RELEVANT AESIs WITH INSIDIOUS ONSET/LATE], see ANNEX 1) will be studied using a case-control study. The diagnosis will be confirmed using [BRIGHTON COLLABORATION CASE DEFINITION IF AVAILABLE (ANNEX 2), OR OTHER PREDEFINED CASE DEFINITION].

The following information on the outcomes will be collected:

- AESI diagnosed
- confirmation of diagnosis using predefined case definition(s)
- level of diagnostic certainty (if applicable)
- date of symptom onset
- date of hospitalization
- date of discharge or date of in-hospital death.

Controls (case-control study only):

For each case, up to (and preferably) four matched controls will be identified. Controls will be identified among patients hospitalized for causes other than the AESI or other AESIs related to COVID-19 vaccine exposure or respiratory illness. Controls will be matched to cases based on age, current place of residence (if not feasible, they will be matched on healthcare facility), and eligibility for COVID-19 vaccination (as per local eligibility criteria, e.g. age-defined policy) four weeks prior to the date of symptom onset.

The following information will be collected for controls:

- diagnosis
- date of symptom onset
- date of hospitalization
- date of discharge or date of in-hospital death

Event dates (SCRI design study):

The date of symptom onset will be the event date for the primary analysis. The date of hospitalization will be the event date for sensitivity analyses. Additionally, sensitivity analysis excluding patients with concurrent COVID-19 may also be considered.

Risk and control intervals (SCRI study only):

Risk and control intervals will be defined with the date of vaccination being the index date (time D0). AESI-specific risk intervals will be defined. It is recommended that the control interval should be three times the length of the risk interval. A washout period of one week between the risk and control intervals is recommended.



<b>Variables</b>	<p>Other variables (for SCRI and case-control studies):</p> <ul style="list-style-type: none"> <li>— The following variables will be collected:</li> <li>— name or patient identifier</li> <li>— date of birth</li> <li>— sex</li> <li>— pregnancy status and estimated date of delivery</li> <li>— lactation</li> <li>— socio-economic class [LEVELS TO BE DEFINED LOCALLY]</li> <li>— risk groups: chronic respiratory disease and asthma, chronic heart, kidney and liver disease, diabetes or immunocompromised/suppressed persons, obesity, allergy, [OTHER RISK GROUPS OF INTEREST DEPENDING ON THE AESI STUDIED]</li> <li>— previous or current COVID-19 disease (defined as probable, laboratory-confirmed with no hospitalization, laboratory-confirmed with hospitalization) and date of onset.</li> </ul> <p>For the case-control study, the following matching variables will be additionally collected for cases and controls:</p> <ul style="list-style-type: none"> <li>— Current place of residence</li> <li>— Eligibility for COVID-19 vaccination (as per local eligibility criteria, e.g. age-defined policy) four weeks prior to symptom onset (i.e. same priority group for rollout of vaccine)</li> </ul>
<b>Data sources</b>	<p>Data sources will include hospital-level patient data (including, but not limited to, admission records, inpatient records), interviews (with patient, with treating physician) and vaccination records (e.g., vaccine card, medical records from the vaccination centre, patient interview).</p>
<b>Study flow and data collection</b>	<p>SCRI study:</p> <ol style="list-style-type: none"> <li>1. Identification of probable cases</li> <li>2. Obtain informed consent</li> <li>3. Case confirmation</li> <li>4. Identification of vaccinated cases and collection of vaccination history</li> <li>5. Identification of vaccinated cases with event date during risk/control intervals</li> <li>6. Data entry.</li> </ol> <p>Case-control study:</p> <ol style="list-style-type: none"> <li>1. Identification of probable cases/control</li> <li>2. Verify eligibility (as per local eligibility criteria, e.g. age-defined policy) for vaccination</li> <li>3. Obtain informed consent</li> <li>4. Case confirmation (cases only)</li> <li>5. Collection of vaccination history</li> <li>6. Data entry.</li> </ol>
<b>Sample size</b>	<p>SCRI study:</p> <p>The minimum total number of cases required for studies with control intervals equal to three times the length of the risk interval will be 75 (30 of which should occur during the risk interval) for a relative incidence of 2, and 13 (8 of which should occur during the risk interval) for a relative incidence of 5.</p> <p>Case-control study:</p> <p>For a case-control study with a control-to-case ratio of 4:1 and 25% vaccine coverage, the minimum total number of cases required to detect an odds ratio (OR) of 2 will be 92, and to detect an OR of 5 will be 16.</p>

<p><b>Data analysis</b></p>	<p>Descriptive analysis of demographics:</p> <p>Demographic and medical characteristics will be summarized by descriptive statistics. Analysis will be performed by [SITE/COUNTRY/REGION].</p> <p>Statistical analysis (SCRI study):</p> <p>The relative incidence of the incidence of the AESI in the risk interval and the incidence of the AESI in the control interval will be calculated by dose and by vaccine brand using conditional Poisson regression, with adjustment for seasonality. For the primary analysis, the event date will be date of symptom onset. A sensitivity analysis will be conducted using the date of hospitalization instead of event date. Further sensitivity analyses may be conducted, as appropriate (e.g. excluding patients with concurrent COVID-19).</p> <p>Statistical analysis (case-control study):</p> <p>The OR of the odds of vaccination among cases with the outcome and the odds of vaccination among controls will be calculated by dose and by vaccine brand using logistic regression (or conditional logistic regression, if matched controls are used), with adjustment for seasonality.</p>
<p><b>Periodic reporting</b></p>	<p>Periodic reporting will be done when appropriate. The final analyses will be performed and a full study report will be written within 4 weeks after database lock.</p>
<p><b>Ethics</b></p>	<p>This study will be conducted under the international ethical guidelines for health-related research involving humans issued by the Council for International Organizations of Medical Sciences (CIOMS) [1], good epidemiological practice (GEP) guidelines [2], the Declaration of Helsinki and its amendments [3] and any applicable national laws, regulations and guidelines.</p> <p>Informed consent will be required from all participants or legal guardians.</p> <p>All parties will ensure protection of patient personal data and will not include patient names or other information that could be used to identify the patient, such as date of birth, address, on any study forms, reports, publications, or in any other disclosures, except when required by law. [LOCAL DATA PROTECTION AND PRIVACY REGULATIONS, to be specified] will be observed in capturing, transferring, processing, and storing patient data.</p> <p>This protocol has been approved by [NAME OF INDEPENDENT ETHICS COMMITTEE].</p>

# Background and rationale

In December 2019, an outbreak of respiratory disease caused by a novel coronavirus strain was reported in Wuhan City, Hubei Province, China. The novel coronavirus was named 'severe acute respiratory syndrome coronavirus 2' (SARS-CoV-2), while the associated disease is referred to as COVID-19 (coronavirus disease 2019). The virus spread to different parts of China and an increasing number of countries worldwide and on 30 January 2020 World Health Organization (WHO) announced that the outbreak was a public health emergency of international concern (PHIC).

The development of safe and effective vaccines is key in containing the SARS-CoV-2 pandemic. Ensuring equitable access to the vaccines across the globe is one of the key strategies to mitigate the public health and economic impact of the pandemic [4]. Vaccine candidates against COVID-19 include traditional virus- and protein-based vaccines and newer platforms such as viral vector-based vaccines and nucleic acid vaccines. Vaccines approved for use in national immunization programmes (NIPs), are considered safe and efficacious based on demonstrable evidence from randomized controlled clinical trials. Despite rigorous safety evaluation during clinical development, they are, however, not completely free of risks, and occasional adverse events will occur following widespread vaccination. Given vaccines are often recommended for otherwise healthy individuals, the key to success of NIPs is public trust in vaccine safety [\[link to safety manual\]](#) [5]. Systematic vaccine safety surveillance is indispensable for ensuring safety of vaccines and public trust in vaccines, across countries with differing pharmacovigilance capacities. Once immunization with COVID-19 vaccines starts, pharmacovigilance efforts should start simultaneously, and specific COVID-19 vaccine safety surveillance should be implemented, as described in the WHO COVID-19 vaccines: safety surveillance manual [5]. Acknowledging that routine passive reporting systems is not sufficient to allow the rapid assessment and appropriate public health response during COVID-19 vaccine introduction, active vaccine safety surveillance is recommended.

In [\[COUNTRY\]](#), vaccination with COVID-19 vaccines as part of the NIP is expected to start in [\[MONTH YEAR\]](#). It is expected that vaccination will take place with [\[VACCINE BRAND\]](#), a [\[VACCINE PLATFORM e.g., mRNA\]](#) vaccine, manufactured by [\[MANUFACTURER\]](#). Based on clinical trial data with [\[INSERT NUMBER\]](#) exposed trial participants, the COVID-19 vaccine has shown a vaccine efficacy of [\[XX\]](#)% [95% CI: xx-yy] against symptomatic COVID-19 disease. [\[DESCRIBE THE SAFETY PROFILE OF THE VACCINE\]](#). The vaccine is indicated for individuals aged [\[AGE GROUP\]](#) and is contraindicated for persons with [\[CONTRAINDICATION\]](#). As several vaccines may be simultaneously used in [\[COUNTRY\]](#), identification of vaccine brand will be an important aspect of post-marketing pharmacovigilance activities.

This protocol describes a hospital-based sentinel surveillance study designed to detect safety signals of rare AESIs or to evaluate AESIs arising from safety signals arising from other sources, following vaccination with [\[VACCINE/COVID-19 vaccines\]](#) in [\[COUNTRY\]](#). The site-specific

protocol will include informed consent forms (ICFs) in [LOCAL LANGUAGE(S)], a statistical analysis plan, and a data management plan.

Findings regarding any study events, whether anecdotal, interim or final, will be carefully communicated correctly, so as not to undermine trust in vaccines locally or globally. Anecdotal sharing should be prevented by reminders about data confidentiality, but even official sharing of aggregate interim and final findings should be carefully done, particularly in light of widespread and growing COVID-19 vaccine hesitancy. Steps must be taken to ensure correct local communication of the study results. To facilitate this, it is important to proactively estimate expected baseline incidence rates (without vaccination) for common study outcomes in the location and the specific population, to ensure that appropriate messaging of results is possible.

## Objectives

The overall aim of this study is to monitor the safety of COVID-19 vaccines in [COUNTRY] in real-life conditions for the purpose of safety signal detection and evaluation.

### 10.1 Primary objective

- To estimate the risk of pre-defined AESIs with acute onset and a short period of increased risk following immunization with a COVID-19 vaccine using a self-controlled risk interval (SCRI), study design;
- To compare the odds of having been vaccinated among cases with the AESI under investigation with the odds of having been vaccinated among controls for AESIs with unpredictable or late onset using a case-control study design.

# 11 Methods

## 11.1 Settings

The study will take place at sentinel hospitals in [COUNTRY]. For participating hospitals (study sites), see section 11.2.

## 11.2 Study sites

Study sites will be hospitals where the AESIs can be diagnosed. Study sites will be selected based on [LIST SELECTION CRITERIA, e.g., ability to diagnose the AESI, size, population covered, vaccination coverage, access to computer for data collection at site-level, availability of sufficient human resources].

<<Paragraph describing the health facilities in which the study will be conducted.>>

**Table 1:** Study sites with principal investigators and contact details

Site	Principal Investigator	Email	Phone number

## 11.3 Study design

This study will collect data through prospective hospital case-based monitoring of pre-defined AESIs (see section 11.5.3.2). All patients with these AESIs will be identified along with their COVID-19 vaccination status, to determine whether COVID-19 vaccination is associated with an increased risk for these AESIs. The study is prospective as individuals are recruited as they are admitted to hospital with an AESI, rather than being identified retrospectively (e.g. from electronic health records). Although, exposure and events of interest (i.e., date of symptom onset, date of admission) will already have passed. Surveillance will be active and two study designs will be used, depending on the type of AESI studied:

- For outcomes with acute onset and a short period of increased risk following vaccination (see AESIs with known risk windows in ANNEX 1), a **self-controlled risk interval (SCRI) study design** will be used [7]. Only vaccinated patients with the AESI (cases) will be included

in this study. For each AESI, a post-vaccination risk interval and a self-control interval will be defined (see section 11.4.3.4), indexed on the date of vaccination. The timing of the occurrence of the AESI in relation to the vaccination will determine whether an AESI event date falls within the risk or the self-control interval, or neither. Vaccinated patients with an AESI event date (see section 11.4.3.3) during the risk or self-control interval will be eligible for inclusion in the analysis. In the analysis, the incidence of the AESI in the risk intervals will be compared with the incidence of the AESI in the self-control intervals (relative incidence). The advantages of the SCRI design include:

- it enables valid inference about the relative incidence of events in the risk interval relative to the self-control interval, using data only from cases;
  - it controls for time-independent confounders; and
  - no post-discharge follow-up for exposure ascertainment is needed when a post-vaccination self-control design is used.
- Optimal use of the SCRI design depends on access to good data on cases, access to good quality vaccination records with the ability to link them to cases, and use of appropriate analysis techniques.
  - For outcomes with unpredictable or late onset (see AESIs with no known risk window in ANNEX 1), a **case-control design** will be used. In the case-control design, cases will be defined as patients with the AESI. Control patients, i.e., without the AESI, will be selected among patients hospitalized for causes other than the AESI or other AESIs related to COVID-19 vaccine exposure or respiratory illness and matched to cases.
  - The COVID-19 vaccination status of the cases and controls will be determined and the odds of vaccination among cases and controls will be compared (odds ratio).

## 11.4 Self-controlled risk interval (SCRI) study

### 11.4.1 Study population

#### 11.4.1.1 Source population

The source population will consist of individuals living in the catchment area of the participating hospitals.

#### 11.4.1.2 Inclusion criteria

<<The inclusion criteria may change if the timing of obtaining informed consent is changed, see section 11.4.5. For example, if vaccination status cannot be collected without obtaining informed consent first, the inclusion criterion on vaccination will be dropped at enrolment; and non-vaccinated cases will be excluded later>>

Patients with a probable AESI will be prospectively recruited from the hospital's inpatient wards by [treating physician/study staff/other to describe as appropriate] if they satisfy the following inclusion criteria:

- have a probable AESI (see section 11.5.3.2 and 11.4.5)
- are resident in the catchment area of the participating hospital
- received at least one dose (first dose) of COVID-19 vaccine
- provide informed consent.

Women are eligible for inclusion and as there are no risks or threats for pregnant women to participate in this study, they should not be excluded.

## 11.4.2 Study period

The study will start as soon as possible after the initiation of the COVID-19 NIP, taking into consideration the feasibility (including vaccine uptake rate).

The study will end as soon as the number vaccinated of cases required to detect a pre-defined level of risk have been recruited (see section 11.4.8). The time required to recruit the number of vaccinated cases needed for a pre-defined risk will vary, depending on various factors, such as the catchment area, vaccination uptake, and the local background rate for the AESI.

Several factors can affect the feasibility of a SCRI study in which only vaccinated cases are included:

- minimum vaccine coverage: if only a small proportion of the population is vaccinated, few cases will be eligible for analysis;
- speed of vaccination uptake: this affects the rate at which individuals will pass through their risk and self-control intervals;
- expected maximum vaccine coverage: if no new individuals are vaccinated, there will be no more potential cases eligible for the analysis passing through their risk and self-control intervals; and
- time to results: for example in a situation where vaccine uptake is low at the start of vaccination programme roll-out, due, for example, to low number of vaccine doses available, but then is higher over time, studies starting immediately at the start of the vaccination programme when there is low vaccine uptake could enrol the required number of cases earlier than studies starting later, when vaccine uptake is higher, although the recruitment of the cases may take longer, and will, therefore, require more resources. See section 11.4.8 for further details.



## 11.4.3 Study variables

### 11.4.3.1 Exposure of interest

The exposure of interest is vaccination with at least one dose of any COVID-19 vaccine administered in routine clinical practice. Section 11.4.5 describes how exposure data will be obtained. The following information about vaccination will be collected for each dose, if available:

- vaccination status
- vaccine dose
- vaccine brand
- vaccination date
- vaccine batch number
- source of vaccination history (vaccination card, medical records from vaccination centre, patient self-report)

### 11.4.3.2 Outcomes

The outcome(s) of interest is(are) the presence of [ONE OR MORE PRE-DEFINED AESIs REQUIRING HOSPITALIZATION].

An event is included in the list of AESI if there is a [1]:

- proven association with immunization that is true for most, if not all, vaccines;
- proven association with a known vaccine platform or adjuvant that is being used in any COVID-19 vaccine;
- theoretical concern based on immunopathogenesis of COVID-19 disease;
- theoretical concern related to viral replication during COVID-19 infection; or
- theoretical concern because it has been demonstrated in an animal model with one or more candidate vaccine platforms.

<<AESIs listed in ANNEX 1 were identified by the Brighton Collaboration's Safety Platform for Emergency vACcines (SPEAC), dated December 2020 [6]. It is noted that the list of relevant AESIs may evolve over time and may vary across vaccine brands as results from clinical studies and other safety studies become available globally. The most up to date information should be taken into account when adapting this protocol template.>>

The diagnosis will be confirmed using [BRIGHTON COLLABORATION CASE DEFINITION IF AVAILABLE (ANNEX 2), OR OTHER PREDEFINED CASE DEFINITION].

<<For outcomes with a Brighton Collaboration case definition available, the level of diagnostic certainty will be ascertained by study site staff. It is recommended to require level 1, 2 or 3 of diagnostic certainty for case confirmation; although this can be tailored to the AESI, in which case a justification should be provided in the protocol.>>

The following details on the AESI will be collected:

- AESI diagnosed
- confirmation of diagnosis using predefined case definitions
- level of diagnostic certainty (if applicable)
- date of symptom onset
- date of hospitalization
- date of discharge or date of in-hospital death

### 11.4.3.3 Event dates

The date of symptom onset will be the event date for the primary analysis. The date of hospitalization will be the event date for sensitivity analysis. Additionally, sensitivity analysis excluding patients with concurrent COVID-19 may also be considered.

The SCRI study is based on the assumption that events are rare and it is unlikely to observe recurrent events within the same patient. In the case of recurrence of an event, the first event should be used in the study analysis.

### 11.4.3.4 Risk and self-control intervals

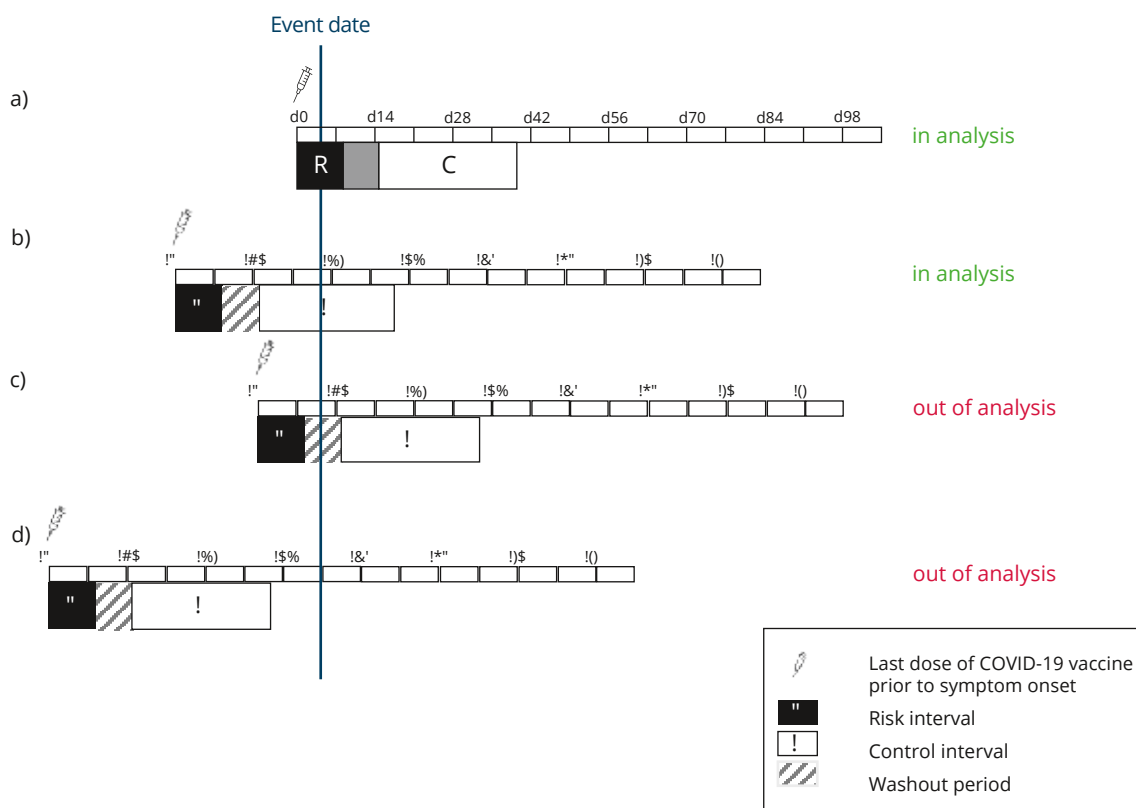
Risk and self-control intervals will be defined with the date of vaccination being the index date (time D0). Risk intervals for AESIs, when known, are listed in ANNEX 1.

A self-control interval three times the length of the risk interval is recommended, to allow expedited accrual of cases within the self-control interval. The self-control interval may be shortened (e.g., to twice the length of the risk interval), if considered appropriate. Examples of when this could be appropriate include when the risk interval is long, as this would lead to a very long self-control interval, which may increase bias due to time-varying confounding factors or if the incidence of the event is high, in which case expedited accrual might be less important.

A washout period (i.e., a period during which the patient is not in the risk or self-control period) between the risk and self-control periods is recommended as the risk interval is not accurately known for many AESIs. The recommended length of the washout period is one week, but may be adapted for specific AESIs, as appropriate.

Fig 1 shows an example of the post-vaccination risk interval and self-control interval for an AESI; event dates between 0 and 7 days fall in the risk interval (Fig 1a) while event dates between day 15 and 38 fall in the self-control interval (Fig 1b). Patients with event dates outside the risk and self-control intervals, including during the washout period are not included in the analysis (Fig 1c, 1d).

**Fig 1:** Schematic representation of the risk and self-control intervals for adverse events with a risk interval from d0 to d7, a washout period of one week (d8-d14), and a self-control interval three times the length of the risk interval (d15-d38), where d0 is the day of the last dose of COVID-19 vaccine received prior to the event date. Patients with an event during the a) risk interval or b) self-control interval are included in the analysis. Patients with an event c) during the washout period or, d) after the end of the self-control interval are not included.



### 11.4.3.5 Other variables

Section 11.4.5 describes how information for other variables will be collected:

- patient identifier
- date of birth
- sex
- pregnancy and estimated date of delivery
- breastfeeding
- socio-economic class [LEVELS TO BE DEFINED LOCALLY]
- risk groups: chronic respiratory disease and asthma, chronic heart, kidney and liver disease, diabetes or immunocompromised/suppressed persons, obesity, allergy, [OTHER RISK GROUPS OF INTEREST DEPENDING ON THE AESI STUDIED]
- previous or current COVID-19 disease (defined as probable, laboratory-confirmed with no hospitalization, laboratory-confirmed with hospitalization) and date of onset.

#### 11.4.4 Data sources

Data sources to be used to collect variables listed in section 11.4.3 may include:

- hospital-level patient data (including, but not limited to admission records, and inpatient records);
- interviews with patient (e.g., to obtain vaccination status, date of symptom onset or other data points if not available from the medical record), or with treating physician (e.g. in the case confirmation step; and
- vaccination records (e.g., vaccine card, medical records in the vaccination centre, self-report).

#### 11.4.5 Study flow and data collection

The different steps, from the identification of patients to data entry, are described below. <<The most appropriate order of the steps may vary between settings, and, in particular the timing of obtaining informed consent may have to be adapted to the local situation in agreement with the ethics committee. For example, if information on vaccination status cannot be obtained without prior informed consent, the order of steps must be adapted.>>

Following the informed consent process:

- a record for the enrolled patient will be created in the data collection tool;
- data on the enrolled patients will be entered at each step into the electronic case report forms (eCRFs). <<The use of electronic reporting is optional if available, otherwise paper forms are sufficient.>>

The roles and responsibilities of investigators and staff involved in this study are summarized in section 6. <<Investigators who are not regular staff at the study site will need to have the necessary authorization to access data. This should be described in the study site procedures and approved by the ethics committee>>

It should be noted that recruitment of patients can be subject to selection bias if medical staff treating patients also recruit them for the study. Participants should be invited to participate, with the option of accepting or declining, and they should never be pressured into consenting. Treating physicians can identify cases that occur under their management, but it is important that study staff, not the treating physician, discuss the study with the patient and obtain consent. The structure of the recruitment process should minimize potential selection bias. Participants should be informed that participating or not in the study will not affect any treatment decisions.

<b>1. Screening for AESIs</b>	<ul style="list-style-type: none"> <li>Investigator will search daily for patients with AESIS cases in hospital records and discussions with treating physicians</li> </ul>
<b>2. Identification of vaccinated probable cases</b>	<ul style="list-style-type: none"> <li>Retrospectively ascertain vaccine exposure</li> <li>Registers or patient interview</li> </ul>
<b>3. Informed consent</b>	<ul style="list-style-type: none"> <li>Inform patient about study and answer questions</li> <li>Obtain signed informed consent</li> </ul>
<b>4. Confirmation of case</b>	<ul style="list-style-type: none"> <li>Confirm AESI by checking against Brighton Collaboration definition (if available)</li> <li>Reviewer will be blinded to vaccination date, dose, brand (if possible)</li> </ul>
<b>5. Collection of vaccination history</b>	<ul style="list-style-type: none"> <li>Use of registers (if available)</li> <li>Interview with patient</li> <li>Ask patient (or vaccination centre) to view vaccination card</li> </ul>
<b>6. Collect data for study variables</b>	<ul style="list-style-type: none"> <li>From medical records or from patient</li> </ul>
<b>6. Include in SCRI analysis</b>	<ul style="list-style-type: none"> <li>If dates of onset of AESI symptoms and hospitalization for AESI (for sensitivity analysis) are available and are within the risk or self-control periods</li> </ul>

#### 1. Identification of probable cases

A patient hospitalized with the AESI ('probable case') will be prospectively identified through [DAILY SEARCHES OF ADMISSION RECORDS/INPATIENT RECORDS OR DISCUSSIONS WITH TREATING PHYSICIANS] at [RELEVANT WARDS] by [TO SPECIFY].

#### 2. Identification of vaccinated probable cases

COVID-19 vaccine exposure status (yes/no) will be ascertained retrospectively for probable cases. Registers will be used, if reliable and available. Otherwise, exposure status will be initially assessed through patient interview.

#### 3. Obtain informed consent and start data collection

Once a vaccinated probable case has been identified, they will be informed about the study by [TO SPECIFY] who will explain the study using [TO COMPLETE AS APPLICABLE]. The patient will have every opportunity to ask questions before being asked to provide signed informed consent to participate (ANNEX 7).

When signing the ICF, patients agree that the study team can collect data regarding the AESI, their COVID-19 vaccination, and any relevant covariates (see section 11.4.3). The study-specific ICF will explain the purpose of the data collection, the foreseeable uses of the data, the intended goal of such use, who will have access to the data, the conditions and duration of data storage, and the ways in which the patient can contact the data custodian and remain

informed about future use of their data. The ICF will explain that the patient's participation is completely voluntary and that they may choose to withdraw at any time during the study.

<<The adult ICF template and process will need to be adapted for special populations (e.g., minors, pregnant women, elderly patients lacking full capacity, migrants, prisoners) that require a tailored approach to consent, including possible surrogate decision-makers (e.g., parents, adult children) or study advocates (e.g., for inclusion of prisoners, orphans) and additional forms (e.g. assent forms), as well as tailoring of the information provided to patients during the consent process. A third party can sign on behalf of the patient if they are unable to sign due to disabilities. Information on relevant ethical considerations can be found in CIOMS guidelines 9-10 and 15-17 [1].>>

#### 4. Case confirmation

The medical records of probable cases will be reviewed to collect variables listed in section 11.4.3 and to confirm the case using predefined case definitions by [TO SPECIFY]. The level of diagnostic certainty will be ascertained for events for which a Brighton Collaboration case definition is available (see section 11.4.3.2). The reviewer will be blinded for about the patient's vaccination (date, dose, brand), as far as is feasible, for example, by collecting detailed vaccination history only after the case has been confirmed, or by having a different staff member collect the vaccination history. Blinding for date is important so that the reviewer can perform an unbiased assessment of date of AESI onset, i.e., without knowing if this date falls in the risk or control period. Blinding for brand is important so that any safety signals that may exist for a particular brand do not bias the reviewer's case ascertainment. Blinding for dose will be important for the same reasons.

<<To be specified if the level of diagnostic certainty will be assessed by the staff at the site (e.g. by the treating physician), or whether the level of diagnostic certainty will be determined at the time of statistical analysis. Automated classification tools (ABC tools) are available for selected case definitions.>>

#### 5. Collection of vaccination history

Registers will be used, if reliable and available. Otherwise, the patient will be asked to provide their vaccination card showing that they have been vaccinated with a COVID-19 vaccine. If the vaccine card is not available at the hospital, efforts will be made to retrieve it from the patient's home. If the card is not available, other written documentation will be accepted; efforts will be made to confirm vaccine history by contacting the vaccination clinic, if needed. If no written documentation is available, the patient's verbal report of vaccine history will be accepted. The data about the COVID-19 vaccine exposure that will be collected are listed in section 11.4.3.1.

#### 6. Collection of relevant study variables

For confirmed cases vaccinated against COVID-19, all other relevant study variables will be collected from their medical records (see section 11.4.3). Any missing information may be obtained by asking the patient directly.

## 7. Identification of vaccinated cases with event date during the risk or self-control intervals

Confirmed cases who have been exposed to a COVID-19 vaccine, who have a date of event i.e., onset of the outcome for the main analysis, and date of hospitalization for the sensitivity analysis, that fall within their specific risk or self-control interval will be included in the analyses.

### 11.4.6 Withdrawal from the study

All patients will have the right to withdraw from the study at any time and for any reason. Should a patient decide to withdraw from the study, data collected up to that point will be retained for analysis but no additional data will be collected.

### 11.4.7 Pregnancy

Any patient found to be pregnant during follow-up will be referred to the [NATIONAL AEFI FOCAL POINT] for follow-up as per national guidelines. As per WHO recommendations, all pregnant women inadvertently exposed to COVID-19 vaccine should be followed up until delivery, and the pregnancy outcome documented. Please refer to the WHO [COVID-19 vaccines: safety surveillance of pregnant and breastfeeding women](#) module for specific guidance on pregnant and breastfeeding women.

### 11.4.8 Sample size

#### 11.4.8.1 Minimum number of cases required

We calculated the minimum sample size needed to reject the null hypothesis that the relative incidence of an AESI during the risk versus the self-control interval is equal to 1 [7]. The sample size calculation depends upon the actual value of the relative incidence, the proportion of the total observation period an individual spends in the risk interval, the power to reject the null hypothesis, and the probability of a type-I error (significance level). The observation period is defined as the sum of the risk and self-control intervals.

In our calculations we set the probability of type-I error at 5%; the power at 80%; and the proportion of observation period (excluding the washout period) a patient spends in the risk interval was set at 25%, 33%, and 50% (corresponding to the length of the self-control interval 3 times, 2 times and equal to the length of the risk interval, respectively). Under these conditions, the minimum number of cases required to reject the null hypothesis when the actual relative incidence is equal to 2, 3, 4 or 5 is shown in Table 2. Fig 2 illustrates the impact of a larger range of proportions of the total observation period a patient spends in the risk interval.

The minimum total number of cases required for studies with self-control intervals that are equal to, twice or three times the length of the risk interval is similar (Table 2, Fig 2). Therefore, a self-control interval that is three times the length of the risk interval is recommended, as this increases the probability that a vaccinated patient presenting to the hospital will have an event date during the observation period, and hence will increase the accrual rate of cases eligible for study participation.

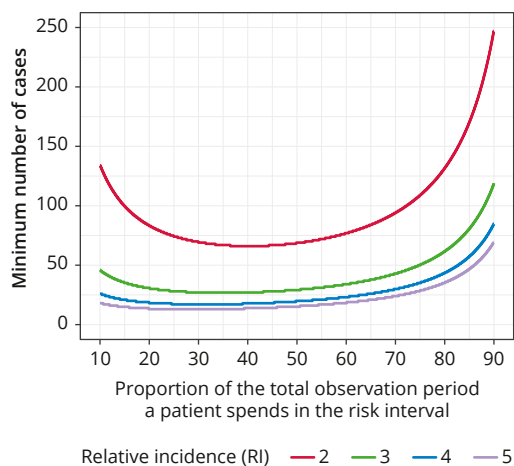


**Table 2:** Minimum number of cases required to reject the null hypothesis that the relative incidence of AESI during risk versus self-control intervals is equal to 1. Probability of type-I error is set at 5%, power at 80%, and proportion of the total observation period a patient spends in the risk interval at 25%, 33%, and 50%.

Relative incidence	Minimum total number of cases required (number of cases during risk interval), by proportion* of observation period patients spend in the risk interval		
	25%*	33%*	50%*
2	75 (30)	68 (34)	68 (45)
3	28 (14)	28 (16)	29 (22)
4	17 (10)	17 (11)	19 (15)
5	13 (8)	13 (9)	15 (13)

\*25%: self-control interval is three times the length of the risk interval; 33%: self-control interval is twice the length of the risk interval; 50%: self-control interval is same length as the risk interval

**Fig 2:** Minimum number of cases required to reject the null hypothesis that the relative incidence of the AESI during the risk versus self-control interval is equal to 1. The probability of type-I error is set at 5%, the power at 80%, and the proportion of the observation period a patient spends in the risk interval varies from 10 to 90%. The lines show the minimum number of patients needed for a relative incidence of 2, 3, 4 or 5.



### 11.4.8.2 Total catchment population

The catchment population needed to observe the minimum number of cases required (Table 2, Fig 2) was calculated for a given background incidence rate of the AESI, the actual length of the risk and self-control intervals and the vaccination uptake during the study period. The methodology is described in ANNEX 3. The catchment populations required to detect a relative incidence of 2, 3, 4, or 5 for AESIs with background rates ranging from 0.1 to 1000 per 100,000 people per year and a risk period of 7 or 42 days, assuming a vaccination uptake during the study period of 25%, 50% and 75% are given in Table 3.

In settings with a high vaccination uptake during the study period, the catchment area required to detect a given relative incidence is lower than in settings with a lower vaccination

uptake (Table 3). Detecting a relative incidence of 2 may be feasible for common AESIs (such as acute aseptic arthritis). For very rare AESIs (such as subacute thyroiditis), the catchment area required to detect a low relative incidence is likely to be prohibitively large, particularly with a low vaccine uptake rate. However, from a public health benefit-risk perspective, being able to detect high relative incidences for rare events may be sufficient, since a low relative incidence for a rare event will result in only a small number of additional cases, which is unlikely to affect the benefit-risk ratio of the vaccination programme.

Background rates of AESIs based on systematic literature reviews are available in the Brighton Collaboration case definition companion guides [7].

**Table 3:** Catchment area sizes required to detect a relative incidence of 2, 3, 4 or 5 for AESIs with annual background rates varying from 0.1-1000 per 100,000 people and a post-vaccination risk interval of 7 or 42 days, at different levels of vaccination uptake (VU) during the study period, assuming the proportion of observation period a patient spends in the risk interval is 25% (probability of type-I error is set at 5%, power at 80%)

Expected relative incidence	Background rate per 100,000 people per year	Catchment area (n) for different levels of vaccination uptake (VU) during the study period and a risk period of 7 days			Catchment area (n) for different levels of vaccination uptake (VU) during the study period and a risk period of 42 days		
		VU=25%	VU=50%	VU=75%	VU=25%	VU=50%	VU=75%
2	0.1	3,172,457,293	1,586,228,647	1,057,485,764	521,785,864	260,892,932	173,928,621
	1	317,245,866	158,622,933	105,748,622	52,178,721	26,089,361	17,392,907
	10	31,724,723	15,862,362	10,574,908	5,218,007	2,609,004	1,739,336
	100	3,172,609	1,586,305	1,057,536	521,936	260,968	173,979
	1000	317,398	158,699	105,799	52,329	26,164	17,443
3	0.1	974,000,056	487,000,028	324,666,685	162,333,389	81,166,695	54,111,130
	1	97,400,056	48,700,028	32,466,685	16,233,389	8,116,695	5,411,130
	10	9,740,056	4,870,028	3,246,685	1,623,389	811,695	541,130
	100	974,056	487,028	324,685	162,389	81,195	54,130
	1000	97,456	48,728	32,485	16,289	8,145	5,430
4	0.1	536,693,913	268,346,957	178,897,971	84,479,626	42,239,813	28,159,875
	1	53,669,424	26,834,712	17,889,808	8,447,993	4,223,997	2,815,998
	10	5,366,975	2,683,487	1,788,992	844,830	422,415	281,610
	100	536,730	268,365	178,910	84,514	42,257	28,171
	1000	53,705	26,853	17,902	8,482	4,241	2,827

Expected relative incidence	Background rate per 100,000 people per year	Catchment area (n) for different levels of vaccination uptake (VU) during the study period and a risk period of 7 days			Catchment area (n) for different levels of vaccination uptake (VU) during the study period and a risk period of 42 days		
		VU=25%	VU=50%	VU=75%	VU=25%	VU=50%	VU=75%
5	0.1	339,160,740	169,580,370	113,053,580	56,526,812	28,263,406	18,842,271
	1	33,916,097	16,958,049	11,305,366	5,652,705	2,826,352	1,884,235
	10	3,391,633	1,695,817	1,130,544	565,294	282,647	188,431
	100	339,187	169,593	113,062	56,553	28,276	18,851
	1000	33,942	16,971	11,314	5,679	2,839	1,893

## 11.4.9 Data analyses

### 11.4.9.1 Descriptive analyses of demographics

Demographic and medical characteristics will be summarized using descriptive statistics. Analyses will be performed by [SITE/COUNTRY/REGION].

The mean and standard deviation or median and range will be calculated for age at vaccination of the cases, overall and by sex. Frequencies (%) of [OTHER VARIABLES] will be provided by age group and sex. The following age groups will be considered for analysis: [TO BE DEFINED DEPENDING ON AESI]. Levels of diagnostic certainty will be described, if applicable.

### 11.4.9.2 Statistical analyses

The relative incidence and 95% confidence intervals comparing the incidence of the outcome in the risk interval with that in the self-control interval will be calculated by dose and by vaccine brand using conditional Poisson regression, with adjustment for calendar time. The analyses will be conducted overall and for the following age groups: [TO BE DEFINED DEPENDING ON AESI]. The date of vaccination will be the index date.

A sensitivity analysis will be conducted using the date of hospitalization instead of date of symptom onset as the event date. Further sensitivity analyses may be conducted as appropriate (e.g., if risk intervals are not precisely known, or excluding patients with concurrent COVID-19).

## 11.5 Case-control study

### 11.5.1 Study population

#### 11.5.1.1 Source population

The source population will consist of individuals living in the catchment area of the participating hospitals.

#### 11.5.1.2 Inclusion criteria

<<The inclusion criteria may change if the timing of obtaining informed consent is changed, see section 11.5.7.>>

### Cases

Patients hospitalized with a probable AESI will be prospectively recruited by [treating physician/study staff/other to describe as appropriate] if they satisfy the following inclusion criteria:

- have a probable AESI, (see section 11.5.3);
- were eligible (as per local eligibility criteria, e.g. age-defined policy) for COVID-19 vaccination four weeks prior to the date of AESI symptom onset;
- are resident in the catchment area of the participating hospital;
- provide informed consent.

### Controls

For each case, up to (and preferably) four matched hospital controls will be identified and prospectively recruited among patients hospitalized for causes other than the AESI or other AESIs related to COVID-19 vaccine exposure or respiratory illnesses. Controls will be matched to cases based on age and (if feasible) current place of residence. Patients who satisfy the following inclusion criteria will be recruited:

- are hospitalized for causes other than the AESI or other AESIs related to COVID-19 vaccine exposure or respiratory illnesses;
- were eligible (as per local eligibility criteria, e.g. age-defined policy) for COVID-19 vaccination four weeks prior to the date of symptom onset;
- are resident in the catchment area of the participating hospital;
- match the index cases' age;
- match the index cases' place of residence (if feasible);
- provide informed consent.

There are no risks or threats from the participation of pregnant women in this study, therefore pregnant women are eligible for inclusion. Pregnant women should not be excluded from this study.

## 11.5.2 Study period

The study will start as soon as possible after of the initiation of the COVID-19 NIP, taking into consideration the feasibility (including vaccine uptake).

The study will end as soon as the number of cases required to detect a pre-defined level of risk have been recruited (see section 11.5.10). The time required to recruit the number of cases needed for a pre-defined risk will vary, depending on various factors, such as the catchment area, vaccination uptake, and the local background rate for the AESI.

For case-control studies, a minimum vaccination coverage of 20% is recommended before starting the study. See section 11.5.10 for further details. This 20% target vaccination coverage is based on the sharp increase in the number of cases required to obtain an OR of 2 that is observed when vaccine coverage is lower than 20% (Fig 4).

## 11.5.3 Study variables

### 11.5.3.1 Exposure of interest

The exposure of interest is vaccination with at least one dose of any COVID-19 vaccine administered in routine clinical practice. Section 11.5.7 describes how exposure data will be obtained. The following details on vaccination will be collected for each dose, if available:

- vaccination status
- vaccine dose
- vaccine brand
- vaccination date
- vaccine batch number
- source of vaccination history (vaccination card, medical records from vaccination centre, patient self-report)

Optional: The following details on diluent will be collected, if applicable and available:

- diluent required
- diluent brand and manufacturer
- diluent batch number.

### 11.5.3.2 Outcomes

The outcome(s) of interest is(are) the presence of [ONE OR MORE PRE-DEFINED AESIs REQUIRING HOSPITALIZATION].

An event is included in the list of AESI if there is a [1]:

- proven association with immunization that is true for most, if not all, vaccines;
- proven association with a known vaccine platform or adjuvant that is being used in any COVID-19 vaccine;
- theoretical concern based on immunopathogenesis of COVID-19 disease;
- theoretical concern related to viral replication during COVID-19 infection; or
- theoretical concern because it has been demonstrated in an animal model with one or more candidate vaccine platforms.

<<AESIs listed in ANNEX 1 were identified by the Brighton Collaboration's Safety Platform for Emergency vACcines (SPEAC), as of December 2020 [6]. It should be noted that the list of relevant AESIs may evolve over time and may vary across vaccine brands as results from clinical studies and other safety studies become available globally. The most up to date information should be taken into account when adapting this protocol template.>>

If the AESI occurs more than once, the first event should be used in the analysis only. However, this is unlikely as the events being studied are very rare.

The diagnosis will be confirmed using [BRIGHTON COLLABORATION CASE DEFINITION IF AVAILABLE (ANNEX 2), OR OTHER PREDEFINED CASE DEFINITION].

<<For outcomes for which a Brighton Collaboration case definition is available, the level of diagnostic certainty will be ascertained by study site staff. It is recommended to require level 1, 2 or 3 of diagnostic certainty for case confirmation; although this can be tailored to the AESI, in which case a justification should be provided in the protocol.>>

The following details on the AESI will be collected:

- AESI diagnosed
- confirmation of diagnosis using predefined case definitions
- level of diagnostic certainty (if applicable)
- date of symptom onset
- date of hospitalization
- date of discharge or in-hospital death.

### 11.5.4 Controls

For each case, up to (and preferably) four matched controls will be identified. Controls will be identified among patients hospitalized for causes other than the AESI or other AESIs related to COVID-19 vaccine exposure or respiratory illness. Controls will be matched to cases based

on age, current place of residence (if not feasible, match on healthcare facility), and eligibility for COVID-19 vaccination (as per local eligibility criteria, e.g. age-defined policy) four weeks prior to the date of symptom onset.

The following details on the condition leading to hospitalization will be collected for controls:

- diagnosis
- date of symptom onset
- date of hospitalization
- date of discharge or in-hospital death

Bias due to confounding of underlying differences in health profiles and risk factors of case and control patients can be addressed by matching or in the analyses. This study describes matching of three variables; age, catchment area and eligibility for COVID-19 vaccination (as per local eligibility criteria, e.g. age-defined policy) four weeks prior to the date of symptom onset. Matching to catchment variables is a useful strategy that can be applied to places without a well enumerated population database or register from which to select controls. It should be noted that matching on excessive numbers of variables can increase the chance of overmatching, which can result in statistical bias due to matching for a variable that is a result of the exposure. If this happens, the controls will be more similar to the cases in terms of exposure than the general population.

### 11.5.5 Other variables

Section 11.5.7 describes how information for other variables will be collected:

- patient identifier
- date of birth
- sex
- pregnancy and estimated date of delivery
- lactation
- socio-economic class [LEVELS TO BE DEFINED LOCALLY]
- risk groups: chronic respiratory disease and asthma, chronic heart, kidney and liver disease, diabetes or immunocompromised/suppressed persons, obesity, allergy, [OTHER RISK GROUPS OF INTEREST DEPENDING ON THE AESI STUDIED]
- previous or current COVID-19 disease (defined as probable, laboratory-confirmed with no hospitalization, laboratory-confirmed with hospitalization) and date of onset.

For the case-control study, the following variables will be collected for cases and controls:

- current place of residence
- eligibility for COVID-19 vaccination (as per local eligibility criteria, e.g. age-defined policy) four weeks prior to symptom onset

## 11.5.6 Data sources

Data sources to be used to collect variables listed in section 11.5.3 may include:

- hospital-level patient data (including, but not limited to admission records, and inpatient records);
- interviews with patient (e.g., to obtain vaccination status, date of symptom onset or other data points if not available from the medical records), or with treating physician (e.g. in the case confirmation step); and
- vaccination records (e.g., vaccine card, medical records from the vaccination centre, patient self-report).

## 11.5.7 Study flow and data collection

The different steps, from the identification of patients to data entry, are described below. <<The most appropriate order of the steps may vary between settings, and, in particular, the timing of obtaining informed consent may have to be adapted to the local situation in agreement with the ethics committee.>>

Following the informed consent process:

- a record for the enrolled patient will be created in the data collection tool;
- data on the enrolled patients will be entered at each step into the electronic case report forms (eCRFs). The use of electronic reporting is optional if available, otherwise paper forms are sufficient.

The roles and responsibilities of investigators and staff involved in this study are summarized in section 6. <<Investigators who are not regular staff at the study site will need to have the necessary authorization to access data. This should be described in the study site procedures and approved by the ethics committee>>

It should be noted that recruitment of patients can be subject to selection bias if medical staff treating patients also recruit them for the study. Participants should be invited to participate with the option of accepting or declining, and should never be pressured into consenting. Treating physicians can identify cases that occur under their management, but it is important that study staff discuss the study with the patient and obtain consent. The structure of the recruitment process should minimize potential selection bias. Participants should be informed that participating or not in the study should not affect any treatment decisions.



**Fig 3:** Summary of study flow and data collection for case-control studies

<b>1. Screening for cases and controls</b>	<ul style="list-style-type: none"><li>• Cases: investigator will identify patients with the study AESI from hospital records and discussions with treating physicians daily</li><li>• Controls: hospitalized patients for causes other than the study AESI or other AESIs related to COVID-19 vaccine exposure or respiratory illness</li></ul>
<b>2. Assess eligibility for COVID-19 vaccine</b>	<ul style="list-style-type: none"><li>• Check that patients were eligible for COVID-19 vaccination (as per local eligibility criteria, e.g. age-defined policy) four weeks prior to onset of symptoms</li></ul>
<b>3. Informed consent</b>	<ul style="list-style-type: none"><li>• Inform patient about study and answer questions</li><li>• Obtained signed informed consent</li></ul>
<b>4. Case confirmation</b>	<ul style="list-style-type: none"><li>• Data in patient's records to be checked against Brighton Collaboration definition (if available)</li><li>• Reviewer will be blinded to the vaccination status (if possible)</li></ul>
<b>5. Vaccination history obtained</b>	<ul style="list-style-type: none"><li>• Use of registers (if available)</li><li>• Obtain vaccination card from patient or vaccination centre</li><li>• Interview with patient</li></ul>
<b>6. Collect data for study variables</b>	<ul style="list-style-type: none"><li>• Data for study variables to be obtained from medical records or by asking the patient</li></ul>

### 11.5.7.1 Cases

#### 1. Identification of probable cases

Patients hospitalized with the AESI ('probable cases') will be identified prospectively through [DAILY SEARCHES OF ADMISSION RECORDS/INPATIENT RECORDS OR DISCUSSIONS WITH TREATING PHYSICIANS] at [RELEVANT WARDS] by [TO SPECIFY].

#### 2. Eligibility for vaccination

The eligibility of probable cases for COVID-19 vaccination (as per local eligibility criteria, e.g. age-defined policy) four weeks prior to symptom onset will be determined.

#### 3. Obtaining informed consent

Once a probable AESI case eligible for COVID-19 vaccination has been identified, [TO SPECIFY] will inform them about the study and explain the study [TO COMPLETE AS APPLICABLE], and then request their informed consent to participate using a study ICF (ANNEX 7). The patient will have every opportunity to ask questions. By signing the ICF, the patient agrees that the study team can collect data about the AESI, COVID-19 vaccination, and any relevant covariates (see section 11.5.3). The study ICF will explain the purpose of the data collection, the foreseeable uses of the data, the intended goals of such uses, who has access to the data, the conditions and duration of data storage, and the ways in which the patient can contact the data custodian and remain informed about future use of their data. The ICF will explain

that patients' participation is completely voluntary and that they may choose to withdraw at any time during the study.

<<The adult ICF template (ANNEX 7) and process will need to be adapted for special populations (e.g., minors, pregnant women, elderly patients lacking full capacity, migrants, prisoners) that require a tailored approach to consent, including possible surrogate decision-makers (e.g., parents, adult children) or study advocates (e.g., for inclusion of prisoners, orphans). Additional forms (e.g. assent forms) may be necessary, as well as specific tailoring of the information provided to patients during the consent process. A third party can sign on behalf of the patient if they are unable to sign due to disabilities. Information on relevant ethical considerations can be found in CIOMS guidelines 9-10 and 15-17 [1].>>

#### 4. Case confirmation

The medical records of probable cases will be reviewed to collect variables listed in 11.5.3.2 and for case confirmation using predefined case definitions. The level of diagnostic certainty will be ascertained for events for which a Brighton Collaboration case definition is available (see section 11.5.3.2). The reviewer will be blinded to the vaccination status as far as possible, for example, by asking about vaccination history only after the case has been confirmed, or by having a different staff member collect the vaccination history.

<<To be specified if the level of diagnostic certainty will be assessed by the staff at the study site (e.g. by the treating physician), or if it will be determined at the time of statistical analysis. Automated classification tools (ABC tools) are available for selected case definitions.>>

#### 5. Collection of information about vaccination history

COVID-19 vaccination status will be retrospectively ascertained for confirmed cases. Registers will be used, if available and reliable. If not, exposure status will be initially assessed through patient interview. The patient will be asked to provide their vaccination card showing that they have been vaccinated with a COVID-19 vaccine. If the vaccine card is not available at the hospital, efforts will be made to retrieve the vaccine card from the patient's home. If the card is not available, other written documentation will be accepted and efforts will be made to confirm vaccine history by contacting the vaccination clinic. If no written documentation is available, the patient's verbal report of vaccine history will be accepted. The data on COVID-19 vaccine exposure that will be collected are listed in section 11.5.3.

#### 6. Collection of relevant study variables

All other relevant study variables (see section 11.5.3) will be collected from the patient's medical records. Any missing information will be obtained by asking the patient directly.

### 11.5.7.2 Controls

#### 1. Screening for controls

For each case, up to (and preferably) four matched controls will be identified among patients hospitalized for causes other than the AESI or other AESIs related to COVID-19 vaccine exposure

or respiratory illness. Controls will be matched to cases based on age, current place of residence (if feasible, if not on healthcare facility), and eligibility for COVID-19 vaccination (as per local eligibility criteria, e.g. age-defined policy) four weeks prior to the date of symptom onset. Cases will be eligible for the analysis only if one or more matched controls can be identified. Controls will be prospectively identified through [DAILY SEARCHES OF ADMISSION RECORDS/ INPATIENT RECORDS OR DISCUSSIONS WITH TREATING PHYSICIANS] at [RELEVANT WARDS] by [TO SPECIFY].

National initial vaccination priority groups will likely include those that are most at risk of severe COVID-19 disease based on age or medical conditions, or those that are most at risk of exposure to SARS-CoV-2 based on profession. Controls should be matched according to the three criteria above to minimize the risk of bias or confounding and to increase comparability of the cases and controls. Calendar week will be adjusted in the analysis to account for any seasonality or other factors that vary over time, in addition to sex, comorbidities and socioeconomic status.

## 2. Eligibility for vaccination

The eligibility of controls for COVID-19 vaccination (as per local eligibility criteria, e.g. age-defined policy) four weeks prior to symptom onset will be determined.

## 3. Obtaining informed consent

Once a control eligible for COVID-19 vaccination has been identified, [TO SPECIFY] will inform them about the study and explain the study through [TO COMPLETE AS APPLICABLE], and they will have every opportunity to ask questions. [TO SPECIFY] will then ask them for signed informed consent to participate using the study ICF (ANNEX 7). When signing the ICF, patients will agree that the study team can collect data about the AESI, COVID-19 vaccination, and any relevant covariates (see section 11.5.3). The study ICF will explain the purpose of the data collection, the foreseeable uses of the data, the intended goal of such use, who has access to the data, the conditions and duration of data storage, and the ways in which the patient can contact the data custodian and remain informed about future use of their data. The ICF will also explain that patients' participation is completely voluntary and that they will be able to withdraw at any time during the study.

<<The adult ICF template and process will need to be adapted for special populations (e.g., minors, pregnant women, elderly patients lacking full capacity, migrants, prisoners) that require a tailored approach to consent, including possible surrogate decision-makers (e.g., parents, adult children) or study advocates (e.g., for inclusion of prisoners, orphans). Additional forms (e.g. assent forms), may be necessary, as well as specific tailoring of the information provided to patients during the consent process. A third party can sign on behalf of the patient if they are unable to sign due to disabilities. Information on relevant ethical considerations can be found in CIOMS guidelines 9-10 and 15-17 [1].>>

## 4. Collection of information about vaccination history

COVID-19 vaccine exposure will be retrospectively investigated for controls. Registers will be used, if available and reliable. If not, COVID-19 vaccination status will be initially assessed through patient interview. Patients will be interviewed and they will be asked to provide

their vaccination card. If this is not available at the hospital, efforts will be made to retrieve it from the patient's home. If the card is not available, other written documentation will be accepted; efforts will be made to confirm vaccine history by contacting the vaccination centre. If no written documentation is available, the patient's verbal report of vaccine history will be accepted. Data will be entered into the eCRF. The use of electronic reporting is optional if available, otherwise paper forms are sufficient. The data on COVID-19 vaccine exposure that will be collected are listed in section 11.5.3.

#### 5. Collection of relevant study variables

All other relevant study relevant study variables (see section 11.5.3) will be collected from the patients' medical records. Any missing data will be obtained from the patient directly.

### 11.5.8 Withdrawal from the study

All patients will have the right to withdraw from the study at any time and for any reason. Should a patient decide to withdraw from the study, data collected up to that point will be retained for analyses, but no additional data will be collected.

### 11.5.9 Pregnancy

All patients found to be pregnant during follow-up will be referred to the [NATIONAL AEFI FOCAL POINT] for follow-up as per national guidelines. As per WHO recommendations, all pregnant women inadvertently exposed to COVID-19 vaccine should be followed up until delivery, and the pregnancy outcome documented. Please refer to the WHO [COVID-19 vaccines: safety surveillance of pregnant and breastfeeding women](#) module for specific guidance on pregnant and breastfeeding women.

### 11.5.10 Sample size

#### 11.5.10.1 Minimum number of cases required

We calculated the sample size required to reject the null hypothesis that the vaccine exposure odds ratio (OR) in cases versus controls is equal to one [8]. This sample size calculation depends on the actual OR, number of controls per case, vaccination coverage in controls, the power to reject the null hypothesis, and the probability of a type-I error (significance level).

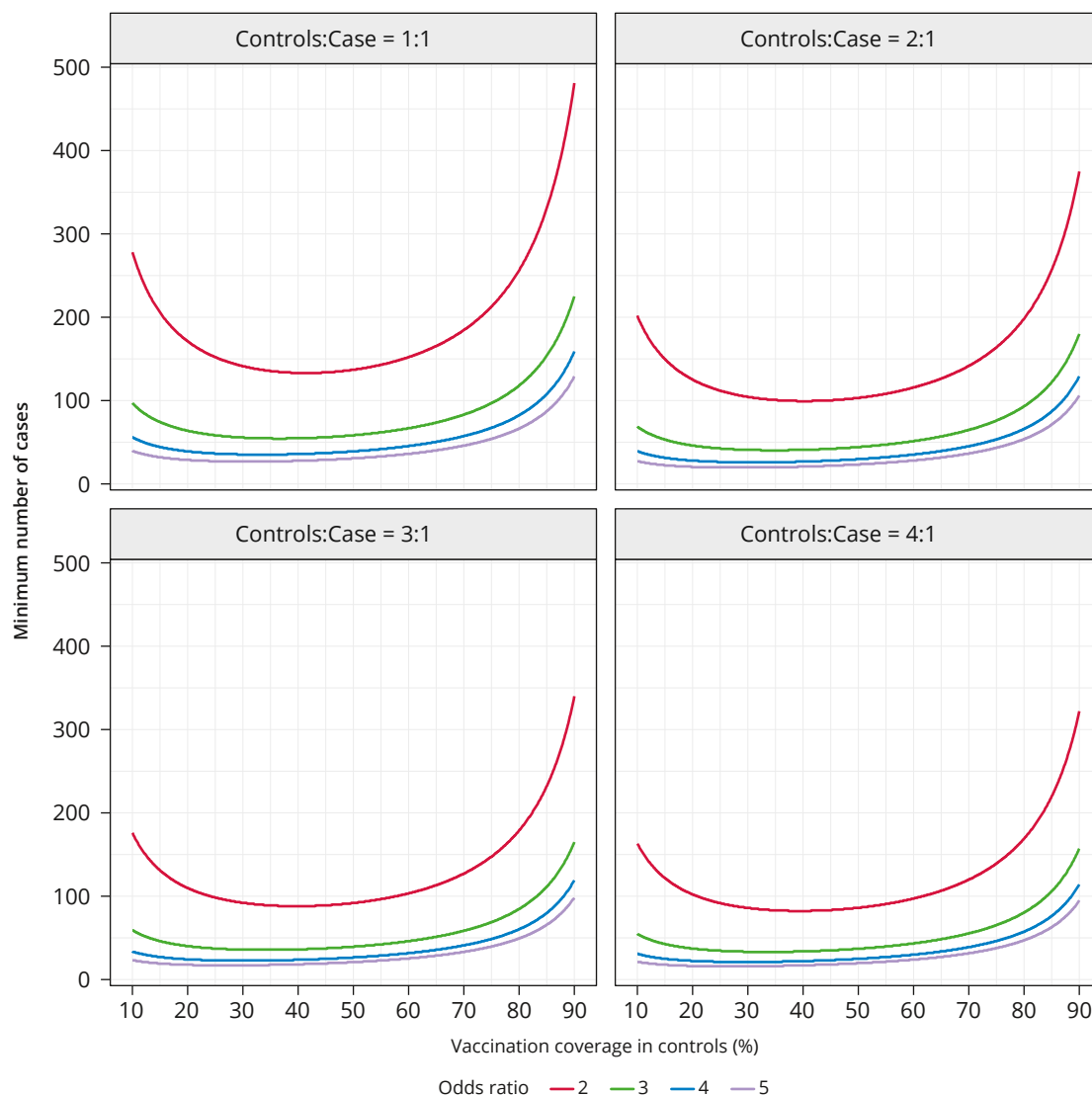
In our calculations we set the probability of type-I error at 5%; power at 80%; vaccination coverage in controls at 25%, 50%, and 75%; and controls to case ratios of 1:1, 1:2, 1:3 and 1:4. Under these settings, the minimum number of cases required to reject the null hypothesis when the actual odds ratio is equal to either 2, 3, 4 or 5 is shown in Table 4. Fig 4 shows the impact of a wider range of vaccination coverage in controls on the minimum number of cases needed.

The minimum total number of cases required decreases as the number of controls per case increases from 1:1 to 4:1. It is therefore recommended to match each case to four controls, if feasible (Table 4). The number of cases required sharply increases with low levels of vaccination coverage (<20%) and higher levels of vaccination coverage (>65%) (Fig 4).

**Table 4:** Minimum number of cases required to detect different odds ratios (ORs) for 25%, 50% and 75% vaccination coverage, assuming a power of 80%, a probability of type-I error at 5%, and a control-to-case ratio of 1:1, 2:1, 3:1 and 4:1.

OR	Controls per case											
	1:1			2:1			3:1			4:1		
	Vaccination coverage in controls											
	25%	50%	75%	25%	50%	75%	25%	50%	75%	25%	50%	75%
2	152	137	213	112	103	164	98	92	147	92	86	139
3	58	58	97	43	44	76	37	39	69	35	37	65
4	36	39	67	26	30	53	23	27	49	21	25	46
5	27	31	54	20	23	43	17	21	40	16	20	38

**Fig 4:** Minimum number of cases required to detect odds ratios (ORs) from 2 to 5 for different levels of vaccination coverage, assuming a power of 80%, a probability of type-I error at 5%, and control-to-case ratio of 1:1, 2:1, 3:1 and 4:1.



### 11.5.10.2 Total catchment population

The methodology for calculating the catchment population is described in ANNEX 4.

Table 5 and Table 6 show the catchment populations required to detect ORs of 2 to 5 for AESIs with background rates from 0.1 to 1000 per 100,000 people per year, 25%, 50% and 75% vaccination coverage, and control-to-case ratios ranging from 1:1 to 4:1. In settings with a mid-level vaccination coverage, the catchment area required to detect a certain relative risk is lower than in settings with a vaccination coverage nearing the lower or higher extremes.

Detecting an OR of 2 may be feasible for common AESIs. For very rare AESIs, the catchment area required to detect a low OR is likely to be prohibitively large. However, from a public health benefit-risk perspective, being able to detect a high OR for rare events may be sufficient; a low OR will only result in a small number of additional cases which is unlikely to affect the benefit-risk balance of the vaccination programme.

**Table 5:** Catchment population required to detect an odds ratio (OR) of 2 to 5 for AESIs with known annual background rates varying from 0.1 to 1,000 per 100,000 people per year at three different levels of vaccination coverage (in controls), control-to-case ratios of 1:1 and 2:1 (probability of type-I error at 5%, and power at 80%)

Expected odds ratio	Background rate per 100,000 people per year	Catchment area (n) for different levels of vaccination coverage (VC) and control-to-case ratio of 1:1			Catchment area (n) for different levels of vaccination coverage (VC) and control-to-case ratio of 2:1		
		VC=25%	VC=50%	VC=75%	VC=25%	VC=50%	VC=75%
2	0.1	121,600,109	91,333,440	121,714,451	89,600,081	68,666,747	93,714,413
	1	12,160,109	9,133,440	12,171,594	8,960,081	6,866,747	9,371,556
	10	1,216,109	913,440	1,217,308	896,081	686,747	937,270
	100	121,709	91,440	121,879	89,681	68,747	93,841
	1,000	12,269	9,240	12,337	9,041	6,947	9,499
3	0.1	38,666,725	29,000,058	38,800,089	28,666,710	22,000,044	30,400,070
	1	3,866,725	2,900,058	3,880,089	2,866,710	2,200,044	3,040,070
	10	386,725	290,058	388,089	286,710	220,044	304,070
	100	38,725	29,058	38,889	28,710	22,044	30,470
	1,000	3,924	2,958	3,969	2,909	2,244	3,110
4	0.1	20,571,474	15,600,045	20,615,452	14,857,176	12,000,035	16,307,746
	1	2,057,188	1,560,045	2,061,606	1,485,747	1,200,035	1,630,823
	10	205,760	156,045	206,221	148,604	120,035	163,130
	100	20,617	15,645	20,683	14,890	12,035	16,361
	1,000	2,102	1,605	2,129	1,518	1,235	1,684
5	0.1	13,500,041	10,333,373	13,500,057	10,000,030	7,666,696	10,750,046
	1	1,350,040	1,033,373	1,350,057	1,000,030	766,696	1,075,046
	10	135,040	103,373	135,057	100,030	76,696	107,546
	100	13,540	10,373	13,557	10,030	7,696	10,796
	1,000	1,390	1,073	1,407	1,030	796	1,121

**Table 6:** Catchment population required to detect an odds ratio (OR) of 2 to 5, for AESIs with known annual background rates varying from 0.1 to 1,000 per 100,000 people per year at three different levels of vaccination coverage (in controls), and control-to-case ratios of 3:1 and 4:1 (probability of type-I error at 5%, and power at 80%)

Expected odds ratio	Background rate per 100,000 people per year	Catchment area (n) for different levels of vaccination coverage (VC) and control-to-case ratio of 3:1			Catchment area (n) for different levels of vaccination coverage (VC) and control-to-case ratio of 4:1		
		VC=25%	VC=50%	VC=75%	VC=25%	VC=50%	VC=75%
2	0.1	78,400,071	61,333,405	84,000,114	73,600,066	57,333,400	79,428,679
	1	7,840,071	6,133,405	8,400,114	7,360,066	5,733,400	7,942,965
	10	784,071	613,405	840,114	736,066	573,400	794,394
	100	78,471	61,405	84,114	73,666	57,400	79,536
	1,000	7,910	6,205	8,514	7,426	5,800	8,051
3	0.1	24,666,704	19,500,039	27,600,063	23,333,368	18,500,037	26,000,060
	1	2,466,704	1,950,039	2,760,063	2,333,368	1,850,037	2,600,060
	10	246,704	195,039	276,063	233,368	185,037	260,060
	100	24,704	19,539	27,663	23,368	18,537	26,060
	1,000	2,503	1,989	2,823	2,368	1,887	2,660
4	0.1	13,142,886	10,800,031	15,076,972	12,000,027	10,000,029	14,153,892
	1	1,314,315	1,080,031	1,507,742	1,200,027	1,000,029	1,415,431
	10	131,458	108,031	150,819	120,027	100,029	141,585
	100	13,172	10,831	15,126	12,027	10,029	14,200
	1,000	1,343	1,111	1,557	1,226	1,029	1,462
5	0.1	8,500,026	7,000,027	10,000,043	8,000,024	6,666,692	9,500,040
	1	850,025	700,027	1,000,042	800,024	666,692	950,040
	10	85,025	70,027	100,042	80,024	66,692	95,040
	100	8,525	7,027	10,042	8,024	6,692	9,540
	1,000	875	727	1,042	824	692	990

## 11.5.11 Data analysis

### 11.5.11.1 Descriptive analysis of demographics

Demographic and medical characteristics will be summarized using descriptive statistics. Analyses will be performed by [SITE/COUNTRY/REGION].

The characteristics of cases and controls will be described. The mean and standard deviation or median and range will be calculated, overall and by sex. Frequencies (%) of the [OTHER VARIABLES] will be provided by age group and sex for cases and controls separately. The following age groups will be considered for analysis [TO BE DEFINED DEPENDING ON AESI]. Levels of diagnostic certainty of the cases will be described, if applicable.



### 11.5.11.2 Statistical analysis

The OR comparing the odds of vaccination among cases with the AESI to the odds of vaccination among controls will be calculated by dose and by vaccine brand using conditional logistic regression, while adjusting for calendar time, sex, presence of chronic conditions and socioeconomic status. The analyses will be conducted overall and for the following age groups: [TO BE DEFINED DEPENDING ON AESI]. Adjusted and unadjusted ORs and their 95% CIs will be calculated.

## Standardized analyses

---

### 12.1 Multi-site recruitment

It is important to achieve a sample that represents a cross-section of the population, but the patients will be recruited for the study at selected hospitals sites that may be specialized for the AESI, and, therefore, the geographical area may not be fully representative of the target population. Better representativity may be achieved if multiple sites within large catchment areas participate. Appropriate measures to collect standardized data from the study sites can facilitate pooling of data. ANNEX 5 provides a data dictionary of information to collect in a standardized manor to aid pooling of data.

### 12.2 Different COVID-19 vaccines

It is important to analyse the OR for the AESI under investigation according to the COVID-19 vaccine brand or platform. Data collection of exposure variables will distinguish which vaccine(s) the patients were exposed to.

# 13

## Data management

---

A data management plan (DMP) and standard operating procedures (SOPs) describing all functions, processes, security, and specifications for data collection, cleaning and validation will be prepared before data collection begins.

### 13.1 Data entry using an electronic tool

An electronic tool will be provided for data entry at the sites. The electronic tool will allow investigators to enter data on the outcomes, the exposure of interest, and other variables. The use of electronic reporting will be optional, if available, otherwise paper forms will be sufficient.

In addition, for the SCRI study, the tool can be used to calculate whether a person is in the risk or self-control period for a particular AESI, by specifying the AESI, the date of vaccination and the event date.

Automated data quality checks will detect and flag up out-of-range or anomalous data, where applicable.

<<The specifications of the electronic tool, the software used, and data storage should be described.>>

User testing of the electronic data entry tool will be performed prior to deployment.

#### 13.1.1 Data security

<<The processes for anonymization, access, storage and destruction of raw data should be described.>>

The key-coded data obtained from this study will be stored in a secured database located in [COUNTRY]. Data will be protected through [TO SPECIFY SECURITY IN PLACE]. Data will be handled in accordance with all applicable data protection and privacy laws. No unauthorized persons will have access to the data. Data will be archived for [XXX] years, as per national regulations, and will then be destroyed.

This information is also included in the informed consent form (ANNEX 7).

### 13.2 Data transfer

<<The processes for data transfer including security should be described.>>

## 13.3 Data retention and archiving

Documents that individually and collectively permit to evaluate the conduct of the study and the quality of the data produced will be retained for [TIME PERIOD AS APPLICABLE] in accordance with [GOOD PHARMACOEPIDEMOLOGICAL PRACTICE (GEP) GUIDELINES/LOCAL REGULATIONS, TO BE DETAILED HERE] [2]. This will include the analytical data, programmes, and all output generated.

# 14 Quality assurance, monitoring and reporting

---

## 14.1 Monitoring

A site initiation visit (either on-site or remote) will be conducted to ensure that the site is ready to start data collection. Study staff will be trained on the study procedures.

Monitoring of the study conduct will be performed throughout the study period to assess compliance with the study protocol, and the accuracy and completeness of the data. The monitoring will be remote or on-site, whichever is the most appropriate taking into account the COVID-19 pandemic situation. Study monitoring will be performed by [INSERT NAME OF MONITORING GROUP].

Study sites may be subject to a quality assurance visit by [TO BE COMPLETED]. If so, the site will be contacted in advance to arrange the visit. The investigator and site study staff will guarantee direct access to all study documents for quality assurance monitors.

## 14.2 Periodic reporting

Periodic reporting will be done [TO BE DEFINE AS APPROPRIATE].

If the observed rates of adverse event are different from the expected rates (as per clinical trial data and reported in the summary of product characteristic of a given vaccine), the study team should alert the national regulatory authorities for regulatory review.

## 14.3 Final analyses and reporting

Final analyses will be performed and a full study report will be written within four weeks after database lock. Study results will be shared with the national regulatory authorities for regulatory review, and with the national immunization programme to inform policy decision.

# 15 Study management

---

This study will be performed, including development of materials, recruitment, training and management of sites, electronic data capture, data management and analyses, by the investigator, with guidance, input, review and approval of the sponsor.

The investigator and all study staff will conduct the study in compliance with the [NAME ETHICS COMMITTEE] approved version of this protocol. All personnel involved in the conduct of this study will be qualified by education, training and experience to perform their tasks.

## 15.1 Data transfer

[PROCESS FOR DATA TRANSFER, INCLUDING SECURITY, TO BE DESCRIBED]

## 15.2 Data retention and archiving

Documents that individually and collectively permit evaluation of the study conduct and the quality of the data produced will be retained for [TIME PERIOD AS APPLICABLE] in accordance with good pharmacoepidemiological practice guidelines [12] and [LOCAL REGULATIONS, to be detailed in the site-specific protocol]. This will include the analytical data, analyses programs, and all output generated.

## 15.3 National pharmacovigilance centre/ AEFI committee/national immunization programme manager/dedicated scientific committee

The [NATIONAL PHARMACOVIGILANCE CENTER/AEFI COMMITTEE/NATIONAL IMMUNIZATION PROGRAMME MANAGER/DEDICATED SCIENTIFIC COMMITTEE] will oversee the implementation and smooth running of this study. They will provide scientific, statistical and technical expertise, as needed.

## 15.4 Changes to the protocol

Changes to the protocol will be documented in written protocol amendments and will be listed in Section 5. Major amendments will usually require submission to the relevant institutional review board (IRB)/independent ethics committee (IEC) for approval. In such cases, the amendment will be implemented only after approval has been obtained.

Minor protocol amendments, including administrative changes, will be filed by the investigator at each participating site and will be submitted to the relevant IRB/IEC. Any amendment that could have an impact on the patient's consent to participate in the study will require signature of a new written- informed consent form prior to continued participation in the study.

## 15.5 Management and reporting of adverse events and adverse reactions

The study team will ensure that healthcare workers in study sites are familiar with the national AEFI reporting and management processes as per national guidelines. The study team will liaise with the national immunization programme/national regulatory authorities to ensure that provisions are in place (including AEFI reporting forms, procedures, and training) for smooth implementation.

Adverse events will be assessed at the level of the population. Individual causality assessment will be done as part of routine vaccine safety surveillance, and not by this study investigation team. Consent will be sought to use patients' medical records in case the [NATIONAL AEFI FOCAL POINT/NATIONAL PHARMACOVIGILANCE CENTRE] needs to investigate further any potential safety signals that arise from the study.

The study team should be reminded that all serious AEs detected and reported in the context of this study should be reported through the routine AEFI surveillance system to the responsible institution within the Ministry of Health (national immunization programme/national regulatory authorities/pharmacovigilance centre), to ensure timely investigation, causality assessment and response as per the country protocol.

<<Describe mechanisms/processes to ensure that all AEsIs detected and reported in the context of this study are also reported through the routine AEFI surveillance system to the responsible institution within the Ministry of Health (national immunization programme / national regulatory authorities/pharmacovigilance centre), to ensure timely investigation, causality assessment and response as per the country protocol.>>

In the event a safety signal is detected, [DESIGNATED STUDY TEAM/NATIONAL AEFI FOCAL POINT/NATIONAL PHARMACOVIGILANCE CENTER] may decide to contact the healthcare provider of patients, for whom safety signals have arisen, for further investigation through [APPROPRIATE NATIONAL ROUTES].

# 16

## Ethical considerations

---

### 16.1 Guiding principles

To ensure the quality and integrity of research, this study will be conducted under the international ethical guidelines for health-related research involving humans published by the Council for International Organizations of Medical Sciences (CIOMS) [1], good epidemiological practice (GEP) guidelines [2], the ethical principles in the Declaration of Helsinki [3] and any applicable national laws, regulations and guidelines.

This is an observational study without medical intervention or changes in clinical and diagnostic practices. Therefore, there is no direct benefit to the participants. Nevertheless, there will be potentially important societal benefits from this vaccine safety study. COVID-19 vaccines are key to controlling the pandemic. Close monitoring of the first cohorts vaccinated with COVID-19 vaccine will be important for these novel vaccines, to ensure safety and to maintain public confidence in vaccines.

### 16.2 Respecting participants' autonomy

The study will use data from medical records collected as part of healthcare provision at participating hospital(s) and data from patients' vaccination histories. Patients eligible as cases or controls will be approached by [TO COMPLETE AS APPROPRIATE], who will inform them about the study and the patients will have the opportunity to ask questions. Informed consent must be obtained prior to the patients' participation in the study (ANNEX 7). The study-specific ICF will explain the purpose of the data collection, the foreseeable uses of the data, the intended goals of such uses, who has access to data, the conditions and duration of data

storage, and the ways in which the participants can contact the data custodian and remain informed about future data use. The ICF will explain that the patients' participation is completely voluntary and that they are free to withdraw at any time during the study.

<<The ICF template and process will need to be adapted for special populations, e.g., those requiring surrogate decision-makers such as parents, or adult children) or study advocates (e.g., prisoners, orphans). The adapted ICF must be approved in the ethics review process.>>

## 16.3 Participant confidentiality

No data will be used, either alone or in conjunction with any other information, to establish the identity of any of the participants from whom data were obtained. All parties will ensure protection of the patients' personal data and will not include patients' names or other information that can be used to identify the patient (e.g., date of birth, address) on any study forms, reports, publications, or in any other disclosures, except where required by law. Local data protection and privacy regulations [TO BE DETAILED IN THE SITE-SPECIFIC PROTOCOL] will be observed in capturing, forwarding, processing, and storing patient data.

## 16.4 Independent Ethics Committee/ Institutional Review Board

Participating study sites will submit the site-specific protocols to [NAME OF ETHICS COMMITTEE(S)/ NAME OF INSTITUTIONAL REVIEW BOARD(S), FOLLOWING LOCAL REGULATIONS< TO BE DETAILED HERE] and will comply with any national ethics committee requirements.

# 17 Dissemination of study results

---

<<Describe how and to whom study results will be made available, including whether study results will be disseminated to participants and how.>>

## Study limitations

---

If reliable vaccination registers are not available to determine COVID-19 vaccine exposure status, this information will be obtained via patient self-report. This could increase the risk of introducing misclassification bias if patients who were vaccinated report that they were not since these patients will be classified as unexposed. These patients will be excluded from the SCRI study (as only vaccinated patients will be enrolled) but they will be analysed as unexposed in the case-control study. Additionally, medical records may also be of poor quality and information may be missing on risk factors and it might be difficult to have accurate timing for events. The protocol is restricted to hospitalized patients hence another limitation is that it will not capture AESIs that do not result in hospitalization.



# 19

## References

---

- [1] (CIOMS) CfIOOMS. International ethical guidelines for health-related research Involving humans. Geneva: CIOMS; 2016. Last accessed 17 March 2021; Available from: <https://cioms.ch/wp-content/uploads/2017/01/WEB-CIOMS-EthicalGuidelines.pdf>.
- [2] Public Policy Committee ISoP. Guidelines for good pharmacoepidemiology practice (GPP). *Pharmacoepidemiol Drug Saf.* 2016;25:2-10.
- [3] World Medical Association. WMA Declaration of Helsinki - ethical principles for medical research involving human subjects. 2013. Last accessed 9 March 2021; Available from: <https://www.wma.net/policies-post/wma-declaration-of-helsinki-ethical-principles-for-medical-research-involving-human-subjects/>.
- [4] World Health Organization. Investigation of safety signals. To strengthen the ability of countries to evaluate vaccine safety signals.: World Health Organization; 2019. Available from: [https://www.who.int/vaccine\\_safety/initiative/investigation/en/#:~:text=A%20vaccine%20safety%20signal%20is,documented%2C%20that%20could%20affect%20health.](https://www.who.int/vaccine_safety/initiative/investigation/en/#:~:text=A%20vaccine%20safety%20signal%20is,documented%2C%20that%20could%20affect%20health.)
- [5] World Health Organization. Covid-19 vaccines: safety surveillance manual. Geneva2020. Last accessed 11 March 2021; Available from: <https://www.who.int/publications/item/10665338400>.
- [6] Law B. SO2-D2.1.2 Priority List of COVID-19 Adverse events of special interest: Quarterly update December 2020. Safety Platform for Emergency vACcines (SPEAC); 2021. Last accessed 11 March 2021; Available from: [https://brightoncollaboration.us/wp-content/uploads/2021/01/SO2\\_D2.1.2\\_V1.2\\_COVID-19\\_AESI-update\\_V1.3.pdf](https://brightoncollaboration.us/wp-content/uploads/2021/01/SO2_D2.1.2_V1.2_COVID-19_AESI-update_V1.3.pdf).
- [7] Brighton Collaboration. Brighton Collaboration case definition companion guides. 2021. Last accessed 19 March 2021; Available from: <https://brightoncollaboration.us/category/pubs-tools/case-definitions/companion-guides/>.

### Annex 1

#### Adverse events of special interest

The following is a list of AESIs based on the SPEAC list version 23 December 2020 [6]. These AESIs have either:

- proven association with immunization that is true for most, if not all, vaccines;
- proven association with a known vaccine platform or adjuvant that is being used in any COVID-19 vaccine;
- theoretical concern based on immunopathogenesis of COVID-19 disease;
- theoretical concern related to viral replication during COVID-19 infection;
- theoretical concern that has been demonstrated in an animal model with one or more candidate vaccine platforms; or
- emerging safety signal during vaccine development and/or deployment.

Please refer to the [WHO COVID-19 vaccines: safety surveillance manual](#) and [SPEAC](#) for updates of the AESIs lists.

**Table A1-1:** Adverse events of special interest (AESI), their risk windows, and recommended study design.

No.	Body system	AESI	Risk interval	Study design
1	Cardiac	Acute cardiovascular injury	D1-D42	SCRI
2	Dermatologic	Chilblain-like lesions	D1-D42	SCRI
3	Dermatologic	Single organ cutaneous vasculitis	D1-D42	SCRI
4	Dermatologic	Erythema multiforme	D1-D42	SCRI
5	Endocrine	Acute pancreatitis	D1-14	SCRI
6	Endocrine	Subacute thyroiditis	D1-42	SCRI
7	Gastrointestinal	Acute liver injury	D1-D42	SCRI
8	Hematologic	Coagulation disorder (thromboembolism)	D1-D42	SCRI
9	Hematologic	Thrombocytopenia	D1-D42	SCRI
10	Hematologic	Thrombosis and thrombocytopenia syndrome (TTS)	D1-*	
11	Immunologic	Vaccine-associated enhanced disease (VAED)	Unknown	CC
12	Immunologic	Multisystem inflammatory syndrome	D1-D42	SCRI
13	Immunologic	Anaphylaxis	D0-D7	SCRI
14	Musculoskeletal	Acute aseptic arthritis	D1-D42	SCRI
15	Musculoskeletal	Rhabdomyolysis	D1-D7*	SCRI
16	Neurologic	Acute disseminated encephalomyelitis (ADEM)	D1-D42	SCRI
17	Neurologic	Bell's Palsy	D1-D48	SCRI
18	Neurologic	Generalized convulsion	D1-D7	SCRI
19	Neurologic	Guillain Barré Syndrome (GBS)	D1-D42	SCRI
20	Neurologic	Meningoencephalitis	D1-D42	SCRI
21	Renal	Acute kidney injury	D1-D42	SCRI
22	Respiratory	Acute respiratory distress syndrome	D1-D42	SCRI

CC: case-control; SCRI: self-controlled risk interval

\*Sensitivity analysis with a risk interval 1-14 days may be considered, or multiple risk windows should be considered and recent literature/insights should be consulted prior to selecting risk interval

## Annex 2

### Case definitions

New Brighton Collaboration case definitions are being developed. The latest status of available Brighton Collaboration case definitions can be accessed at: <https://brightoncollaboration.us/covid-19/>. Case definition companion guides are available from: <https://brightoncollaboration.us/category/pubs-tools/case-definitions/companion-guides/>

**Table A2-1:** Adverse events of special interest (AESI), and Brighton Collaboration (BC) case definitions (if available).

No.	Body system	AESI	Brighton Collaboration case definition
1	Cardiac	Acute cardiovascular injury	Definition of myocarditis/pericarditis is under development, expected in pre-publication form end of February/early March 2021. No other Brighton Collaboration case definition currently available.
2	Dermatologic	Chilblain-like lesions	No Brighton Collaboration case definition currently available.*
3	Dermatologic	Single organ cutaneous vasculitis	Zanoni G, Girolomoni G, Bonetto C, Trotta F, Häusermann P, Opri R, et al. Single organ cutaneous vasculitis: Case definition & guidelines for data collection, analysis, and presentation of immunization safety data. <i>Vaccine</i> . 2016;34:6561-71. 10.1016/j.vaccine.2016.09.032
4	Dermatologic	Erythema multiforme	No Brighton Collaboration case definition currently available.*
5	Endocrine	Pancreatitis	No Brighton Collaboration case definition currently available.*
6	Endocrine	Subacute thyroiditis	No Brighton Collaboration case definition currently available.*
7	Gastrointestinal	Acute liver injury	No Brighton Collaboration case definition currently available.*  It is proposed to use the following definition: — >3-fold elevation above the normal upper limit for ALT or AST; or — >2-fold elevation above the normal upper limit for total serum bilirubin or GGT or ALP — As done by Cai, measuring all four liver enzymes (ALT, AST, GGT, ALP) and total serum bilirubin will enable to define the pattern of injury as hepatocytic, cholangiocytic or mixed and whether it is a type 1 ALI (ALT/AST > GGT/ALP) or Type 2 ALI (ALT/AST < GGT/ALP).

No.	Body system	AESI	Brighton Collaboration case definition
8	Hematologic	Coagulation disorder (thromboembolism)	Thrombotic disorders, including stroke, deep vein thrombosis, pulmonary embolism etc.: Under development, expected in pre-publication form end of February/early March 2021. Coagulopathy-bleeding disorder: Under development, expected in pre-publication form in May/July 2021.
9	Hematologic	Thrombocytopenia	Wise RP, Bonhoeffer J, Beeler J, Donato H, Downie P. Thrombocytopenia: case definition and guidelines for collection, analysis, and presentation of immunization safety data. <i>Vaccine</i> . doi: 2007;25:5717-24. 10.1016/j.vaccine.2007.02.067  Brighton Collaboration standardized case definitions and guidelines for adverse events following immunization ( <a href="https://brightoncollaboration.us/thrombocytopenia-case-definition-companion-guide/">https://brightoncollaboration.us/thrombocytopenia-case-definition-companion-guide/</a> ).
10	Hematologic	Thrombosis and thrombocytopenia syndrome (TTS)	<a href="https://brightoncollaboration.us/draft-case-definition-of-thrombosis-and-thromboembolism/">https://brightoncollaboration.us/draft-case-definition-of-thrombosis-and-thromboembolism/</a>
11	Immunological	Vaccine-associated enhanced disease (VAED)	Munoz FM, Cramer JP, Dekker CL, Dudley MZ, Graham BS, Gurwith M, et al. Vaccine-associated enhanced disease: Case definition and guidelines for data collection, analysis, and presentation of immunization safety data. <i>Vaccine</i> . 2021:S0264-410X(21)00094-3. doi: 10.1016/j.vaccine.2021.01.055.
12	Immunological	Multisystem inflammatory syndrome	Vogel TP, Top KA, Karatzios C, Hilmers DC, Tapia LI, Mocerri P, et al. Multisystem inflammatory syndrome in children and adults (MIS-C/A): Case definition & guidelines for data collection, analysis, and presentation of immunization safety data. <i>Vaccine</i> . 2021:S0264-410X(21)00093-1. doi: 10.1016/j.vaccine.2021.01.054.
13	Immunological	Anaphylaxis	Rüggeberg J, Gold M, Bayas J, Blum M, Bonhoeffer J, Friedlander S, et al. Anaphylaxis: case definition and guidelines for data collection, analysis, and presentation of immunization safety data. <i>Vaccine</i> . 2007;25:5675-84. doi: 10.1016/j.vaccine.2007.02.064
14	Musculoskeletal	Acute aseptic arthritis	Woerner A, Pourmalek F, Panozzo C, Pileggi G, Hudson M, Caric A, et al. Acute aseptic arthritis: case definition and guidelines for data collection, analysis, and presentation of immunisation safety data. <i>Vaccine</i> . 2019;37:384-91. doi: 10.1016/j.vaccine.2017.08.087
15	Musculoskeletal	Rhabdomyolysis	No Brighton Collaboration case definition available currently*.

No.	Body system	AESI	Brighton Collaboration case definition
16	Neurological	Acute disseminated encephalomyelitis (ADEM)	Sejvar JJ, Kohl KS, Bilynsky R, Blumberg D, Cvetkovich T, Galama J, et al. Encephalitis, myelitis, and acute disseminated encephalomyelitis (ADEM): case definitions and guidelines for collection, analysis, and presentation of immunization safety data. <i>Vaccine</i> . 2007;25:5771-92. doi: 10.1016/j.vaccine.2007.04.060
17	Neurological	Bell's Palsy	Rath B, Gidudu JF, Anyoti H, Bollweg B, Caubel P, Chen Y-H, et al. Facial nerve palsy including Bell's palsy: case definitions and guidelines for collection, analysis, and presentation of immunisation safety data. <i>Vaccine</i> . 2017;15:1972-83. doi: 10.1016/j.vaccine.2016.05.023
18	Neurological	Generalized convulsion	Bonhoeffer J, Menkes J, Gold MS, de Souza-Brito G, Fisher MC, Halsey N, et al. Generalized convulsive seizure as an adverse event following immunization: case definition and guidelines for data collection, analysis, and presentation. <i>Vaccine</i> . 2004;22:557-62. doi: 10.1016/j.vaccine.2003.09.008
19	Neurological	Guillain Barré Syndrome (GBS)	Sejvar J, Kohl K, Gidudu J, Amato A, Bakshi N, Baxter R, et al. Guillain-Barré syndrome and Fisher syndrome: case definitions and guidelines for collection, analysis, and presentation of immunization safety data. <i>Vaccine</i> . 2011;29:599-612. doi: 10.1016/j.vaccine.2010.06.003
20	Neurological	Meningoencephalitis	Tapiainen T, Prevots R, Izurieta HS, Abramson J, Bilynsky R, Bonhoeffer J, et al. Aseptic meningitis: case definition and guidelines for collection, analysis and presentation of immunization safety data. <i>Vaccine</i> . 2007;25:5793-802. doi: 10.1016/j.vaccine.2007.04.058  Sejvar JJ, Kohl KS, Bilynsky R, Blumberg D, Cvetkovich T, Galama J, et al. Encephalitis, myelitis, and acute disseminated encephalomyelitis (ADEM): case definitions and guidelines for collection, analysis, and presentation of immunization safety data. <i>Vaccine</i> . 2007;25:5771-92. doi: 10.1016/j.vaccine.2007.04.060
21	Renal	Acute kidney injury	No Brighton Collaboration case definition available currently*.
22	Respiratory	Acute respiratory distress syndrome (ARDS)	Serazin NA, Edem B, Williams SR, Ortiz JR, Kawade A, Das MK, et al. Acute respiratory distress syndrome (ARDS) as an adverse event following immunization: Case definition & guidelines for data collection, analysis, and presentation of immunization safety data. <i>Vaccine</i> . 2021:S0264-410X(21)00092-X. doi: 10.1016/j.vaccine.2021.01.053

\* A Brighton Collaboration case definition could be rapidly developed if signal detected

## Annex 3

### Catchment population calculation for SCRI study design

First, we assume:

- everyone is vaccinated at once, at time  $t$ , and AESIs are detectable for everyone.
- adverse events are so rare that they either happen in the risk interval or in the self-control interval (but not in both).

Let:

- the incidence rate of an AESI in the self-control period be  $r$  per person per day. That is, the cumulative incidence in a self-control interval of length  $T_c$  days is  $1 - e^{-r \times T_c}$ ;
- the relative incidence of an AESI in the risk interval versus the self-control interval be  $RI$ . That is, the incidence rate of the AESI is  $r \times RI$  per person per day, and the cumulative incidence in the risk interval of  $T_r$  days is  $1 - e^{-r \times RI \times T_r}$ ;
- vaccination coverage be  $p_v$ . That is, if the catchment population is  $N$ , then only  $N \times p_v$  people belong to the target population for this study.

Under these assumptions, the relationship between the total number of cases  $C$  we will observe in the whole observation period, and the catchment population  $N$ , is given by:

$$C = (1 - e^{-(r \times T_c + r \times RI \times T_r)}) \times (N \times p_v)$$
$$\Rightarrow N = \frac{C}{(1 - e^{-(r \times T_c + r \times RI \times T_r)}) \times p_v}$$

## Annex 4

### Catchment population calculation for case-control study design

First, we assume:

- the total follow-up period of the case-control study is  $T$  days;
- the catchment population is  $N$ , out of which  $N \times p_v$  people are vaccinated, where  $p_v$  is vaccination coverage in the population;
- all vaccinations happen at time 0.

Let the following be the table of vaccination status and case or control status:

	Case ( $c$ )	Control ( $nc$ )
Vaccinated ( $v$ )	$p_c v$	$1 - p_c v$
Unvaccinated ( $nv$ )	$p_c nv$	$1 - p_c nv$

Here,  $p_c|v$  is the probability of being a case when a person is vaccinated, and  $p_c|nv$  is the probability of being a case when a person is not vaccinated, over the follow-up period of  $T$  days. If the background rate of the AESI in unvaccinated people is  $r$  per person per day, then  $p_c|nv = 1 - e^{-r \times T}$ . In general, in a  $2 \times 2$  table, the exposure (vaccination) odds ratio is equal to disease odds ratio. We denote this odds ratio by  $OR$  and it is given by:

$$OR = \frac{\frac{p_c|v}{1 - p_c|v}}{\frac{p_c|nv}{1 - p_c|nv}}$$

$$\Rightarrow p_c|v = \left( 1 + \frac{1}{OR \times \frac{p_c|nv}{1 - p_c|nv}} \right)^{-1}$$

$$\Rightarrow p_c|v = \left( 1 + \frac{e^{-r \times T}}{OR \times (1 - e^{-r \times T})} \right)^{-1}$$

Under these assumptions, the relationship between the total number of cases  $C$  we will observe in the whole observation period  $T$ , and the catchment population  $N$ , is given by:

$$C = p_c|nv \times N \times (1 - p_v) + p_c|v \times N \times p_v$$

$$\Rightarrow C = N \times (p_c|nv \times (1 - p_v) + p_c|v \times p_v)$$

$$\Rightarrow N = \frac{C}{p_c|nv \times (1 - p_v) + p_c|v \times p_v}$$



# Annex 5

## Data dictionary

Note: Some variables are only applicable for case-control design (with a note [ONLY FOR CASE-CONTROL STUDY] in the values and coding column)

Variables in purple are unique variables that can potentially play the role as the key for a specific table in the relational database.

Variable name	Type	Values and coding	Definition
<b>Table 1: Site information</b>			
siteID	Type of variable at the discretion of site	[needs to be unique]	Unique and persistent identifier for each site
PIID	Type of variable at the discretion of site	[needs to be unique]	Unique and persistent identifier for each investigator at each site. This field might be a unique combination of <i>siteID</i> and a specific character assigned to an investigator
siteName	Text	Text	Name of the site
siteAdd	Text	Text	Address of the site
siteCity	Text	Text	City/province of the site
siteCountry	Text	Text	Country of the site
<b>Table 2: Investigator information</b>			
Table 2 is linked to Table 1 by <i>PIID</i>			
PIID	Type of variable at the discretion of site	[needs to be unique]	Unique and persistent identifier for each investigator at each site. This field might be a unique combination of <i>siteID</i> and a specific character assigned to an investigator
PIworkAdd	Text	Text	Work address for the investigator
PIphone	Number	Number	Phone number for the investigator
<b>Table 3: Patient information</b>			
Table 3 is linked to Table 1 by <i>siteID</i>			
siteID	Type of variable at the discretion of site	[needs to be unique]	Unique and persistent identifier for each site

Variable name	Type	Values and coding	Definition
subjectID	Type of variable at the discretion of site	[needs to be unique]	Unique and persistent identifier for each subject
caseControl	Numeric (binary)	0 = Control 1 = Case [ONLY FOR CASE-CONTROL STUDY]	If a selected patient is a case or a control.
screeningYes	Numeric (binary)	0 = No 1 = Yes	If the investigators decided to contact the patient about the study.
consent	Numeric (binary)	0 = No 1 = Yes	informed consent provided (Only if screening Yes = 1)
subjAdd	Text	Text [ONLY FOR CASE-CONTROL STUDY]	Current place of residence
subjAddProvince	Text	Text [ONLY FOR CASE-CONTROL STUDY]	Current place of residence (Province)
subjEligibleVacc	Numeric (binary)	0 = No 1 = Yes [ONLY FOR CASE-CONTROL STUDY]	Is the participant eligible for COVID-19 vaccination (as per local eligibility criteria, e.g. age-defined policy) four weeks prior to symptom onset?
<b>Patient covariates</b>			
subjDoB	Date	mm/dd/yyyy	Patient's date of birth
subjSex	Numeric (multinomial)	0 = Male 1 = Female 2 = Other	Sex of patient
subjPreg	Numeric (multinomial)	0 = No 1 = Yes 2 = Not applicable	Is the patient pregnant (Only if subjSex = 1)
subjDeliveryDate	Date	mm/dd/yyyy	The estimated date of delivery (Only if subjPreg = 1)
subjLactation	Numeric (binary)	0 = No 1 = Yes 2 = Not applicable	Is the participant breastfeeding. (Only if subjSex = 1)
subjSocioEco	Text	[levels to be defined locally] [Recommendation: creation of dropdown list with a list of predefined socio-economic class]	The socio-economic class of the patient

Variable name	Type	Values and coding	Definition
subjRisk	Numeric (binary)	0 = No 1 = Yes	Does the patient belong to a risk group of interest?
subjRiskGrp	Text	[Recommendation: Creation of a dropdown list with a list of risk groups of interest, e.g., asthma, chronic heart, etc. Have one category as "Other" to specify any other risk groups not listed in the text]	Which risk group does the patient belong to? (Only if subjRisk = 1)
subjRiskGrpComment	Text	Text	Comment related to patient's risk group (Only if subjRiskGrp = "Other")
subjPrevCOVID19	Numeric (binary)	0 = No 1 = Yes	Has the patient experienced previous or current COVID-19 disease?
subjPrecCOVID19onsetdate	Date	mm/dd/yyyy	Date of onset
subjPrevCOVID19Dig	Numeric (binary)	0 = Probable COVID-19 1 = COVID-19 diagnosis with laboratory-confirmed & no hospitalization 2 = COVID-19 diagnosis with laboratory-confirmed & hospitalization	Details regarding the COVID-19 diagnosis of the patients (Only if subjPrevCOVID19 = 1)
<b>Patient exposure of interest</b>			
subjVaccExposure	Numeric (binary)	0 = No 1 = Yes	Patient received at least one dose of any COVID-19 vaccine administered in routine clinical practice
doseReceive	Numeric	1 = 1 vaccine dose 2 = 2 vaccine doses	Number of COVID-19 vaccine doses received by the patient
firstDoseID		[needs to be unique]	A unique identification number of the first vaccine dose
secondDoseID		[needs to be unique]	A unique identification number of the second vaccine dose (Only if doseReceive = 2)
<b>Patient outcomes of interest</b>			
aeSiTotal	Numeric		Number of AESIs (that are study outcomes) experienced by the participant?

Variable name	Type	Values and coding	Definition
aes11ID		[needs to be unique]	A unique identification number of the first recorded AESI.
aes21ID		[needs to be unique]	A unique identification number of the second recorded AESI.
aes31ID		[needs to be unique] [This list can include up to a maximum of 10 AESIs]	A unique identification number of the third recorded AESI.

**Table 4:** Vaccine exposure information

Table 4 can be linked to Table 3 by *doseID* & Table3 *firstDoseID*, Table3 *secondDoseID*

doseID	Numeric	[needs to be unique]	Unique identification number of vaccine dose
vaccDate	Date	dd/mm/yyyy	Date of vaccination
vaccBrand	Numeric (multinomial)	1 – to list all brand/ manufacturers available in the country	Vaccine brand and manufacturer
vaccBatch	Text		Vaccine batch number
vaccSource	Numeric (multinomial)	1 = Use of registers 2 = Interview with patients 3 = Seen patient’s vaccine card 4 = Medical records 5 = Other (specify)	How vaccination history was obtained.
diluentRequired	Numeric (binary)	0 = No 1 = Yes	If details on diluent will be collected.
diluentBrand	Text	Diluent brand [Optional: Creation of a dropdown list of common diluent brands]	Only if diluentRequired = 1
diluentManf	Text	Diluent manufacturer [Optional: Creation of a dropdown list of common diluent manufacturers]	Only if diluentRequired = 1
diluentBatch	Text	Diluent batch number	Only if diluentRequired = 1

**Table 5:** Outcome information

Table 5 can be linked to Table 3 by *aesiID* & Table 3 *aesi1ID*, Table 3 *aesi2ID* to *aesiNID*

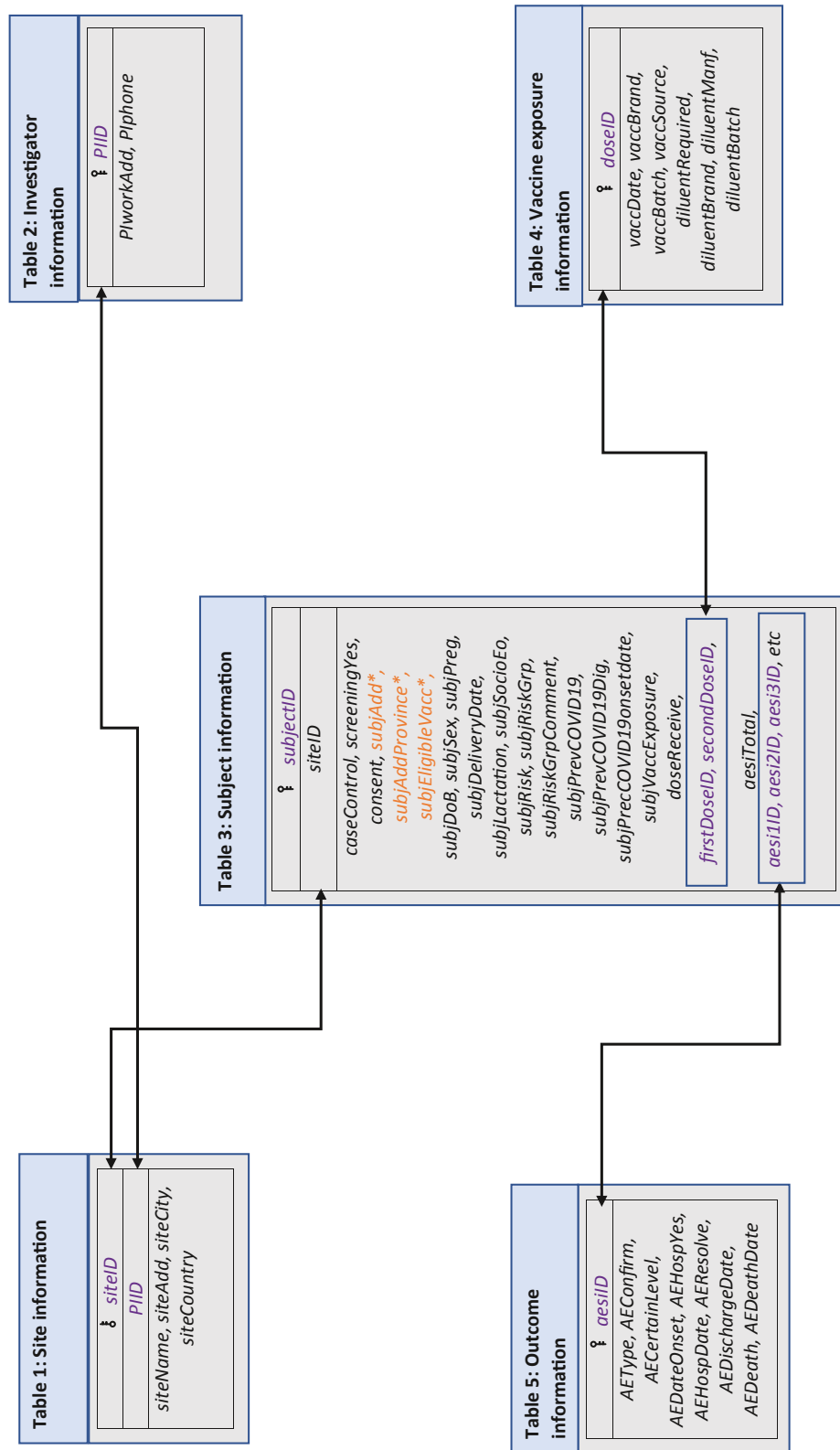
aesiID	Numeric	[needs to be unique]	A unique identification number of AESI
AEType	Text	AESI in the list provided in Annex 1, can be updated at the moment of the study [Recommendation: Creation of a dropdown list of AESIs, with a last option as “other” to record any relevant information]	AESI diagnosed

Variable name	Type	Values and coding	Definition
AEConfirm	Numeric (binary)	0 = No 1 = Yes	Confirmation of the AESI using predefined case definitions
AECertainLevel	Text (multinomial)	Text [Recommendation: Creation of a dropdown list of certainty level, as appropriate for each AESI]	Level of diagnostic certainty (if applicable)
AEDateOnset	Date	dd/mm/yyyy	Date of symptom onset
AEHospYes	Numeric (binary)	0 = No 1 = Yes	Patient hospitalized for this AESI
AEHospDate	Date	dd/mm/yyyy	Date of hospitalization for this AESI (Only if AEHospYes = 1)
AEResolve	Numeric (binary)	0 = No 1 = Yes	AESI already resolved?
AEDischargeDate	Date	dd/mm/yyyy	Date of discharge? (Only if AEResolve = 1)
AEDeath	Numeric (binary)	0 = No 1 = Yes	Patient died in hospital
AEDeathDate	Date	dd/mm/yyyy	Date of in-hospital death (Only filled in if AEDeath = 1)

# Annex 6

## Relationships between study tables

The following figure shows the relationship between the tables described in Annex 5.



Note: Variables with a \* are only applicable for case-control study

## Annex 7

### Informed consent form

#### Patient information sheet

<<The adult ICF template and process will need to be adapted for special populations (e.g., minors, pregnant women, elderly patients lacking full capacity, migrants, prisoners) that require a tailored approach to consent, including possible surrogate decision-makers, such as parents or adult children, or study advocates (e.g., for the inclusion of prisoners, orphans) and additional forms (e.g. assent forms), as well as tailoring of the information provided to participants during the consent process. Information on relevant ethical considerations can be found in CIOMS guidelines 9-10 and 15-17 [1].>>

Study name	
Sponsor	
Institution	
Principal investigator	
Contact in case of questions	

This hospital is taking part in observational research to monitor the safety of COVID-19 vaccines in [POPULATION OF INTEREST]. This study is taking place in [NUMBER] hospitals in [COUNTRY]. The study will collect information on adverse events that are of special interest. These events are: [LIST AESIs BEING STUDIED]. These events can occur in the general population, in the absence of vaccination.

#### [FOR CASE-CONTROL STUDY]

The aim of this study is to investigate if the proportion of patients vaccinated with a COVID-19 vaccine among those who have experienced <<AESI of interest>> is similar to the proportion among those who have not experienced <<AESI of interest>>. This information is important to allow us to evaluate if the benefits from vaccination with COVID-19 vaccines are greater than any potential risks.

You have been invited to participate in this study as you have been diagnosed with one of the conditions that is being monitored, or you have been selected as a control (i.e., a patient without the condition being studied).

#### [FOR SSRI STUDY]

The aim of this study is to investigate if there is any reason to suspect that the <<AESI of interest>> that you, and other participants, have experienced could be associated with a

COVID-19 vaccine. This information is important to evaluate if the benefits from vaccination with COVID-19 vaccines are greater than any potential risks.

You have been invited to participate in this study as you have been diagnosed with one of the conditions that is being monitored.

If you participate in the study, data will be collected from your medical records, and directly from you, if any clarifications are needed. Should we need to contact you, [\[insert information about who will contact the patient\]](#), by [\[telephone / email\]](#) to ask for further information about your hospitalization, or your medical and vaccination history, as required. This will not take more than five to ten minutes of your time. In addition, you will be requested to provide documentation on any COVID-19 vaccinations that you have received.

The key-coded data obtained from this study will be stored in a secured database located in [\[COUNTRY\]](#). Your personal data will always be handled in accordance with all applicable data protection and privacy laws. All information about you as an individual is confidential and will be protected and only communicated to authorized persons. Any information collected from other doctors will be handled in the same confidential manner as those collected by the study doctor. Data will be archived for [\[XXX\]](#) years, as per national regulations, and will then be destroyed. Should you decide to withdraw from the study, data collected up until the time of the time of withdrawal will be used in the analyses, but no further data will be collected.

In accepting to participate in the study you agree:

- to provide access to any documentation on the COVID-19 vaccine(s) that you have received and agree that the study team can contact your vaccine provider, if necessary;
- that data from your medical records may be used in the present study;
- to answer any questions from the study team on data that may not be available in your medical records (e.g., whether you have received a COVID-19 vaccine, what date your symptoms started);
- that data from your medical records may be used in case the [\[NATIONAL AEFI FOCAL POINT/ NATIONAL PHARMACOVIGILANCE CENTER\]](#) needs to investigate any potential safety signals that are observed during the study; and,
- if you were pregnant at the time of your COVID-19 vaccination, that the [\[NATIONAL AEFI FOCAL POINT/NATIONAL PHARMACOVIGILANCE CENTER\]](#) may follow you until the time of birth [\[OR DEFINE ANOTHER PERIOD, AS APPROPRIATE\]](#), to monitor the safety of COVID-19 vaccines administered during pregnancy. **Further information on the national guidance is available at [\[INSERT HYPERLINK\]](#).**

This study will not lead to any changes in your routine care. You will not be receiving any intervention (vaccine, drug, other) as part of the study. Therefore, there will be no direct benefits to you from your participation in this research study. However, information gathered from persons vaccinated with COVID-19 vaccines will be important for the safety surveillance of COVID-19 vaccines.

The final data used for the research project will not be linked with your name, contact details or any other personal information about you that could be used to trace your identity. So,



your individual identity will be protected. The hospital will assign a responsible person to use and store the research data in a safe place. The key-coded data obtained from this study will be stored in a secured database located in [COUNTRY]. Your personal data will always be handled in accordance with all applicable data protection and privacy laws. All information about you as an individual will be confidential and will be protected. The information will only be communicated to authorized persons who will respect the same confidentiality. Any information collected from other physicians will be handled in the same confidential manner as that collected by the study doctor. Data will be archived for [XXX] years, as per national regulations.

If you are willing to participate in this study that monitors the safety of COVID-19 vaccines, please sign and date this form. You are free to contact [XXX] to understand how your information will have been made use of in the study. If at any time you do not wish to share your information, you are free to contact [XXX] and withdraw from this study.

You also have the choice to say no and opt out of this research study. Not participating in, or withdrawing from, this study will not impact your access to healthcare in any way.

Should you decide to withdraw from the study, data collected up to that point will be retained for analyses, but no additional data will be collected.

**I have read the above information, or it has been read to me. I have had the opportunity to ask questions about it and all questions have been answered to my satisfaction. I consent voluntarily to be a participant in this study.**

**Print name of participant**

Signature of participant

Date .....

*(Day/month/year)*



**Statement by the researcher/person taking consent:**

**I have accurately read out the information sheet to the potential participant. I confirm that the participant was given every opportunity to ask questions about the study, and all the questions asked by the participant have been answered correctly and to the best of my ability. I confirm that the individual has not been coerced into giving consent, and the consent has been given freely and voluntarily.**

**A copy of this informed consent form has been provided to the participant.**

Print name of researcher/person taking the consent .....

**Signature of researcher/  
person taking the consent**

Date .....

*(Day/month/year)*





COVID-19 VACCINES:

# SAFETY SURVEILLANCE MANUAL