World Health Organization

PROTOCOL TEMPLATE

to be used as template for observational study protocols for

Cohort event monitoring (CEM) for safety signal detection after vaccination with COVID-19 vaccines

Pre-publication version
17 March 2021
Last updated: 17 March 2021

ACKNOWLEDGEMENTS

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

Special acknowledgements to Steven Anderson, Barbara Law and Saad B. Omer, members of the Scientific Committee, who provided expert advice throughout the project. The protocol was written by Kaatje Bollaerts and Anke Stuurman with technical input from Wendy Hartig-Merkel, Omar Okasha, Elodie Sole, 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 pharmacovigilance (PVG) team in WHO headquarters are 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] Centers for Disease Control and Prevention. V-safe active surveillance for COVID-19 vaccine safety 2020 [updated 19 November 2020; cited 2021-01-15], (https://www.cdc.gov/vaccinesafety/pdf/V-safe-Protocol-508.pdf, accessed 9 March 2021).

[3] ACCESS (vACCinecovid-19 monitoring readinESS). Cohort event monitoring to assess safety of COVID-19 vaccines using patient reported events, a protocol template from the ACCESS project - EUPAS 38915. 2020 [updated 10 January 2021]. (https://vac4eu.org/wp-content/uploads/2021/02/3a.Cohort-event-monitoring-to-assess-safety-of-COVID-19-vaccines-using-patient-reported-events-a-protocol-template-from-the-ACCESS-project.pdf, accessed 9 March 2021)

INTRODUCTION

WHO has published the COVID-19 vaccines: safety surveillance manual to guide the processes for collecting, analysing and sharing safety data and information on COVID-19 vaccines within and across countries.[4] To accompany this manual and facilitate the conduct of active safety surveillance studies using harmonized tools and methods, a protocol template for cohort event monitoring (CEM) studies has been developed. **The present template protocol is for CEM studies of COVID-19 vaccines for the purpose of safety signal detection**. The protocol synopsis was developed under the guidance of a scientific committee including former and current Global Advisory Committee on Vaccine Safety (GACVS) committee members, and reviewed by the GACVS during its meeting held on 1-3 December 2020.[5]

CEM is a flexible active safety surveillance study design that can be used for signal detection and evaluation. CEM has been successfully used in the context of the H1N1 influenza pandemic in 2009, both in high income countries (HICs) and low- and middle-income countries (LMICs).[6] CEM is a prospective, observational, single-arm cohort study design for the early launch of a new medicine or vaccine. CEM studies are designed to capture all adverse events that occur in a defined group of individuals who are exposed to the new medicine or vaccine during routine clinical practice, in a defined period of time.[7,8] Vaccinees are enrolled in the cohort at the moment they are vaccinated for the first time with the monitored vaccine. Demographic and medical information are recorded at this initial encounter. Vaccinees are then followed up at defined intervals. Any adverse events (AEs), either any severity or of a defined severity, occurring after vaccination are recorded, regardless of whether they are suspected to be caused by the vaccine or not are recorded. By capturing these events, regardless of suspicion of causality, the CEM study has the potential to identify previously unrecognised and unsuspected adverse reactions to the vaccine.[9]

How to use this template to develop a CEM study protocol

The protocol template should be completed by adapting it to the specific country(ies) and study population(s). The sections of the protocol template to be adapted have been marked with blue square brackets.

[4] World Health Organization. Covid-19 vaccines: safety surveillance manual. Geneva2020. Last accessed 11 March 2021; Available from: https://www.who.int/publications/i/item/10665338400.
[5] GACVS. Report of the meeting of the WHO Global Advisory Committee on Vaccine Safety (GACVS), 1–3 December 2020. WER. 2021;96:13-20.
[6] Torre CM, Cary M, Borges FC, Ferreira PS, Alarcão J, Leufkens HG, et al. Intensive monitoring studies for assessing medicines: a systematic review. Front Med. 2019;6:147.
[7] World Health Organization. A practical handbook on the pharmacovigilance of antimalarial medicines: World Health Organization; 2008.
8 Pal SN, Duncombe C, Falzon D, Olsson S. WHO strategy for collecting safety data in public health programmes: complementing spontaneous reporting systems. Drug Saf. 2013;36(2):75-81. doi: 10.1007/s40264-012-0014-6.
[9] Suku CK, Hill G, Sabblah G, Darko M, Muthuri G, Abwao E, et al. Experiences and lessons from implementing cohort event monitoring programmes for antimalarials in four African countries: results of a questionnaire-based survey. Drug Saf. 2015;38:1115-26.

It is important also to note that the adult informed consent form (ICF) template, provided in this template, and the informed consent process must be adapted to local situations, local languages and 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, such as parents or guardians for young children, or study advocates for inclusion of prisoners, or orphans and additional forms, such as assent forms, as well as tailoring to correspond to the study information provided to participants during the consent process.

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, or at the level of the study sites, or at the institution of the sponsor, as required by applicable laws and regulation.

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 immunisation (AEFI) committee, and academia.
- Step 2: Identify the role and responsibilities of the different institutions, and nominate a person to lead and coordinate the process of protocol development and obtain the consensus of the study coordination team. Complete section 7 of the template with this information.
- Step 3: Define the target population, identify study sites, review list of adverse events of special interest (AESI) for the COVID-19 vaccine(s) in use,[10] and complete the protocol (including informed consent forms and data collection tools). If technical assistance from WHO is required at this stage, send an e mail request to gvsi@who.int and the WHO country office focal person.
- Step 4: Discuss the draft protocol with the study coordination team and study site representatives to obtain their input and endorsement and then finalise the protocol.
- Step 5: The final protocol should be reviewed by an independent scientific committee to ensure that it is scientifically sound, and should then be reviewed by the national ethics committee or the independent ethics committee (IEC) or institutional review board (IRB) of participating institution(s)
- Step 6: Develop the study procedures, data management plan and statistical analysis plan.

[10] 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

Start of CEM study protocol template

Cohort event monitoring (CEM) study for safety signal detection after vaccination with COVID-19 vaccines

1 TITLE PAGE

Abbreviated study title	COVID-19-CEM-[COUNTRY]- [NUMBER]
Full study title	Cohort Event Monitoring (CEM) study for safety signal detection in [PRIORITY GROUP OF INTEREST] after vaccination with COVID-19 vaccines in [COUNTRY]
Study ID	
Research question and objectives	
Country(ies) of study	
Protocol version	
Date of protocol version	
Protocol authors	

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5 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:
Cohort event monitoring (CEM) study for safety signal detection in [PRIORITY GROUP OF INTEREST] after vaccination with COVID-19 vaccines in [COUNTRY]

Version: [Version number]

I have reviewed and approved the protocol.

Name of scientific committee member: .....

Signature: .....

Date: .....

6 DOCUMENTATION OF PROTOCOL AMENDMENTS

Version	Version date	Reason for new version

7 STUDY TEAM AND RESPONSIBILITIES

7.1 Study team

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

7.2 Responsibilities

Organisation/Capacity	Responsibilities

8 ABBREVIATIONS

AE	Adverse event
AESI	Adverse event of special interest
CDC	Centers for Disease Control and Prevention
CEM	Cohort event monitoring
CIOMS	Council for International Organisations of Medical Sciences
COVID-19	Coronavirus disease 2019
DMP	Data management plan
EMA	European Medicines Agency
GEP	Good epidemiological practice
ICF	Informed consent form
IEC	Independent ethics committee
IRB	Institutional review board
MedDRA	Medical Dictionary for Regulatory Activities
NIP	National immunisation programme
PT	Preferred term
SAE	Serious adverse event
SARS-CoV-2	Severe acute respiratory syndrome Coronavirus 2
SAP	Statistical analysis plan
SCRI	Self-controlled risk interval
SIR	Standardized incidence ratio
SPEAC	Safety platform for emergency Vaccines
VAED	Vaccine-associated enhanced disease
WHO	World Health Organization

9 SYNOPSIS

Full title of study	Cohort Event Monitoring (CEM) study for safety signal detection in [PRIORITY GROUP OF INTEREST] after vaccination with COVID-19 vaccines in [COUNTRY].
Background and rationale	Vaccines approved for use in national immunisation programmes (NIPs), are considered safe and efficacious based on demonstrable evidence from randomized controlled clinical trials. They are, however, not completely free of risks, and occasional adverse events will inevitably occur following vaccination at the population level. Given vaccines are often recommended for otherwise healthy individuals, the key to success for NIPs is public trust in vaccine safety [1]. Thus, systematic vaccine safety surveillance is indispensable for ensuring safety of vaccines and public trust. COVID-19 vaccine pharmacovigilance should start simultaneously with the implementation of plans for immunisation with COVID-19 vaccines. This protocol describes a cohort event monitoring (CEM) study designed to capture adverse events occurring in a cohort of [PRIORITY GROUP OF INTEREST FOR THIS STUDY] vaccinated with [VACCINE/COVID-19 vaccines] during routine clinical practice in [COUNTRY] for the purpose of signal detection.
Objectives	The overall aim of this observational study is to monitor the safety of COVID-19 vaccines in [PRIORITY GROUP OF INTEREST FOR THIS STUDY] in [COUNTRY] for the purpose of safety signal detection as soon as the vaccine is used in routine vaccination programmes. **Specific objectives** 1. To estimate the incidence of serious adverse events (SAEs) in all enrolled vaccinated individuals after each COVID-19 vaccine dose, by COVID-19 vaccine brand. 2. To estimate the incidence of adverse events of special interest (AESIs) that result in hospitalisation in all enrolled vaccinated individuals after each COVID-19 vaccine dose, by COVID-19 vaccine brand. 3. To estimate the reactogenicity within 7 days following each COVID-19 vaccine dose within a subset of patients (‘reactogenicity subset’), by COVID-19 vaccine brand. 4. To estimate the incidence of severe COVID-19 in all enrolled vaccinated individuals, to assess the risk of vaccine-associated enhanced disease (VAED) at a population level
Study design	Active COVID-19 vaccine safety surveillance through an observational prospective single-arm cohort study that will be conducted in vaccination centres in [COUNTRY].
Study period	There will be an intensive enrolment period from the date of the study start until a predefined number of individuals have been enrolled. The time point for

	enrolment is first vaccination with any authorized COVID-19 vaccine in participating study sites. Each subject enrolled will be actively followed-up until 3 months after their last COVID-19 vaccine dose. The anticipated follow-up time for every individual is 3 months (for single dose vaccines) and about 4 months (for two-dose vaccines), assuming an interval of up to one month between the first and the second dose.
Population	Participants will be recruited among [PRIORITY GROUP OF INTEREST FOR THIS STUDY], vaccinated at [PLACE OF VACCINATION] participating in this CEM study. Study participation will be strictly voluntary. **Inclusion criteria** • Written informed consent; • [PRIORITY GROUP OF INTEREST FOR THIS STUDY] vaccinated with the first dose of any COVID-19 vaccine at one of the vaccination centres participating in the study. **Exclusion criteria** • Individuals already vaccinated with any COVID-19 vaccine before study enrolment, irrespective of the brand. • Individuals unable to comply with study procedures. The first 1,000 participants will be analysed in the reactogenicity subgroup analyses.
Variables	**Exposure of interest** Vaccination with the first dose of any of the COVID-19 vaccine brands that are available in [COUNTRY]. The COVID-19 vaccine brand, dose, date of vaccination and batch number will be recorded. Details on the second dose will also be collected if it is administered within 3 months of the first dose. **Outcomes** • SAEs (hospitalization, death) • AESIs that result in hospitalization • Reactogenicity • Severe COVID-19 disease
Data sources	Data collection is a mix of investigator site data entry and subject self-reported data through [A MOBILE APP/WEBLINKS/TELEPHONE CALLS/PAPER DIARY].
Sample size	The target study size is 30,000 individuals vaccinated with one or more dose(s) of a COVID-19 vaccine. This study size can rule out events occurring with a frequency of at least 1 per 10,000 if no event is observed, with at least 95% confidence. For the reactogenicity subset, the target sample size is 1,000 individuals; the first 1,000 individuals enrolled will be included in this subset.
Data analyses	Participation rates and demographic characteristics will be summarized using descriptive statistics. The mean/median and standard deviation/range will be summarized for age at enrolment, overall and stratified by sex and by country,

	when appropriate. Frequencies and percentages of outcomes will be provided by age group, sex and country when appropriate. Analyses of SAEs and AESIs will include all individuals, and analyses of reactogenicity will include the reactogenicity subset (the first 1,000 participants enrolled). The frequencies and proportions of individuals with identified SAEs and AESIs will be calculated by time since vaccination, in weeks. For proportions, 95% confidence intervals will be calculated using an exact method. For SAEs and for AESIs with an unknown risk window, observed-to-expected analyses will be performed. The observed incidences for AESIs and SAEs will be compared with expected incidences obtained from the most appropriate sources (e.g., clinical trials, epidemiological studies). The expected rates will be age-stratified, and standardized incidence ratios (SIRs) will be calculated. For acute AESIs with a known risk window, a self-controlled risk interval (SCRI) analysis will be performed. The control interval will be the follow-up time after the risk window for the AESI. For reactogenicity, the frequency and proportion of individuals with at least one solicited AE will be calculated overall, by event type and severity and by time since vaccination, in days. For proportions, 95% confidence intervals will be calculated using an exact method. For each type of reactogenic event and severity, the duration (in days) with their mean/median and standard deviation/range will be calculated. Observed-to-expected analyses will be performed. Incidence of severe COVID-19 disease (any COVID-19 disease diagnosed by a healthcare professional, laboratory-confirmed COVID-19, hospitalization for COVID-19, COVID-19 requiring intensive care unit (ICU) admission, COVID-19 disease resulting in death) will be calculated by dose, by timing between doses, and by time since each vaccination in months. It should be noted that the 3-month follow up period is unlikely to be sufficiently long to detect VAED.
Periodic reporting	Interim analyses will be performed weekly for the reactogenicity outcomes. For the other outcomes, interim analyses will be performed monthly.
Ethics	This non-interventional study will be conducted in accordance with the international ethical guidelines for epidemiology studies published by the Council for International Organizations of Medical Sciences (CIOMS) [2], the Declaration of Helsinki and its amendments [3], good epidemiological practice (GEP) guidelines and any applicable national laws and guidelines [SPECIFY AS APPROPRIATE]. Data protection and privacy regulations will be strictly observed in capturing, forwarding, processing, and storing individuals' data.

	Written informed consent will be obtained from all participating individuals. The study protocol and informed consent forms will be reviewed and approved by [NAME OF ETHICS COMMITTEE(S)/NAME OF INSTITUTIONAL REVIEW BOARD(S)].

10 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 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 the 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 vaccines across the globe is one of the key strategies to mitigate the public health and economic impact of the pandemic [link to safety manual] [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. They are, however, not completely free of risks, despite rigorous safety evaluation during clinical development, and occasional adverse events will occur following vaccination at the population level. Given vaccines are often recommended for otherwise healthy individuals, the key to success of NIPs is public trust in vaccine safety [1]. Thus, systematic vaccine safety surveillance is indispensable for ensuring safety of vaccines and public trust of vaccines, across countries with various pharmacovigilance capacities. Once plans for immunization with COVID-19 vaccines are set-up, pharmacovigilance systems should start simultaneously, and specific COVID-19 vaccine safety surveillance should be implemented, as described in the WHO COVID-19 vaccines: safety surveillance manual [4]. Acknowledging that routine passive reporting systems might not be sufficient to allow rapid assessment and appropriate public health response during COVID-19 vaccine introduction, active safety surveillance is recommended.

In [COUNTRY], vaccination with COVID-19 vaccines as part of the NIP is expected to start in [XXX]. It is expected that vaccination will take place with [VACCINE BRAND], a [VACCINE PLATFORM e.g. mRNA] vaccine, manufactured by [MANUFACTURER]. The vaccine is indicated for [AGE GROUP], and is contraindicated for persons with [CONTRAINDICATION]. [Any known safety concerns]. At the initiation of the COVID-19 NIP, there will be limited supplies of the COVID-19 vaccines. [PRIORITY GROUP OF INTEREST FOR THIS STUDY] will be (among) the first groups to be vaccinated, other priority groups are [PRIORITY GROUPS]. [PRIORITY GROUP OF INTEREST FOR THIS STUDY] will be primarily vaccinated at [PLACE OF VACCINATION]. As one or more vaccines may be used in [COUNTRY], identification of vaccine brand will be an important aspect of post-marketing pharmacovigilance activities.

This protocol describes a cohort event monitoring (CEM) study designed to capture adverse events occurring in a cohort of [PRIORITY GROUP OF INTEREST FOR THIS STUDY] vaccinated with [VACCINE/COVID-19 vaccines] during routine clinical practice in [COUNTRY] for the purpose of signal detection. The site-specific protocol will include informed consent forms (ICFs) in [LOCAL LANGUAGE(S)]. A statistical analysis plan, and a data management plan will be developed.

Findings regarding any study events, whether anecdotal, interim or final, will be communicated carefully and correctly, so as not to undermine trust in vaccines locally or globally. Anecdotal sharing should be prevented by reminding staff about confidentiality. However, even when official sharing aggregate interim and final findings occurs, it should be carefully done, particularly in the 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 and to maintain trust in the vaccination programme.

11 OBJECTIVES

The overall aim of this observational study is to monitor the safety of COVID-19 vaccines in [PRIORITY GROUP OF INTEREST FOR THIS STUDY] in [COUNTRY] for the purpose of safety signal detection as soon as the vaccine is introduced.

The specific objectives are to:

1. estimate the incidence of SAEs in all enrolled vaccinated individuals after each COVID-19 vaccine dose, by COVID-19 vaccine brand;
2. estimate the incidence of AESIs in all enrolled vaccinated individuals after each COVID-19 vaccine dose, by COVID-19 vaccine brand;
3. estimate the reactogenicity within 7 days after each COVID-19 vaccine dose, by COVID-19 vaccine brand;
4. To estimate the incidence of severe COVID-19 disease, to assess the risk of VAED at a population level.

12 METHODS

12.1 Study design

Active COVID-19 vaccine safety surveillance through an CEM observational prospective single-arm cohort study that will be conducted through [PLACE OF VACCINATION] under the [NAME OF NATIONAL HEALTH AUTHORITIES]. Study participants will be actively followed up until 3 months after their last COVID-19 vaccine dose, if administered within 3 months of the first dose. The anticipated follow-up time for participants is 3 months (for single dose vaccines) and about 4 months for two-dose vaccines, assuming an interval of up to one month between the first and the second dose.

12.2 Study population

Participants will be recruited among [PRIORITY GROUP OF INTEREST FOR THIS STUDY] vaccinated at [PLACE OF VACCINATION] participating in this CEM study. Study participation will be strictly voluntary.

12.2.1 Inclusion criteria

- Written informed consent.
- [PRIORITY GROUP OF INTEREST FOR THIS STUDY] vaccinated with the first dose of any COVID-19 vaccine at one of the vaccination centres participating in the study.

12.2.2 Exclusion criteria

- Individuals already vaccinated with any COVID-19 vaccine before study enrolment, irrespective of the brand.
- Individuals unable to comply with study procedures (illiterate, [to be completed as per study set up: e.g., use of mobile phone for data collection).

The first 1,000 individuals enrolled will be included in the reactogenicity subset.

12.2.3 Withdrawal from the study

Participants will have the right to withdraw from the study for any reason at any time. A participant will be considered lost-to-follow-up after [NUMBER] unsuccessful attempts to contact them by phone, followed by [NUMBER] unsuccessful attempts to contact their next of kin. The attempts to contact will be documented.

All attempts will be made to determine the underlying reason for withdrawal and, where possible, the primary underlying reason will be recorded.

Withdrawn participants and those lost-to-follow-up will not be replaced after the enrolment period has ended.

Should a participant decide to withdraw from the study, data collected up to the time of withdrawal will not be withdrawn and will be used in the analyses.

12.3 Study sites

[Paragraph describing the health facilities in which the study will be conducted]
Study sites are defined as [groups of] vaccination centres where COVID-19 vaccines are administered to [STUDY POPULATION OF INTEREST].

Study sites will be selected based on [SELECTION CRITERIA TO BE LISTED, e.g., study population has access to secondary/tertiary hospitals with the capacity to diagnose the AESIs, size, population covered, vaccination coverage, access to computer for data collection at site-level, availability of sufficient human resources].

Table 1. Study sites with principal investigators and contact details

Site	Principal investigator	Email	Phone number

12.4 Study period

12.4.1 Start of study and duration of follow-up

There will be an intensive enrolment period from the date of the start of the NIP until the predefined target number (study sample size) of enrolled individuals has been reached. The time point for enrolment will be first vaccination with any licensed COVID-19 vaccine in one of the participating sites. Study recruitment will be monitored during the study to assess whether recruitment goals are being reached.

Each individual will be followed-up for 3 months after the first dose of COVID-19 vaccine. If a second dose is administered within 3 months of the first dose, the subject will be followed up till 3 months after the second dose. A 3-month follow-up period was chosen because this covers the most common risk windows for AESIs (42 days), with a similar amount of time after the risk window, to be used as a control period.

12.4.2 Study completion and end of study

Participants will be considered to have completed the study when they have completed the questionnaire 3 months after their last COVID-19 vaccine dose.

End of study is defined as the point at which the last subject enrolled has reached the 3 months follow up period.

12.5 Sample sizes

12.5.1 Sample size for overall cohort

To guide the decision for suitable sample sizes, sample sizes were calculated taking into consideration different event frequencies. Table 2 shows the sample sizes required to rule out an event with a given

frequency with 95% confidence. If no event is observed with 30,000 participants, events with a frequency of 1 per 10,000 would be ruled out with 95% confidence. Studies conducted following the same protocol in different countries will provide strengthened evidence on COVID-19 vaccine safety.

Table 2. Sample sized required to rule out events with the indicated frequency if no event is observed with 95% confidence

Sample size	Event frequency
10,000	1 per 3,333
20,000	1 per 6,666
30,000	**1 per 10,000**
40,000	1 per 12,500
50,000	1 per 16,666
60,000	1 per 20,000
80,000	1 per 25,000
100,000	1 per 33,333
150,000	1 per 50,000
500,000	1 per 100,000

The probability of observing at least one event was calculated based on a binomial distribution as shown in Figure 1 (example shown for sample sizes up to 60,000). This figure shows the probabilities of observing at least one event in different scenarios corresponding to different sample sizes and event frequencies. The two vertical dotted lines correspond to sample sizes of 10,000 and 30,000, respectively. The horizontal dotted lines correspond to a 95% probability of observing at least one event. With a sample size of 10,000, it is likely (probability ~ 95%) to observe at least one event with an event frequency of 1 per 3,333. A sample size of 20,000 will enable to observe at least one event with an event frequency of 1 per 6,666 people whilst a sample size of 30,000 will enable to observe at least one event with an event frequency of 1 per 10,000 people, with 95% confidence.

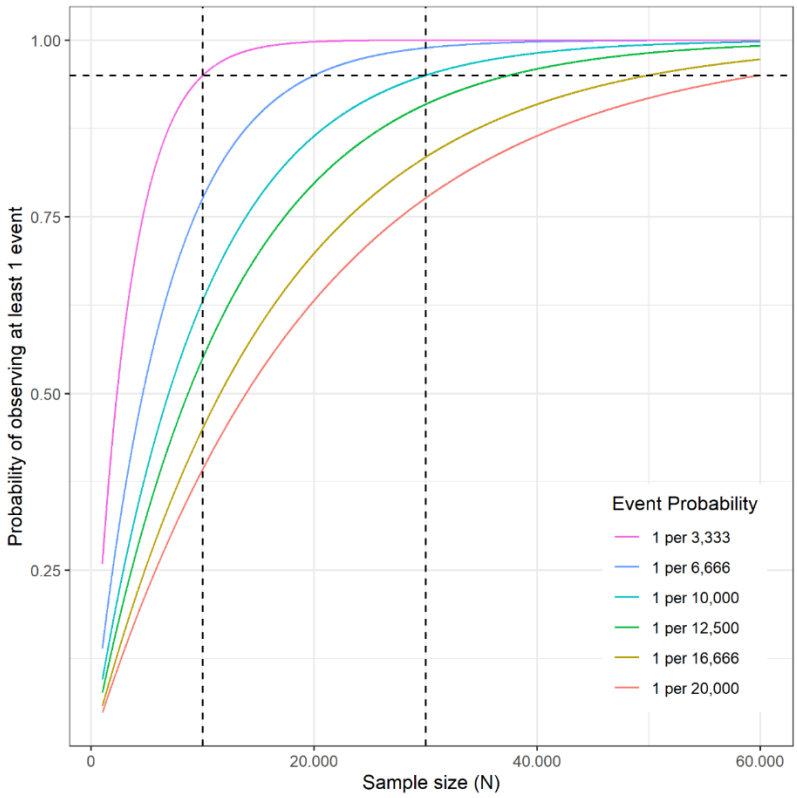


Figure 1. Probability of observing at least one event assuming a given event probability, by varying sample sizes up to 60,000. The horizontal dotted lined correspond to a 95% probability of observing at least one event.

The sample size required to rule out a given relative risk (RR) with 95% confidence if no event is observed in the risk window was calculated, taking into account the background incidence rate and the length of the risk window for some AESIs. For example, for an expected background rate for acute respiratory distress syndrome (ARDS) of 39 per 100,000 person-years [5, 6] and a risk window of 40 days, sample sizes of 34,300 and 13.700 subjects would be needed to rule out a RR of 2 and 5, respectively, with 95% confidence (Table 3).

Table 3. Sample size needed to rule out a relative risk if no event is observed within the risk window with 95% confidence.

AESI	Risk window (days)*	Background rate** (/100,000)	Sample size needed for RR = 2	Sample size needed for RR = 5
Generalized convulsions	0-7	10	6,836,000	2,735,000
ARDS	2-42	39	34,300	13,700
Thrombosis	2-42	80	16,700	6,700
Acute aseptic arthritis	2-42	100	13,400	5,400

*Days post-vaccination; **Using the lowest value in case of multiple references.
Sources for background rates: generalized convulsions: [7]; acute respiratory distress syndrome (ARDS): [5, 6]; thrombosis [8];acute aseptic arthritis: [9, 10].
***Disclaimer:** incidence rates provided are only rough estimates as they are not from systematic literature reviews*

For some AESIs, a range of background rates were identified. Additional sample sizes for different rates within the range were calculated (Table 4).

Table 4. Sample size needed to rule out different levels of relative risk if no event is observed within the risk window with 95% confidence. Additional results correspond to different values of background rates.

AESI	Background rate (/100,000)	Risk window	Sample size needed for RR=2	Sample size needed for RR=5
Generalized convulsion	30	D0-D7	2,279,000	91,200
	50	D0-D7	1,368,000	54,700
	80	D0-D7	85,500	34,200
ARDS	90	D2-D42	14,900	6,000
	150	D2-D42	8,900	3,600
	193	D2-D42	7,000	2,800
Acute aseptic arthritis	500	D2-D42	2,700	1,100
	1000	D2-D42	1,400	600
	1600	D2-D42	900	400

Sources for background rates: generalized convulsion [7]; acute respiratory distress syndrome (ARDS) [5, 6]; acute aseptic arthritis: [9, 10]

12.5.2 Sample size for reactogenicity subset

To guide the selection of the sample size for the reactogenicity subset, the precision was calculated for a range of prevalence values (Table 5). The precision was defined as the half-width of the 95% exact confidence interval calculated using the Clopper-Pearson exact method [11]. Based on a

sample size of 1,000 participants, an anticipated prevalence of 5 to 10% can be estimated with 2% precision. The first 1,000 participants enrolled will be included in the reactogenicity subset analyses.

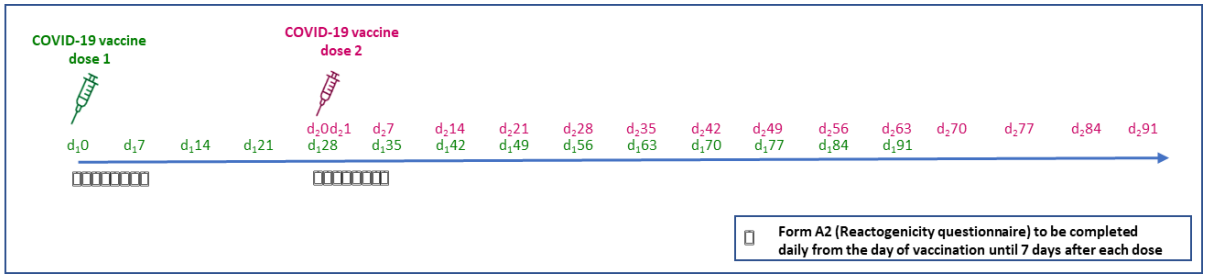
Table 5. Sample size required to estimate reactogenicity prevalence with the indicated level of precision with 95% confidence interval using Clopper-Pearson exact calculation for the proportion.

Sample size	Precision (%) for different levels of reactogenicity prevalence						
	1	2	5	10	15	25	50
200	0.03	0.03	0.04	0.05	0.06	0.07	0.07
500	0.01	0.02	0.02	0.03	0.03	0.04	0.04
1,000	0.01	0.01	**0.02**	**0.02**	0.02	0.03	0.03

12.6 Study variables

Study staff will collect data for covariates and vaccination on the day of vaccination. All participants will complete questionnaires through [A MOBILE APP/WEBLINKS/TELEPHONE CALLS/PAPER DIARY] at weekly intervals for 3 months (D7, D14, …, Dd91, with D0 being the day of vaccination) after each vaccine dose administration (Figure 2a). Participants in the reactogenicity subset will also be followed-up daily from the day of vaccination until 7 days after each dose (D0, D1, … D7, with D0 being the day of vaccination) (Figure 2b).

a)



b)

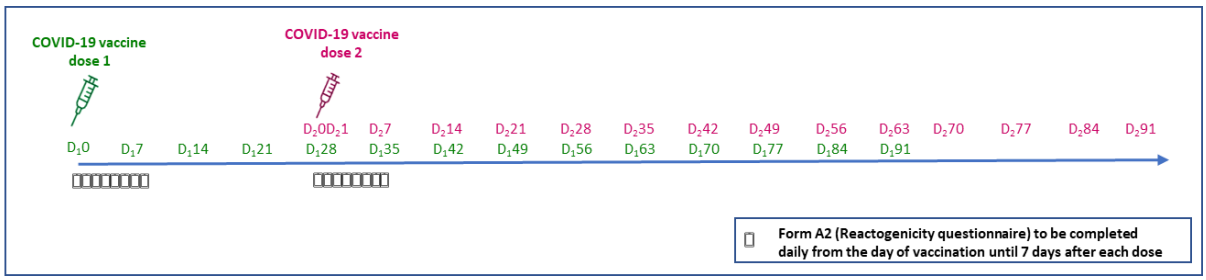


Figure 2. Data collection and timing (a) for all study participants, and (b) additional data collection for participants in the reactogenicity subset; illustrated for two doses of COVID-19 vaccines 28 days apart (timing between doses may differ)

12.6.1 Exposure of interest

Vaccination with the first dose of any of the COVID-19 vaccine brands that are available in [COUNTRY]. The COVID-19 vaccine brand, dose, date at vaccination and batch number will be recorded. If a second

dose is administered within 3 months of the first dose, same details on the second dose will also be collected.

12.6.2 Study outcomes

12.6.2.1 Serious adverse events

SAEs that require over-night hospitalization or result in death will be identified. SAEs that result in in-patient hospitalizations will be reported by the participant or their next of kin, and SAEs that results in death will be reported by their next of kin (APPENDIX 1: DATA DICTIONARY, form A3 and form E3).

12.6.2.2 Adverse events of special interest resulting in hospitalization

The list of AESIs includes events that have a:

- 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 [5].

[*It should be noted that the list of relevant AESIs may evolve over time and 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 template protocol.]*

AESIs (listed in APPENDIX 2: ADVERSE EVENTS OF SPECIAL INTERES) that result in hospitalization will be identified among diagnoses reported by the participant (or their next of kin) during follow-up (APPENDIX 1: DATA DICTIONARY, form A3 and form E3).

12.6.2.3 Reactogenicity

The first 1,000 participants will be enrolled in the reactogenicity subset. Reactogenicity will be categorized as local or systemic reactogenicity. Local reactogenicity is defined as the presence of pain, redness, warmth, swelling, hardening/induration, haematoma, or itching at, or near, the injection site. Systemic reactogenicity is defined as the presence of fever, chills, headache, nausea, muscle ache, joint pain, or malaise. Local and systemic reactogenicity (including grade) will be solicited and recorded daily for 7 days following each vaccination (D0, D1, …, D7 where D0 is the day of vaccination). See form A2 in APPENDIX 1: DATA DICTIONARY for the daily reactogenicity questionnaire. Additionally, subjects in the reactogenicity subset will be asked to report retrospectively any systemic symptoms in the 3 days prior to enrolment (excluding the day of enrolment) (APPENDIX 1: DATA DICTIONARY, form A1).

12.6.2.4 Severe COVID-19 disease

Severe COVID-19 disease is defined as COVID-19 disease resulting in hospitalization, requiring intensive care, and/or resulting in death. Occurrence of COVID-19 disease will be solicited throughout follow-up to collect Information on (APPENDIX 1: DATA DICTIONARY, Forms A3 and E3):

- laboratory-confirmed diagnosis or not:
- hospitalization for COVID-19 disease;
- intensive care necessary or not; and
- COVID-19 resulted in death.

In view of the challenges in differentiating between VAED and severe COVID-19 on an individual level only severe COVID-19 will be solicited. The occurrence of severe COVID-19 after immunization will serve as trigger pointing towards potential cases of VAED. It should be noted that the recommended 3-month post vaccine follow up is unlikely to be sufficiently long to detect VAED.

12.7 Study flow: data sources and data collection

Data will be collected at the time of enrolment, at time of vaccination, and during follow-up. Data collection by the study site staff at the time of enrolment and vaccination will take place through [AN ELECTRONIC TOOL OR OTHER MEANS] at the site. Data collection by the participants during follow-up will take place through [A MOBILE APP/WEBLINKS/TELEPHONE CALLS/PAPER DIARY]. All data variables are listed in APPENDIX 1: DATA DICTIONARY, and a graphic summary is available in APPENDIX 3: RELATIONSHIPS BETWEEN STUDY TABLES.

12.7.1 Vaccination and enrolment

Potential participants will be informed about the study through [APPROPRIATE ROUTE, e.g. occupational health service department for healthcare workers, or study staff at vaccination centre], and study staff will be available to answer any questions. Enrolment will take place immediately after vaccination, the study staff will collect the signed ICF, complete the participants' baseline information (demographic and medical) and contact information for the participant and their next of kin (APPENDIX 1: DATA DICTIONARY, form E1), and record the details of vaccination (APPENDIX 1: DATA DICTIONARY, form E2). A unique participant identifier will then be generated.

To increase the quality of the self-reported data, participants will be asked to report any physician-made diagnoses and, if they are hospitalized, to provide data from their discharge report, if available. In addition, the participants will be asked to return to the same vaccination centre to receive their second dose of COVID-19 vaccine (if applicable).

12.7.2 Vaccination during the follow-up period

If participants receive a second COVID-19 vaccine dose during the follow-up period, details of the second vaccination are also collected (APPENDIX 1: DATA DICTIONARY, form E2).

12.7.3 Follow-up

The participants will complete the study questionnaires at predefined time points during follow-up.

Reminders will be sent to participants who do not complete the questionnaire [TO DESCRIBE APPROPRIATE FORMAT AND FREQUENCY OF REMINDERS DEPENDING ON DATA COLLECTION TOOL AND ON TYPE OF QUESTIONNAIRE, e.g., push notification in app, SMS]. If the questionnaire is still not completed, the participant will be called by telephone. After [NUMBER] unsuccessful attempts to contact the participant by phone, their next of kin will be contacted. After [NUMBER] unsuccessful attempts to contact their next of kin, the participant will be considered as lost to follow-up.

The online questionnaires will expire at the end of the day (time 23:59) preceding the next data collection point. It will be possible to complete reactogenicity questionnaires (APPENDIX 1: DATA DICTIONARY, forms A1 and A2) until 23:59 every day, after which they expire. It will be possible to complete follow-up questionnaires (APPENDIX 1: DATA DICTIONARY, forms A3) for one week, after which they expire.

12.7.4 Identification of AESIs and SAEs

The diagnoses reported by the participants during follow-up will be coded using Medical Dictionary for Regulatory Activities (MedDRA) by [TO BE DEFINED BY STUDY TEAM]. SAES and AESIs will be identified using MedDRA codes by [TO BE DEFINED BY STUDY TEAM].

12.7.5 Pregnancy

Participants who are reported 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 recommendation, all pregnant women inadvertently exposed to COVID-19 vaccine should be followed up until delivery, and the pregnancy outcome documented. Please refer to the module on safety surveillance of pregnant and lactating women manual WHO's COVID-19 vaccines: safety surveillance manual [4].

12.7.6 Data collection at withdrawal/lost to follow-up

If a participant withdraws from the study or is lost-to-follow-up, the follow-up for that participant will be terminated early and the date of and, if possible, the reason for withdrawal/lost-to-follow-up will be recorded.

If a safety signal is detected, [DESIGNATED STUDY TEAM/NATIONAL AEFI FOCAL POINT/NATIONAL PHARMACOVIGILANCE CENTER] may decide to contact the healthcare provider of participant with the potential safety issue, for further investigation through [APPROPRIATE NATIONAL ROUTES].

12.8 Data analysis

The analysis plan will be fully described in a written and approved statistical analysis plan (SAP). All analyses will be documented in the final study report. Missing data will be acknowledged in the analyses and interpretation of data.

12.8.1 Descriptive analysis of demographics and baseline characteristics

Participation rates over time will be described. Demographic characteristics will be summarized. The mean/median and standard deviation/range will be given for age at enrolment, overall and stratified

by sex and by country, when appropriate. Frequencies and percentages will be provided by age group, sex, and country, when appropriate.

12.8.2 Statistical analyses

The analyses of SAEs and AESIs will include data for all participants, while analyses of reactogenicity will include only data from the participants in the reactogenicity subset. Participants that completed the follow-up forms but do not report any event(s) will be considered as participants without event(s).

Diagnoses will be coded, using MedDRA preferred terms (PTs), by [TO BE DEFINED BY STUDY TEAM]. All analyses for AESIs will be at the PT levels. The frequency and proportion of participants reporting AESIs and SAEs will be calculated by time since vaccination (in weeks). For the proportions, 95% confidence intervals will be calculated using an exact method [11].

Observed-to-expected analyses will be performed for SAEs and AESIs with an unknown risk window. The observed incidences for AESIs will be compared with background rates from the most appropriate sources. Good quality national background rates will be used if available. If these are not available, good quality background rates from neighbouring countries with comparable healthcare systems will be used. If these are also not available, quality background rates obtained from the Centers for Disease Control and Prevention (CDC) or European Medicines Agency (EMA) will be used. Sensitivity analyses will be performed if deemed appropriate. The expected rate will be age-stratified, and the standardised incidence ratio (SIR) will be calculated.

For acute AESIs with a known risk window (see APPENDIX 2: ADVERSE EVENTS OF SPECIAL INTERESt), self-controlled risk interval (SCRI) analyses will be performed. The control interval will consist of the follow-up time after the risk window for the acute outcomes.

For reactogenicity, the frequency and proportion of participants with at least one solicited AE will be calculated overall and by event type, by event type and severity, and by time since vaccination, in days. For the proportions, the 95% confidence intervals will be calculated using an exact method. For each type of event and severity, the duration (in days) will be calculated and their mean/median and standard deviation/range will be reported. Observed-to-expected analyses will be performed using the retrospectively collected data for the 3 days prior to vaccination and, when available, using data from controls groups from appropriate clinical trial sources from the same or similar countries.

The incidence of COVID-19 disease (any COVID-19 disease diagnosed by a healthcare professional, laboratory-confirmed COVID-19, hospitalization for COVID-19, COVID-19 requiring intensive care unit admission, COVID-19 resulting in death) will be calculated by dose, by timing between doses, and by time since each vaccination in months. Participants with COVID-19 symptom onset within [APPROPRIATE TIME INTERVAL] after vaccination may be excluded.

13 Data management

A data management plan (DMP) will be developed before data collection begins and will describe all functions, processes, and specifications for data collection, cleaning and validation.

Study staff will enter data in [APPROPRIATE TOOL] at several time points. Study staff will enter data on informed consent, contact details and covariates at the time of enrolment, data on the exposure at the time of vaccination, [DATA FROM THE QUESTIONNAIRE IF COLLECTED THROUGH TELEPHONE/PAPER-BASED DIARIES], and any data obtained in the event of additional follow-up after initial non-response. [TO DESCRIBE SPECIFICATIONS OF MEANS OF DATA COLLECTION, SOFTWARE IF ANY, DATA STORAGE]

Participants will complete the questionnaires through [A MOBILE APP/WEBLINKS/TELEPHONE CALLS/PAPER DIARIES]. The questionnaires will be available in [LANGUAGE]. [SPECIFICATIONS OF MEANS OF DATA COLLECTION, SOFTWARE IF ANY, DATA STORAGE TO BE DESCRIBE].

For all electronic data entry, automated quality checks will detect out-of-range or anomalous data, where applicable.

User testing of any data entry methods, whether electronic or on paper, will be performed prior to deployment.

13.1.1 Data security

[PROCESSES FOR ANONYMIZATION, ACCESS, STORAGE, AND DESTRUCTION OF RAW DATA TO BE DESCRIBE].

The key-coded data obtained from this study will be stored in a secured database located in [COUNTRY]. 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.

These security measures will also apply to the ICFs.

13.1.2 Data transfer

[PROCESS FOR DATA TRANSFER INCLUDING SECURITIY TO BE DESCRIBE]

13.1.3 Source documents

The data sources for the exposure of interest will be [TO BE COMPLETE AS APPLICABLE].

The data source for covariates will be the participants.

The data sources for the study outcomes will be the questionnaires completed by the participants (or their next of kin).

13.1.4 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.

14 Quality assurance, monitoring and reporting

14.1.1 Monitoring

A site initiation [VISIT (PREFERRED IF FEASIBLE)/TELEPHONE CALL] will be conducted to ensure the site is ready to start data collection. Study staff will be trained on the study procedures.

[REMOTE/ON-SITE] monitoring of the study conduct will be performed throughout the study period to assess the accuracy and completeness of the data.

The study site may be subject to a quality assurance visit. If so, the site will be contacted in advance to arrange a monitoring visit. The investigator and site staff will guarantee direct access to all study documents for quality assurance monitors.

14.1.2 Interim analyses and reporting

Interim analyses will be performed by [TO BE DEFINED BY STUDY TEAM] on a weekly basis for the reactogenicity outcomes, as data will be collected daily. For the other outcomes, for which data will be collected weekly, interim analyses will be performed on a monthly basis.
Should the rates of adverse event be different from the expected rates (as per clinical trials data and reported in the summary product characteristic of a given product), the study team will have to inform the national regulatory authorities for regulatory review.

14.1.3 Final analyses and reporting

Final analyses will be performed and a full study report will be written within 4 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 by the investigator, with guidance, input, review and approval of the sponsor, including development of materials, recruitment, training and management of sites, electronic data capture and data management and analyses.

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

15.1.1 [NATIONAL PHARMACOVIGILANCE CENTRE/AEFI COMMITTEE/NATIONAL IMMUNIZATION PROGRAMME MANAGER/DEDICATED SCIENTIFIC COMMITTEE]

The [NAME OF NATIONAL PHARMACOVIGLANCE CENTRE/AEFI COMMITTEE/NATIONAL IMMUNIZATION PROGRAMME MANAGER/DEDICATED SCIENTIFIC COMMITTEE (to be detailed in the site-specific protocol)] will oversee the implementation and smooth running of the project. They will provide scientific, statistical and technical expertise, as needed.

15.1.2 Changes to the protocol

Changes to the protocol will be documented in written protocol amendments. 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 an individual's agreement to participate in the study will requires the renewed informed consent prior to continued participation in the study.

15.1.3 Management and reporting of adverse events/adverse reactions

The study team will ensure that the healthcare workers in charge of vaccine administration 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. No individual causality assessment will be done as part of the study.

Contact information of the participants and their healthcare providers will be collected, and consent will be sought to use this contact information in case the [NAME OF NATIONAL AEFI FOCAL POINT/NATIONAL PHARMACOVIGILANCE CENTER] needs to investigate any potential safety signals that arise from the study.

The study team will be responsible to ensure that all SAEs detected and reported in the context of this study will also be reported through the routine AEFI surveillance system to the responsible organization within the health ministry (NPI/national regulatory authorities/pharmacovigilance centre), to ensure appropriate healthcare, timely investigation, causality assessment and response as per the country's protocol.

[Describe mechanisms/processes to ensure that all serious adverse events detected and reported in the context of this study, are also reported through the routine AEFI surveillance system to the responsible institution within the health ministry (NPI/ national regulatory authorities / pharmacovigilance centre), to ensure timely investigation, causality assessment and response as per the country protocol].

16 Ethical considerations

16.1.1 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 issued by the Council for International Organizations of Medical Sciences [2] , good epidemiological practice (GEP) guidelines, 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 change in the clinical and diagnostic practices. Therefore, there will be 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 vaccines will be important for these novel vaccines, to ensure safety and to maintain public confidence in vaccines.

16.1.2 Respecting participants' autonomy

The study will use self-reported data and data collected as part of healthcare provision at designated hospital(s).

Participants will be informed about the study through [TO COMPLETE AS APPLICABLE] and will have the opportunity to ask questions to study staff. An ICF must be signed prior to the individual's participation in the study (APPENDIX 4: ADULT INFORMED CONSENT FORM). When signing the ICF, individuals agree that the study team will be able to contact designated hospital(s) at which they may have sought care during the study period. The purpose of this contact is to obtain medical confirmation of the adverse event that led to the hospital visit. The study-specific ICF will spell out 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 participant can contact the custodian and remain informed about future use. The ICF will explain that individual's participation is completely voluntary and that they can decide 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 or guardians, adult children) or study advocates (e.g. for inclusion of prisoners, orphans) and additional forms (e.g., assent forms), as well as tailoring some details provided to participants during consent].

16.1.3 Participant confidentiality

No data whatsoever 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 participant personal data and will not include participant's names 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 SPECIFICPROTOCOL] will be observed in capturing, forwarding, processing, and storing patient data.

16.1.4 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 in the site-specific protocol] and will comply with any national ethics committee requirements.

Informed consent will be required from all participants or legal representatives.

17 Limitations

The exclusion of individuals who have already been vaccinated with COVID-19 vaccine precludes the possibility to monitor effects of repeat vaccinations as part of this study.

The study is limited to sites located in areas where the study population has access to secondary or tertiary hospitals with the capacity to diagnose the AESIs. Consequently, populations in rural areas with only community clinics will be excluded.

18 References

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APPENDIX 1: DATA DICTIONARY

Variable name	Type	Values and coding	Question to be asked
Data from electronic tool **Table 1: Participant's information**			
Form E1: Participant registration, informed consent, contact, and covariates			
siteID	Type of variable at discretion of site	[needs to be unique]	Unique and persistent identifier for each site
subjectID	Type of variable at discretion of site	[needs to be unique]	Unique and persistent identifier for each participant
subjName	Text		Name of participant
consent	Numeric (binary)	0 = No 1 = Yes	Informed consent provided
reactoSubset	Numeric (binary)	0 = No 1 = Yes	Is the participant part of the reactogenicity subset?
Subject contact details			
subjPhone	Numeric		Participant's phone number
NOKname	Text		Name of next of kin
NOKphone	Numeric		Phone number of next of kin
Subject covariates			
subjDoB	Date	dd/mm/yyyy	Date of birth of participant
subjSex	Numeric (multinomial)	0 = Male 1 = Female 2 = Other	Sex of participant
subjPreg	Numeric (multinomial)	0 = No 1 = Yes 2 = Not applicable	Is the participant pregnant
subjLact	Numeric (multinomial)	0 = No 1 = Yes 2 = Not applicable	Is the participant lactating?

Variable name	Type	Values and coding	Question to be asked
subjMedHist	Numeric (multinomial)	0 = No medical history 1 = Chronic respiratory disease or asthma 2 = Chronic heart disease 3 = Chronic liver disease 4 = Chronic renal disease 5 = Diabetes 6 = Immunocompromised/ immunosuppressed 7 = Obesity 8 = Allergy	Medical history, presence of diseases?
subjPriorCovid	Numeric (multinomial)	0 = No 1 = Yes, laboratory confirmed 2 = Probable but not laboratory-confirmed	Previous COVID-19 disease
subjPriorRxn	Numeric (multinomial)	0 = No 1 = Yes 2 = Do not know	History of reaction to vaccination
subjPriorRxn	Text		Indicate which vaccine and describe reaction (Only filled in if *subjPriorRxn == 1)*
subjSocioE	Numeric (multinomial)	*(classes to be defined locally)*	Socioeconomic class
Data from electronic tool **Table 2: Vaccine exposure information** Table 2 can be linked to Table 1 by subjectID			
Form E2: Subject exposure dose 1 & 2			
doseID	Numeric	1 = 1st vaccination 2 = 2nd vaccination	1st or 2nd dose of vaccine
vaccDate	Date	dd/mm/yyyy	Date of vaccination
vaccTime	Time	HH:MM	Time of vaccination
vaccBrand	Numeric (multinomial)	1 – to list all brand/ manufacturers available in the country	Vaccine brand and manufacturer
vaccBatch	Text		Vaccine batch number
vaccDiluent	Numeric (binary)	0 = No 1 = Yes	Was a separate diluent required?

Variable name	Type	Values and coding	Question to be asked
vaccDiluentBrand	Numeric (multinomial)	1 – to list all brand/ manufacturers available in the country	Diluent brand and manufacturer (Only filled in if *vaccDiluent == 1)*
vaccDiluentBatch	Text		Diluent batch number (Only filled in if *vaccDiluent == 1)*
vaccOther	Numeric (binary)	0 = No 1 = Yes	Co-administration of vaccine against any disease other than COVID
vaccOtherDis	Text		Specify which disease was vaccinated against (Only filled in if *vaccOther == 1)*
Data from the app **Table 3: Pre-vaccination reactogenicity** Table 3 can be linked to Table 1 by *subjectID* Trigged only if *reactoSubset == 1 & prevaccFU == 1*			
Form A1: Reactogenicity (pre-vaccination)			
preLogID	Numeric	Numbers from 1 to 7	Unique ID for the record of pre-vaccination reactogenicity
preLogDate	Date	dd/mm/yyyy	Date of record
preFebrile	Numeric (binary)	0 = No 1 = Yes	Did you feel **febrile** in the past 3 days?
preTempY	Numeric (binary)	0 = No 1 = Yes	Did you measure your temperature in the past 3 days?
preTemp	Numeric (multinomial)	1 = Below 38.0°C (below 100.4°F) 2 = 38.0°C to 38.4°C (100.4°F to 101.12 °F) 3 = 38.5°C to 38.9°C (101.3°F to 102.02°F) 4 = Higher than 39.0°C (higher than 102.2°F)	What was your **temperature**? (Only filled in if *preTempY == 1)*
preTempWhere	Numeric (multinomial)	1 = Oral (in the mouth) 2 = Rectum (in the anus) 3 = Armpit 4 = Ear 5 = Forehead	Where did you measure the temperature? (Only filled in if *preTempY == 1)*

Variable name	Type	Values and coding	Question to be asked
preNausea	Numeric (binary)	0 = No 1 = Yes	Did you feel **nauseous** in the past 3 days, or did you vomit?
preNauseaSev	Numeric (multinomial)	1 = The nausea/vomiting did not interfere with my activities 2 = The nausea/vomiting somewhat interfered with my activities 3 = The nausea/vomiting was considerable and prevented my daily activities	How severe was the nausea/vomiting? (Only filled in if *preNausea == 1)*
preMalaise	Numeric (binary)	0 = No 1 = Yes	Did you experience general **malaise** in the past 3 days (feeling of weakness, not feeling well)?
preMalaiseSev	Numeric (multinomial)	1 = The malaise did not interfere with my activities 2 = The malaise somewhat interfered with my activities 3 = The malaise was considerable and prevented my daily activities	How severe was the general malaise? (Only filled in if *preMalaise == 1)*
preChill	Numeric (binary)	0 = No 1 = Yes	Did you have **chills** in the past 3 days?
preChillSev	Numeric (binary)	1 = The chills did not interfere with my activities 2 = The chills somewhat interfered with my activities 3 = The chills were considerable and prevented my daily activities	How severe were the chills? (Only filled in if *preChill == 1)*
preHeadache	Numeric (binary)	0 = No 1 = Yes	Did you have a **headache** in the past 3 days?
preHeadacheSev	Numeric (multinomial)	1 = The headache did not interfere with my activities 2 = The headache somewhat interfered with my activities 3 = The headache was considerable and prevented my daily activities	How bad was the headache? (Only filled in if *preHeadache == 1)*
prePain	Numeric (binary)	0 = No 1 = Yes	Did you have **joint pain** in the past 3 days?

Variable name	Type	Values and coding	Question to be asked
prePainSev	Numeric (multinomial)	1 = The joint pain did not interfere with my activities 2 = The joint pain somewhat interfered with my activities 3 = The joint pain was considerable and prevented my daily activities	How bad was the joint pain? (Only filled in if *prePain == 1)*
preMuscle	Numeric (binary)	0 = No 1 = Yes	Did you have **muscle aches** in the past 3 days?
preMuscleSev	Numeric (multinomial)	1 = The muscle aches did not interfere with my activities 2 = The muscle aches somewhat interfered with my activities 3 = The muscle aches were considerable and prevented my daily activities	How bad were the muscle aches? (Only filled in if *preMuscle == 1)*
preTired	Numeric (binary)	0 = No 1 = Yes	Did you feel **tired (fatigued)** in the past 3 days?
preTiredSev	Numeric (multinomial)	1 = The tiredness did not interfere with my activities 2 = The tiredness somewhat interfered with my activities 3 = The tiredness was considerable and prevented my daily activities	How bad was the tiredness?
Data from the app **Table 4: Post-vacc dose ID** Trigged only if *reactoSubset == 1*			
posDoseID	Numeric (binary)	1 = 1st vaccine dose 2 = 2nd vaccine dose [unique per each subject]	Identifier if the subsequent record is for reactogenicity after the 1st or 2nd vaccine dose
Table 5: Post-vaccination reactogenicity Table 5 can be linked to Table 4 by *posDoseID* Trigged only if *reactoSubset == 1*			
Form A2: Reactogenicity (post-vaccination)			
posLogID	Numeric	Numbers from 1 to 8 [unique per each *posDoseID* per each *subjectID*]	ID for the record of pre-vaccination reactogenicity corresponding to each date
posLogDate	Date	dd/mm/yyyy	Date of record
posInjectPain	Numeric (binary)	0 = No 1 = Yes	Did you have **pain at the injection site** today?

Variable name	Type	Values and coding	Question to be asked
posPainSev	Numeric (multinomial)	1 = The pain did not interfere with my activities 2 = The pain somewhat interfered with my activities 3 = The pain was considerable and prevented my daily activities	How much pain did you have? (Only filled in if *posInjectPain == 1)*
posRedness	Numeric (binary)	0 = No 1 = Yes	Was your **skin red around the injection site** today?
posRedBig	Numeric (multinomial)	1 = Less than 2.,5 cm 2 = 2.5 to 5.0 cm 3 = 5.1 to 10 cm 4 = More than 10 cm 5 = Unknown/not measured	How big was the red area? (Only filled in if *posRedness == 1)*
posSwell	Numeric (binary)	0 = No 1 = Yes	Did you have **swelling around the injection site** on today?
posSwellBig	Numeric (multinomial)	1 = Less than 2.5 cm 2 = 2.5 to 5.0 cm 3 = 5.1 to 10 cm 4 = More than 10 cm 5 = Unknown/not measured	How big was the swelling? (Only filled in if *posSwell == 1)*
posHard	Numeric (binary)	0 = No 1 = Yes	Was the area **around the injection site hard (induration)** today?
posHardBig	Numeric (multinomial)	1 = Less than 2.5 cm 2 = 2.5 to 5.0 cm 3 = 5.1 to 10 cm 4 = More than 10 cm 5 = Unknown/not measured	How big was the hardened area? (Only filled in if *posHard == 1)*
posBruise	Numeric (binary)	0 = No 1 = Yes	Did you have a **bruise (haematoma) around the injection site** today?
posBruiseBig	Numeric (multinomial)	1 = Less than 2.5 cm 2 = 2.5 to 5.0 cm 3 = 5.1 to 10 cm 4 = More than 10 cm 5 = Unknown/not measured	How big was the bruise? (Only filled in if *posBruise == 1)*
posWarm	Numeric (binary)	0 = No 1 = Yes	Was the area **around the injection site warm** today?

Variable name	Type	Values and coding	Question to be asked
posWarmSev	Numeric (multinomial)	1 = The warmth did not interfere with my activities 2 = The warmth somewhat interfered with my activities 3 = The warmth was considerable and prevented my daily activities	How severe was the warmth? (Only filled in if *posWarm == 1)*
posItch	Numeric (binary)	0 = No 1 = Yes	Did you have an **itch around the injection site** today?
posItchSev	Numeric (multinomial)	1 = The itch did not interfere with my activities 2 = The itch somewhat interfered with my activities 3 = The itch was considerable and prevented my daily activities	How severe was the itch? (Only filled in if *posItch == 1)*
posFebrile	Numeric (binary)	0 = No 1 = Yes	Did you feel **febrile** today?
posTempY	Numeric (binary)	0 = No 1 = Yes	Did you measure your **temperature** today?
posTemp	Numeric (multinomial)	1 = Below 38.0°C (below 100.4°F) 2 = 38.0°C to 38.4°C (100.4°F to 101.12°F) 3 = 38.5°C to 38.9°C (101.3°F to 102.02°F) 4 = Higher than 39.0 °C (higher than 102.2°F)	What was your temperature? (Only filled in if *posTempY == 1)*
posTempWhere	Numeric (multinomial)	1 = Oral (in the mouth) 2 = Rectum (in the anus) 3 = Armpit 4 = Ear 5 = Forehead	Where did you measure the temperature? (Only filled in if *posTempY == 1)*
posNausea	Numeric (binary)	0 = No 1 = Yes	Did you feel **nauseous** today, or did you vomit?

Variable name	Type	Values and coding	Question to be asked
posNauseaSev	Numeric (multinomial)	1 = The nausea/vomiting did not interfere with my activities 2 = The nausea/vomiting somewhat interfered with my activities 3 = The nausea/vomiting was considerable and prevented my daily activities	How severe was the nausea/vomiting? (Only filled in if *posNausea == 1)*
posMalaise	Numeric (binary)	0 = No 1 = Yes	Did you experience **general malaise** today (feeling of weakness, not feeling well)?
posMalaiseSev	Numeric (multinomial)	1 = The malaise did not interfere with my activities 2 = The malaise somewhat interfered with my activities 3 = The malaise was considerable and prevented my daily activities	How severe was the general malaise? (Only filled in if *posMalaise == 1)*
posChill	Numeric (binary)	0 = No 1 = Yes	Did you have **chills** today?
posChillSev	Numeric (binary)	1 = The chills did not interfere with my activities 2 = The chills somewhat interfered with my activities 3 = The chills were considerable and prevented my daily activities	How severe were the chills? (Only filled in if *posChill == 1)*
posHeadache	Numeric (binary)	0 = No 1 = Yes	Did you have a **headache** today?
posHeadacheSev	Numeric (multinomial)	1 = The headache did not interfere with my activities 2 = The headache somewhat interfered with my activities 3 = The headache was considerable and prevented my daily activities	How bad was the headache? (Only filled in if *posHeadache == 1)*
posPain	Numeric (binary)	0 = No 1 = Yes	Did you have **joint pain** today?

Variable name	Type	Values and coding	Question to be asked
posPainSev	Numeric (multinomial)	1 = The joint pain did not interfere with my activities 2 = The joint pain somewhat interfered with my activities 3 = The joint pain was considerable and prevented my daily activities	How bad was the joint pain? (Only filled in if *posPain == 1)*
posMuscle	Numeric (binary)	0 = No 1 = Yes	Did you have **muscle aches** today?
posMuscleSev	Numeric (multinomial)	1 = The muscle aches did not interfere with my activities 2 = The muscle aches somewhat interfered with my activities 3 = The muscle aches were considerable and prevented my daily activities	How bad were the muscle aches? (Only filled in if *posMuscle == 1)*
posTired	Numeric (binary)	0 = No 1 = Yes	Did you feel **tired** (fatigued) today?
posTiredSev	Numeric (multinomial)	1 = The tiredness did not interfere with my activities 2 = The tiredness somewhat interfered with my activities 3 = The tiredness was considerable and prevented my daily activities	How bad was the tiredness? (Only filled in if *posTired == 1)*
Data from the app (and the electronic tool if participant did not complete the follow-up questionnaire in the app) **Table 6: FU identifier** Table 6 can be linked to Table 1 by *subjectID*			
Form E3: Follow-up questionnaire			
fuID	Numeric	1 = FU one week after 1st dose 2 = FU one week after 2nd dose 3 = FU one month after 2nd FU 4 = FU one month after 3rd FU --- [needs to be unique for each *subjectID*]	Identifier of the follow-up questionnaire
fuBySujb	Numeric (binary)	0 = No 1 = Yes	Form completed by participant (via the app) or site staff (via the electronic tool)?

Variable name	Type	Values and coding	Question to be asked
fuWhyLoss	Numeric (multinomial)	0 = No reason given 1 = The study takes too much time 2 = Not interested anymore 4 = Death 5 = Other	Reason for no completed-follow-up form. (Only if *fuBySujb == 1)*
fuWhyDeath	Text		Reason for death (Only if *fuWhyLoss* == 4)
fuMedCare	Numeric (multinomial)	0 = No 1 = 1 times 2 = 2 times etc	How many times did the participant seek medical care between [date X and date Y]? (e.g., at a local health centre, or hospital)
Table 7: FU information Table 7 can be linked to Table 6 by *fuID* Triggered by *fuMedCare > 0*			
Form A3: Follow-up questionnaire			
fuHosp	Numeric (binary)	0 = No 1 = Yes	Were you hospitalized since [date of last contact]? (Only if *fuEventType* == 3)
fuHospDate	Date	mm/dd/yyyy	What was the date of hospital admission? (Only if *fuHosp == 1)*
fuHospOut	Numeric (binary)	0 = No 1 = Yes	Have you been discharged from hospital? (Only if *fuHosp == 1)*
fuHospOutDate	Date	dd/mm/yyyy	What was the date of hospital discharge (Only if *fuHosp == 1* and *fuHospOut == 1)*
fuReason	Text		Indicate reason for your hospitalization
fuDiag	Text		Indicate diagnosis by healthcare provider, if available
fuReport	Picture/ Attachment		Take a picture/attach your discharge report, if available
fuHospID	Text		Name and place of hospital
fuCovid	Numeric (binary)	0 = No 1 = Yes	Were you diagnosed with COVID-19 disease by a healthcare professional?

Variable name	Type	Values and coding	Question to be asked
fuCovidTest	Numeric (multinomial)	0 = No 1 = Yes 2 = I do not know	Was the diagnosis based on a laboratory test (for the virus causing COVID-19 disease or antibodies against COVID-19 disease) (Only if *fuCovid == 1)*
fuCovidSympOnset	Date	dd/mm/yyyy	What was the date of symptom onset? (Only if *fuCovid == 1)*
fuCovidICU	Numeric (binary)	0 = No 1 = Yes	Was admission to the intensive care unit necessary? (Only if *fuCovid == 1)*
fuPreg	Numeric (multinomial)	0 = No 1 = Yes 2 = Not applicable	Are you pregnant? *(Only if subjSex == 1 or 2)*
Data from electronic tool **Table 8: Site information** Table 8 can be linked to Table 1 by siteID			
SiteID	Type of variable at discretion of site	[needs to be unique]	Unique and persistent identifier for each site
siteName	Text		Name of the site
siteCountry	Text		Site country
siteLocation	Text		Location of the site
sitePI	Text		Site principal investigator
SiteContact	Text		Contact information for the site

APPENDIX 2: ADVERSE EVENTS OF SPECIAL INTEREST

Based on SPEAC list, version December 2020 [13].

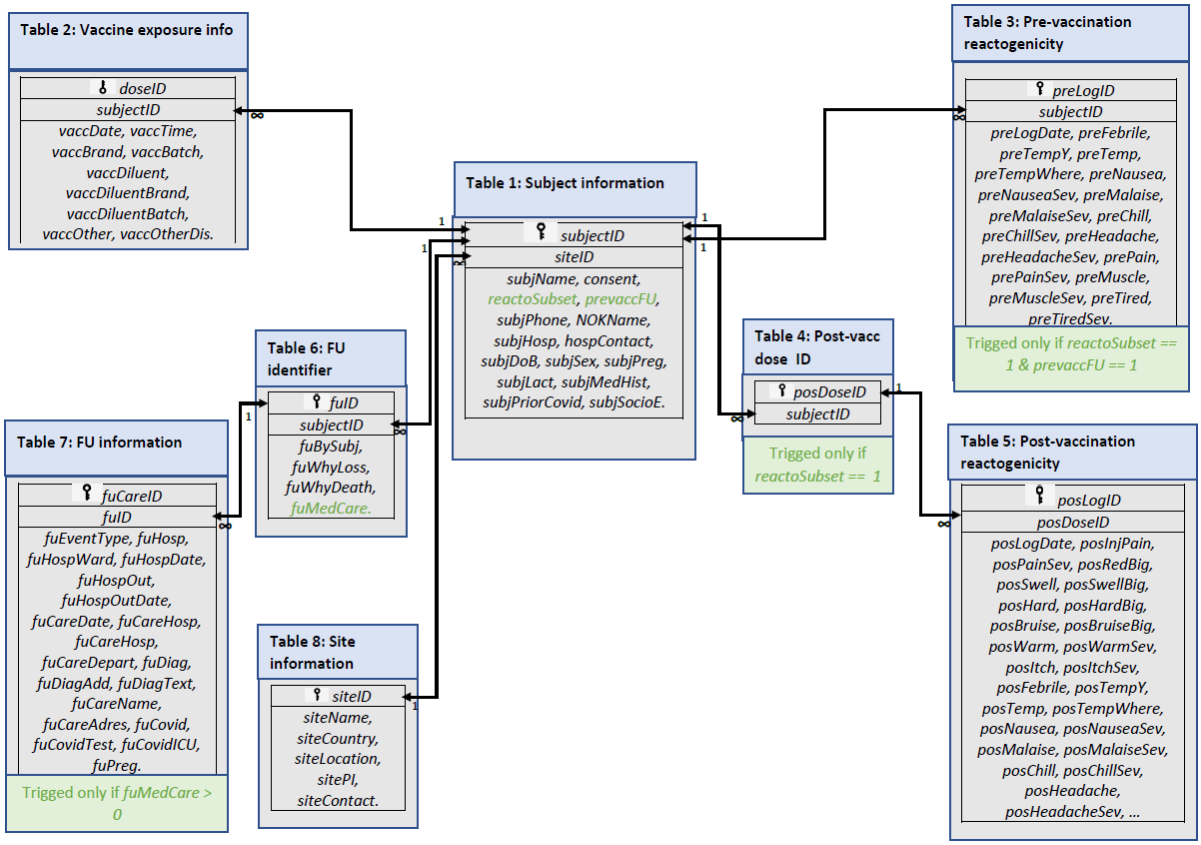
Adverse events of special interest (AESIs) and their risk windows.

No.	Body system	AESI	Risk interval
1	Cardiac	Acute cardiovascular injury	D1-D42
2	Dermatologic	Chilblain like lesions	D1-D42
3	Dermatologic	Single organ cutaneous vasculitis	D1-D42
4	Dermatologic	Erythema multiforme	D1-D42
5	Endocrine	Pancreatitis	D1-14
6	Endocrine	Subacute thyroiditis	D1-42
7	Gastrointestinal	Acute liver injury	D1-D42
8	Hematologic	Coagulation disorder (thromboembolism)	D1-D42
9	Hematologic	Thrombocytopenia	D1-D42
10	Immunologic	Vaccine-associated enhanced disease (VAED)	Unknown
11	Immunologic	Multisystem inflammatory syndrome in children (MIS-C) [TO REMOVE IN STUDIES LIMITED TO ADULTS]	D1-D42
12	Immunologic	Anaphylaxis	D0-D7
13	Musculoskeletal	Acute aseptic arthritis	D1-D42
14	Musculoskeletal	Rhabdomyolysis	D1-D7*
15	Neurologic	Acute disseminated encephalomyelitis (ADEM)	D1-D42
16	Neurologic	Bell's palsy	D1-D42
17	Neurologic	Generalized convulsion	D1-D42
18	Neurologic	Guillain-Barré syndrome (GBS)	D1-D42
19	Neurologic	Meningoencephalitis	D1-D42
20	Renal	Acute renal injury	D1-D42
21	Respiratory	Acute respiratory distress syndrome	D1-D42

*Sensitivity analysis with a risk interval 1-14 days may be considered

APPENDIX 3: RELATIONSHIPS BETWEEN STUDY TABLES

The following figure shows the relationship between the tables described in APPENDIX 1: DATA DICTIONARY.



APPENDIX 4: ADULT INFORMED CONSENT FORM

[The adult ICF template and process should 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 to the details provided to participants during consent].

Participant information sheet

You are visiting this vaccination centre to receive the first dose of COVID-19 vaccine as part of routine care. This vaccination centre is participating in observational research to monitor the safety of COVID-19 vaccines in [POPULATION OF INTEREST]. This study is taking place in [NUMBER] vaccination centres in [COUNTRY]. Around 30,000 persons vaccinated with COVID-19 vaccine will be included in the study and followed up for 3 months after the last dose of COVID-19 vaccine for specific health events of interest.

The study sponsor is [STUDY SPONSOR], and the principal investigators are [PRINCIPAL INVESTIGATORS].

If you participate in the study, data will be collected from you by interview at the time of enrolment and through regular questionnaires throughout the study period. By participating in the study you agree:

- to complete the study questionnaires [THOUGH MOBILE/WEBLINK/TELEPHONE] (weekly after each COVID-19 vaccine dose, until 3 months after the second COVID-19 vaccine dose) (or more frequently if selected for the reactogenicity subset);
- to be contacted by phone in case of non-response, if no answer is received, your next of kin can be contacted;
- that the [NATIONAL AEFI FOCAL POINT/NATIONAL PHARMACOVIGILANCE CENTER, to be detailed in the protocol] may contact your healthcare provider if further investigation is required;
- that, in the event you learn you are pregnant during the study, the [NATIONAL AEFI FOCAL POINT/NATIONAL PHARMACOVIGILANCE CENTER, to be detailed in the protocol] may follow you until the time of delivery, to monitor the safety of COVID-19 vaccines administered during pregnancy.

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. So, there will be no direct benefit to you from this research. However, information gathered from individuals vaccinated with COVID-19 vaccines will contribute to the safety surveillance of COVID-19 vaccines.

Your individual identity will be protected because the final information used for the research study will not bear your name, contact details or any other personal information about you that will allow

you to be identified. The vaccination centre 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 is confidentially and will be protected and only communicated to authorized persons. Any information collected from other physicians 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.

If you are willing to participate in this study that will monitor the safety of COVID-19 vaccines, please sign and date this form. You are free to contact [XXX] to understand how your information will be used. 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. Not participating, or withdrawing from this study, will not impact your access to healthcare.

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