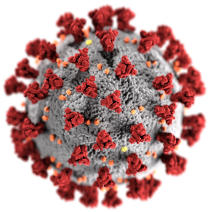
Safety Protocol for Hospital Case–Based Monitoring of Specific Adverse Events Following COVID-19 Vaccines: A Protocol Template from the ACCESS project

ACCESS

vACCine covid-19  monitoring readinESS

This protocol can be used by organizations for developing protocols to monitor COVID-19 vaccines post-introduction. Please reference as

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DISCLAIMER

This template protocol has been accepted by EMA as a deliverable of the framework contract No EMA/2018/28/PE, taking into account the comments received in a large consultation of EMA's stakeholders. The protocol expresses the expertise of the authors and the ACCESS consortium as well as feedback received from EMA and stakeholders. It may not be understood or quoted as being made on behalf, or reflecting the position of the European Medicines Agency or one of its Committees or Working Parties

Study Information

Title	Safety Protocol for Hospital Case–Based Monitoring of Specific Adverse Events Following COVID-19 Vaccines: A Protocol Template from the ACCESS project
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Product reference	*Reference number(s) of centrally authorised products and/or, if possible, of nationally authorised products subject to the study*
Procedure number	*If applicable, Agency or national procedure number(s), e.g., EMA/X/X/XXX*
Marketing authorisation holder(s)	*Marketing authorisation holder(s) which initiate(s), manage(s) or finance(s) the study*
Research question and objectives	To examine the risk of specific adverse events following <<COVID-19 vaccine product>>
Country(-ies) of study	To be determined; countries where <<COVID-19 vaccine product>> is available and in which participating hospital sites are located.
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Trademarks

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2 List of Abbreviations

ACCESS	vACcine Covid-19 monitoring readinESS
AESI	adverse event of special interest
CCO	case-crossover
CDM	common data model
COVID-19	illness caused by the SARS-CoV-2 virus
CRF	case report form
EMA	European Medicines Agency
ENCePP	European Network of Centres for Pharmacoepidemiology and Pharmacovigilance
EU PAS Register	European Union Electronic Register of Post-Authorisation Studies
GPP	Good Pharmacoepidemiology Practices
GVP	Good Pharmacovigilance Practices
ISPE	International Society for Pharmacoepidemiology
SARS-CoV-2	severe acute respiratory syndrome coronavirus 2
SCCS	self-controlled case series
SCRI	self-controlled risk interval
WHO	World Health Organization

3 Responsible Parties

To be completed by study investigator(s):

[Principal investigator institution name] **Address**	
name, degrees, job title	name, degrees, job title
name, degrees, job title	name, degrees, job title
name, degrees, job title	name, degrees, job title

[Sponsor name] **Address**	
name, degrees, job title	name, degrees, job title
name, degrees, job title	name, degrees, job title
name, degrees, job title	name, degrees, job title

Collaborating Institutions	**Study Sites**

4 Abstract

This section should be filled out with the following information.

Title:

Rationale and background:

Research question and objectives:

Study design:

Population:

Variables:

Data sources[1]:

Study size:

Data analysis:

Milestones[2]:

[1] Database custodians and research partners will be contacted to explore interest in and availability to participate in the study.

[2] Contracts between the sponsor and research organisation(s) and approvals by data protection, data custodian, ethics, and scientific review bodies are pending. Timelines may be impacted by approvals of these bodies, duration of contract reviews, and availability of data and staff at research institutions once contracts and approvals are finalised.

5 Amendments and Updates

None to date.

6 Milestones and Timeline

This section should be filled out with the following information.

Milestone	Date
Start of data collection[a]	
End of data collection[b]	
<Study progress report(s) 1>	
<Study progress report(s) 2>	
<Study progress report(s) 3>	
<Interim report 1>	
<Interim report 2>	
<Interim report 3>	
<Registration in the EU PAS Register>	
Final report of study results	

EMA = European Medicines Agency; EU PAS Register = European Union Electronic Register of Post-Authorisation Studies.

Note: Contracts between the sponsor and research organisation(s) and approvals by data protection, data custodian, ethics, and scientific review bodies are pending. Timelines may be impacted by approvals of these bodies, duration of contract reviews, and availability of data and staff at research institutions once contracts and approvals are finalised.

[a] Start of data collection is "the date from which information on the first study subject is first recorded in the study data set or, in the case of secondary use of data, the date from which data extraction starts." [1]

[b] End of data collection is "the date from which the analytical data set is completely available." [1]

7 Rationale and Background

The novel coronavirus SARS-CoV-2, the cause of COVID-19, has led to a global pandemic. Several COVID-19 vaccine candidates are currently under research and in development. COVID-19 vaccines may be licensed by the European Medicines Agency (EMA) after thorough review of data on quality, efficacy, and safety. Because the prelicensure period is short and the number of participants in clinical studies may be too small to enable the detection of extremely rare events, efficient monitoring of vaccine safety in the postmarketing phase will be needed, with the objective of identifying as rapidly as possible any unintended side effects of vaccination. Because it is likely that a large number of individuals would be vaccinated against COVID-19 as a preventive measure, it is crucial to detect even rare serious adverse events shortly after licensure.

As part of its preparedness activities, the vACcine Covid-19 monitoring readinESS (ACCESS) project has developed several template protocols that address vaccine coverage, vaccine effectiveness, and vaccine safety. To allow all countries to participate and to use maximum capacity in Europe, protocols are divided into those that use primary data collection (hospital based) and those that rely on the secondary use of population-based electronic health records databases.

This template protocol provides a framework for designing a hospital-based study to examine the risk of prespecified adverse events following COVID-19 vaccination using a self-controlled or other case-based study design. The template protocol may be used to investigate adverse events of special interest (AESI) (hypothesis generation), but the principles described can be applied to the study of unanticipated adverse events (signal evaluation). The ACCESS protocol templates based on secondary use of population-based electronic health records databases require those types of data to identify the study population, exposures, and outcomes. In contrast, this protocol template does not require data for the full source population or the use of population-based registers; the approach involves the recruitment of individual hospital sites. Hospital sites will identify eligible cases that have been treated at the hospital (whether in inpatient, emergency department, or outpatient ambulatory care) using locally held electronic records (e.g., discharge databases) and collect additional data from other sources (e.g., medical records, vaccination cards). This template will allow countries or other geographic locations that do not have population-based registers to participate in COVID-19 vaccine safety studies in a valid and efficient manner.

Irrespective of whether a signal has been identified, AESI are proposed as high priorities for assessment because they represent potential risks that would need immediate investigation or regulator action, based on experience with the specific vaccine being monitored or similar vaccines in terms of manufacturing process, composition (e.g., adjuvants), immunogenicity, and novelty.

As part of the harmonisation of COVID-19 vaccine safety monitoring during the clinical development phase, the Coalition for Epidemic Preparedness Innovations (CEPI) and the

Brighton Collaboration have created a preliminary list of AESI for COVID-19 vaccine safety monitoring [2]. Within the ACCESS project, a list of AESI was created and was approved by the EMA (EUPAS37273), as follows. The listed AESI may not become real safety concerns, but this template provides a framework to evaluate them. Additionally, the principles and study designs described in this protocol template may be used to address potential unexpected safety signals that may arise during product development or after licensure.

- Enhanced disease following immunisation
- Multisystem inflammatory syndrome in children
- Acute respiratory distress syndrome
- Acute cardiovascular injury, including microangiopathy, heart failure, stress cardiomyopathy, coronary artery disease, arrhythmia
- Coagulation disorder, including deep vein thrombosis, pulmonary embolus, cerebrovascular stroke, limb ischaemia, haemorrhagic disease
- Generalised convulsion
- Guillain Barré syndrome
- Diabetes (type 1 and unspecified type)
- Acute kidney injury
- Acute liver injury
- Anosmia, ageusia
- Chilblain-like lesions
- Single organ cutaneous vasculitis
- Erythema multiforme
- Anaphylaxis
- Death (any cause)
- Sudden death
- Acute aseptic arthritis
- Meningoencephalitis
- Acute disseminated encephalomyelitis
- Narcolepsy
- Thrombocytopenia
- Transverse myelitis
- Fetal and pregnancy outcomes (preterm birth, major congenital anomalies, microcephaly, fetal growth restriction, gestational diabetes, preeclampsia, spontaneous abortion, stillbirth, induced abortion, termination of pregnancy for fetal anomaly, neonatal death, maternal death)

Historically, vaccine safety studies have often used self-controlled designs such as the self-controlled case series (SCCS) and its variant, the self-controlled risk interval (SCRI) design, and the case-crossover (CCO) design because they make comparisons between exposed versus unexposed person-time within the same individual, rather than between exposed and unexposed individuals. Because of this, self-controlled designs inherently adjust for time-invariant confounders (both measurable and unmeasurable), such as chronic conditions present before the start of the follow-up period that are associated with the likelihood of vaccination (due to the increased risk of complications due to the disease vaccinated against) and adverse events under study. These designs are appropriate for studying the effect of transient exposures on outcomes that have acute onset and short latency, a short induction period (i.e., the outcome occurs within days or weeks of exposure), and a hypothesised period of increased risk (referred to as "risk windows") following exposure. Self-controlled designs are useful when coverage rates of immunisation are high, which makes it difficult to identify an appropriate comparator [3]. Only vaccinated individuals who have experienced an event are informative to risk estimation in the SCRI and CCO designs; thereby avoiding bias due to exposed persons being wrongly classified as unexposed because the data source for vaccinations is incomplete, and due to confounding by indication or contraindication [4]. Finally, because the SCRI and CCO designs both include in risk estimation only vaccinated persons who have experienced an event, no separate controls are required, and capture of all events in the population is not required [4].

Three designs have been identified as appropriate for use in a case-based hospital setting: the SCRI with a postvaccination control interval, the CCO, and vaccinated case-coverage designs. A vaccinated case-coverage design, a variant of the case-coverage design proposed in this template, will use the distribution of vaccine exposures in a population of persons similar to the cases to adjust for time trends in exposure present in a CCO design. An overview of each design as well as its assumptions, requirements, strengths, and limitations within the context of hospital-based studies are described in Annex 3.

Only AESIs that are typically treated in the hospital (inpatient, outpatient specialist, or emergency department) are appropriate to study with the approaches described in this template. Based on the assumptions and requirements of each proposed design, Table 1 comprises a decision framework for determining when the SCRI (with postvaccination control interval), CCO, and vaccinated case-coverage design can be used to study the specific AESIs with this protocol template. The framework takes into consideration outcome and vaccination characteristics, including the outcome latency and onset, ability to define the risk period for outcome following vaccination, effect of the outcome on likelihood of vaccination, and presence of temporal trends in vaccination. Annex 4 describes which of the AESIs are suitable to be studied using each of the three designs using outcome-based criteria. In addition to AESIs, unanticipated adverse events for which signals arise during clinical development or postlicensure can be assessed for

suitability of use of the SCRI, CCO, or vaccinated case-coverage design based on the full decision framework.

Table 1. Decision Framework for Determining Suitability of the SCRI, CCO, or Vaccinated Case-Coverage Design[a]

Criteria	Suitability of the SCRI (Postvaccination Control Window)	Suitability of the CCO	Suitability of the Vaccinated Case-Coverage Design
Outcome is treated in the hospital			
Yes	✓	✓	✓
No	X	X	X
Outcome latency			
Short latency	✓	✓	✓
Long latency	X	X	X
Outcome onset			
Acute onset	✓	✓	✓
Gradual onset	X	X	X
Ability to define risk period for outcome following exposure			
Can be clearly defined	✓	✓	✓
Cannot be clearly defined	X	X	X
Effect of outcome on likelihood of vaccination			
Outcome does not affect likelihood of vaccination	✓	✓	✓
Outcome temporarily decreases or increases likelihood of vaccination and the vaccine is a single dose	✓	O[b]	O[b]
Outcome temporarily decreases or increases likelihood of vaccination and the vaccine is multidose	O[c]	O[b]	O[b]
Outcome is a (permanent) contraindication to vaccination and the vaccine is single dose	✓	O[b]	O[b]
Outcome is a (permanent) contraindication to vaccination and the vaccine is multidose	O[c]	O[b]	O[b]
Outcome censors the period of observation for exposure (e.g., the outcome is death)	O[d]	✓	✓
Recurrence of outcome			
Outcome is independently recurrent	✓	✓	✓
Outcome is non-recurrent but rare	✓	✓	✓

Criteria	Suitability of the SCRI (Postvaccination Control Window)	Suitability of the CCO	Suitability of the Vaccinated Case-Coverage Design
Outcome is recurrent, and recurrent events are not independent (e.g., stroke)	✓[e]	✓	✓
Temporal trends in vaccination			
Temporal trends in vaccination are not present during the study period	✓	✓	✓
Temporal trends in vaccination are present during the study period	✓	X	✓

CCO = case-crossover; SCRI = self-controlled risk interval.

Key: Checkmark (✓) indicates design is suitable; X indicates not suitable; O indicates that the study design is possible under certain circumstances.

[a] Adapted from Baker et al. [4], Petersen et al. [5], and Madigan et al. [6].

[b] Suitable if prodromal symptoms before diagnosis of the outcome do not cause or prevent vaccination, either temporarily or permanently. To address this potential source of bias, every effort should be made to identify the onset of symptoms from the available data such as medical records, rather than relying on the date of diagnosis.

[c] The impact of bias due to the potential interference of the outcome on subsequent vaccination could be explored using Farrington's pseudolikelihood method for censored, perturbed, or curtailed postevent exposures [7].

[d] Farrington's pseudolikelihood method for censored, perturbed, or curtailed postevent exposures should be used to address bias due to censoring of exposures by events [7].

[e] If the event can be recurrent, and recurrent events are not independent, only the first event during follow-up should be studied.

8 Research Question and Objectives

Primary objective: To assess the risk of prespecified adverse events << (list the AEs) >> following vaccination with <<specific COVID-19 vaccine product>>

Secondary objectives:

- To assess the risk of prespecified adverse events << (list the AEs) >> in specific vaccine groups defined by platform and/or components (e.g., adjuvant)
- To assess the risk of <<adverse events>> after COVID-19 vaccination by age at vaccination, race, sex, pregnancy status, <<comorbidities>>, <<infections>>, <<concomitant vaccinations>>, <<concomitant medications>>, and <<dose number>>

[Note: If a specific outcome is only relevant to specific subgroups (e.g., multiple inflammatory syndrome would only occur in children), the specific subgroups would be studied in the primary analysis].

[This protocol may be used to either study AESIs and/or unanticipated adverse events. If both AESIs and unanticipated adverse events are investigated, an alternative to the above designation of primary and secondary objectives is that the primary objectives would focus on unanticipated adverse events while the secondary objectives would focus on AESIs].

[The secondary analysis of vaccine groups defined by vaccine platforms or components will be done if the products are hypothesised to have a similar safety profile across the grouped products.]

[Not all objectives may be feasible to study at all sites, depending on data collection capabilities. Investigators may adapt the objectives based on local settings and specific adverse events. This may include the option to study adverse events, as additional safety data become available.]

Note to future investigators using this template as a starting point to develop a study protocol: the wording of some sections of this protocol can be retained as-is or modified as appropriate in a final study protocol. Notes directly to the investigators in these sections are indicated in square brackets. As there are multiple potential COVID-19 vaccine products under development and additional adverse events may be identified, this protocol template refers generically to a <<COVID-19 vaccine product>> and at times, <<adverse event>> which may be replaced with the name of the specific vaccines or adverse events being investigated. The language in some sections, however, describes general principles, issues, and considerations for the investigator and will require the investigator to develop those sections with study-specific content, as appropriate for the specific study being considered.

9 Research Methods

9.1 Study Design

In this section, the investigator(s) should provide an overview of the study design(s) and specify which of the three study designs (SCRI, CCO, and/or vaccinated case-coverage designs) will be used for each AESI and the rationale for selecting the design(s). Please see Annex 3 for descriptions of each design and methodological considerations within the context of hospital-based studies.

If more than one study design approach is proposed for an AESI, it should be specified which design is primary and which is secondary.

Based on hypothetical scenarios defined by the presence of temporal trends in vaccination and the availability of data to adjust for these trends, Table 2 provides guidance on the selection of the specific study design. When more than one design is suitable for an outcome, the specific designs to be used and their designation as a

primary or secondary analytic approach (when more than one study design is possible) will depend on these factors.

In general, the CCO design and the vaccinated case-coverage design, are preferred over the SCRI because they do not require any assumptions about follow-up after the occurrence of the adverse event that may be necessary in the hospital-based setting, namely that any recurrent events would also be treated in the same hospital. Compared with the SCRI, another key advantage of the CCO and the vaccinated case-coverage design, is that they provide more timely results because they include all cases previously vaccinated in the risk or control intervals prior to the event. By contrast, the SCRI only includes cases if both the exposure and control intervals after vaccinations have accrued. Finally, the CCO and the vaccinated case-coverage designs can be used to study events that affect the probability of vaccination without requiring complex analytically techniques (which the SCRI requires under this circumstance).

However, a major threat to validity of the CCO is that one's likelihood to be vaccinated may change over time if the availability of the vaccine or recommendations of populations to be vaccinated change over time (e.g., if the vaccine recommendations change from high-risk individuals only to a more universal recommendation). Additionally, other time-varying factors such as levels of circulating natural SARS-CoV-2 may affect an individual's decision to be vaccinated. If temporal trends in vaccination are observed during the study period, resulting bias may be reduced by selecting a control window that is relatively close in time to the exposure window, if the risk window itself is short. If that is not possible, then the vaccinated case-coverage design may be used to adjust for time trends in exposure. To implement a vaccinated case-coverage design, data to estimate temporal trends in vaccination among groups of vaccinees defined by key confounders (e.g., daily number of vaccinated persons stratified by important risk factors) must be available in the target population in catchment areas for participating hospitals.

Table 2. Guidance for Selecting Primary and Secondary Analytic Approaches

Scenario	Primary Analysis	Secondary Analysis	Notes
No temporal trends in vaccination are observed	CCO	None	Scenario requires data to test for temporal trends in exposure.
Temporal trends in vaccination are observed and data are available to estimate temporal trends in vaccination among groups of vaccinees defined by key confounders	Vaccinated case-coverage design	SCRI	A vaccinated case-coverage design is proposed as the primary approach because it does not require follow-up on time-varying confounders after the adverse event, which may not be available following hospital discharge. Matching cases to the reference population on the calendar date accounts for temporal trends in vaccination. The SCRI design is proposed as the secondary approach because the vaccinated case-coverage design assumes that temporal trends in vaccination of controls represent that of the cases.
No data available to verify presence/absence of temporal trends in vaccination in the source population and temporal trends are not suspected	CCO	SCRI	The CCO is proposed as the primary analytic approach because it does not require follow-up on time-varying confounders after the adverse event, which may not be available following hospital discharge; further it is not susceptible to bias due to the outcome affecting the probability of vaccination (relevant for multidose vaccines). The SCRI design is proposed as the secondary approach to assess potential bias in the CCO design because it does not assume the absence of temporal trends in exposure.
Temporal trends are suspected, but no data are available to assess or adjust for temporal trends in vaccination, or temporal trends in vaccination are observed but data are not available to estimate temporal trends in vaccination among groups of vaccinees defined by key confounders	SCRI		Temporal trends in exposure may be suspected if there are changes over time in the availability of vaccines or in recommendations regarding who should be vaccinated.

Primary: preferred/recommended, secondary means alternative

CCO = case-crossover design; SCRI = self-controlled risk interval design.

9.2 Setting

9.2.1 Source Population

This will be a multisite study across several hospitals in European countries in which <<COVID-19 vaccine product>> is approved and recommended for use. The source population for the study will comprise individuals eligible to receive COVID-19 vaccination, considering the product-specific indications and availability of the vaccine, and residing in the catchment areas of participating hospitals. If the COVID-19 vaccine is indicated for a given population, but because of a vaccine shortage is only administered in a more restricted population, the source population will be limited accordingly.

9.2.2 Study Period

9.2.2.1 Self-controlled Risk Interval Design

A guiding principle for defining the study period for the SCRI design is that a full history of timing of both events and exposures must be available throughout the study period [3]. The study period will begin in each hospital when the vaccine becomes available in the catchment area for the hospital and will end on the last date on which data on vaccinations and hospital discharges is available.

9.2.2.2 Case-Crossover and Vaccinated Case-Coverage Designs

For the CCO and vaccinated case-coverage designs, a full history of timing of exposures must be available in the risk and comparison windows preceding captured events. Therefore, the study period should comprise a period during which data on both exposures and outcomes are available.

For the CCO study, the study period should be selected to cover a time frame during which the propensity to receive the vaccine is relatively constant over time in the source population. If a such a study period is not available, the CCO design should not be used.

9.2.3 Study Population and Follow-up Period

This section should explicitly describe the study population and follow-up periods for the SCRI, CCO, and vaccinated case-coverage designs.

9.2.3.1 Self-controlled Risk Interval Design

To be included in the SCRI, individuals must meet the following criteria. Note that the study population for analysis of each outcome of interest will be different.

- Meets criteria for source population, assessed at the time of vaccination
- Received <<COVID-19 vaccine product>> during the study period
- Must have experienced an event meeting case-identification criteria within the risk or control intervals following vaccination

The follow-up period will begin at the date of vaccination and finish at the end of the control window.

9.2.3.2 Case-Crossover and Vaccinated Case-Coverage Designs

To be included as a case in the CCO or vaccinated case-coverage study, individuals must meet the following criteria. Note that the study population for analysis of each outcome of interest will be different.

- Meets criteria for the source population, assessed at the time of the event
- At least one occurrence of an event meeting case-identification criteria during the study period
- Data on exposures available through the beginning of comparison window

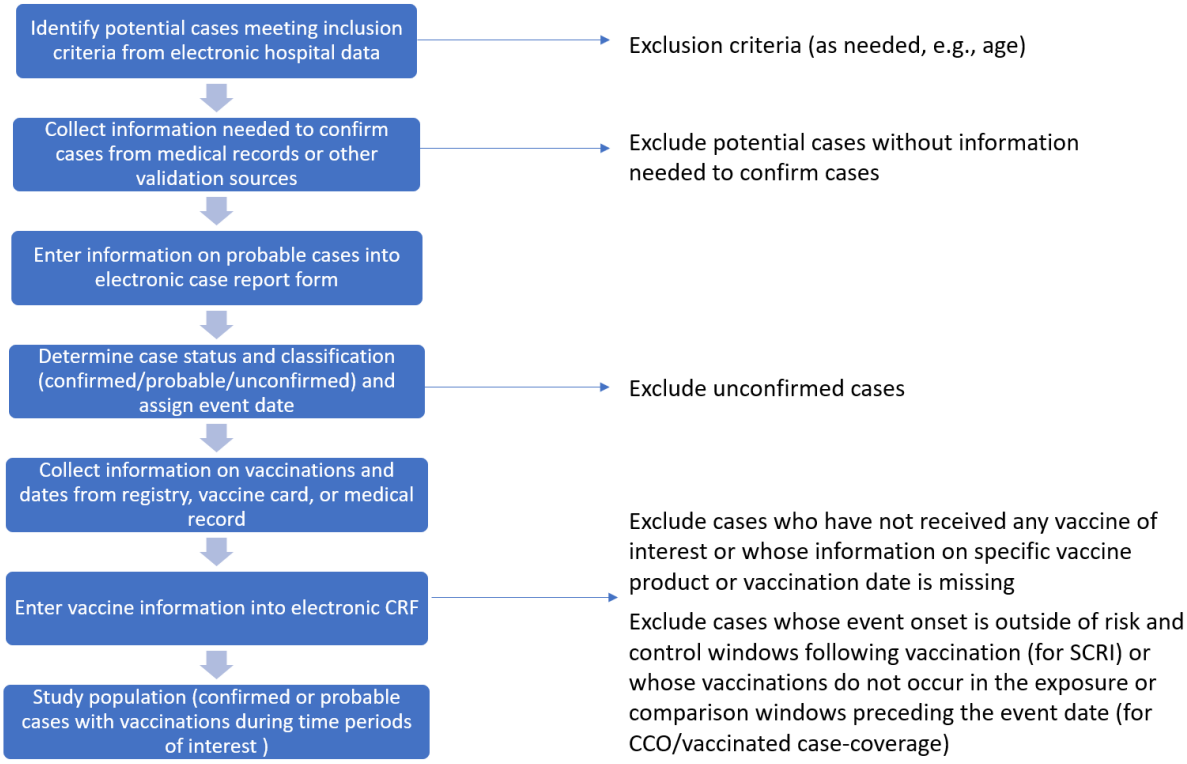
The follow-up period will begin at the start of the comparison window (that precedes the exposure window) and will finish at the date of outcome onset.

9.2.4 Data Collection

Data collection will occur at the site level in accordance with the process outlined in Figure 1. Data for case ascertainment of each outcome will be collected in an electronic case report form (eCRF). Since non-cases will be excluded from the study, vaccination information should be collected only on cases that have been confirmed by medical record review adjudication. Data on COVID-19 vaccination for the confirmed and probable cases will be collected in a separate eCRF, to allow for blinding of timing of the event relative to vaccination when collecting exposure information.

[The investigators should describe the data collection tools to be used].

Figure 1. Operational Steps to Identify Cases and Exposure Information for the SCRI, CCO, and Vaccinated Case-Coverage Designs



CCO = case-crossover; CRF = case report form; SCRI = self-controlled risk interval.

9.2.5 Variables

In this section, outcomes, exposures, covariates, and their operational definitions will be described. As general reference and for the opportunity to harmonise study methods, it is recommended that investigators review the output of the Safety Platform for Emergency vACcines (SPEAC) project, which is developing event definitions, code lists, lists of risk factors, and risk window definitions for many of the AESI. This information will be released on the Brighton Collaboration website in the coming year (https://brightoncollaboration.us).

9.2.5.1 Outcome Assessment

In this section, the operational definitions for identifying <<adverse event>> in electronic data should be described, with reference to code lists included in a separate protocol appendix.

[Outcome definitions for the proposed adverse events, including code lists, are currently being developed by another workgroup in this project and will be incorporated in this protocol when they become available.]

<<Adverse event>> will be identified in each participating hospital's discharge database or other electronic data bases using diagnosis codes, or a combination of diagnosis with

procedure or treatment codes in the inpatient, emergency department, or ambulatory speciality care settings. Additionally, electronic laboratory data could be used to identify events, if applicable to the outcome.

For recurrent events in the SCRI design, "washout periods" anchored on the outcome date will be used to identify incident events when multiple visits or codes for the same event occur during follow-up; any events with another event (in any care setting, including inpatient, emergency room, hospital outpatient, or primary care) within the washout period will be excluded. For recurrent events in the case-cross over and vaccinated case-coverage designs, only the first event observed during the study period will be included.

Case validation will be undertaken by clinical reviewers blinded to vaccination status and timing of the event relative to vaccination. Case status and date of outcome onset will be confirmed using medical records, physician questionnaire, or other official documentation (e.g., clinical case notes), depending on the data source. Case status will be determined based on Brighton Collaboration definitions where available [2]. SPEAC is developing a toolbox for case definitions that can be obtained on the Brighton Collaboration website or through the following e-mail address: bc-coordinator@brightoncollaboration.us. The comparative analysis will only include confirmed cases and the dates of onset assigned by the clinical reviewers.

9.2.5.2 Exposure Assessment in Cases

In this section, operational definitions for identifying exposure should be described, including type of vaccine codes.

Exposure status will be identified in confirmed and probable cases. For this study, an indicator for each dose of <<COVID-19 vaccine product>> and date of vaccination will need to be identified for all cases. In the SCRI design, if multiple doses of vaccine are given during the study period, each individual dose will be evaluated separately. To the extent feasible, in the case of multidose vaccines, exposure information should be captured following hospital discharge to avoid bias due to the outcome impacting the observation period for exposure. If collecting exposure information after hospital discharge is not possible, the impact of this potential bias could be explored in a sensitivity analysis using Farrington's pseudolikelihood method for censored, perturbed, or curtailed postevent exposures [7].

In the primary analysis, exposure will be based on a specific COVID-19 vaccine product; a secondary analysis will be conducted stratified by vaccine groupings defined by technology, platform, or components (e.g., mRNA, adenovirus backbone, protein recombinant vaccines, adjuvant). If the concern for a particular outcome is related to a specific product (as per data existing at the time of full protocol development), the analysis for the particular outcome will only be conducted for the specific product, and a combined analysis of products will not be conducted.

Exposure information will be obtained from pharmacy dispensing records, general practice records, immunisation registers, vaccination cards, medical records, and/or other secondary data sources. The availability and feasibility of data sources to obtain vaccination information will likely vary by jurisdiction. Depending on the data source, vaccines may be identified via Anatomical Therapeutic Chemical codes, nationally used codes, local codes, or free text. If vaccination cards are used, and if feasible, a sample of vaccine records could be validated against other sources such as medical records or health care provider questionnaire to confirm the vaccine product and date of vaccination.

If the vaccine is administered in multiple doses, then each exposure code will be considered to be a separate instance of vaccination, provided that sufficient time has passed between the dates of the codes, based on the vaccine dosing schedule and taking into account the possibility that some persons may receive subsequent doses slightly earlier than indicated in the vaccine dosing schedule (for example: if the vaccine dosing schedule calls for two doses at least 28 days apart, then any code for vaccination that occurs fewer than 21 days after the first code would be excluded, under the assumption that any additional codes after the first code are duplicates of the same dose). If the vaccine is administered as a single dose, then only the first exposure code during the study period will be considered, which assumes that the remaining codes are errors.

9.2.5.3 Risk and Control Windows

In this section, risk/exposure windows will be defined for <<adverse event>> in table format.

SCRI

If the SCRI is used, a risk window, in which person-time will be considered exposed, will be selected after vaccination to reflect the hypothesised period of increased risk of the outcome due to vaccination. By convention, the risk window will index on the date of vaccination, which will be time = 0. A postvaccination control window will be selected to estimate the baseline rate of the outcomes. The control window definition (length and timing relative to vaccination) will be the same across individuals and will balance the need to obtain adequate statistical power against the threats of bias due to loss to follow-up and time-varying confounding. A washout period following the risk window may be incorporated to avoid any carryover effects of the vaccine into the postvaccination unexposed person-time.

If multiple doses of vaccine are given during the study period, the risk and control windows of one dose must not overlap with the risk or control windows of a subsequent dose, based on the vaccine dosing schedule. Some possible approaches to define the control interval, depending on the length of the risk interval and spacing between doses of the vaccine, are provided below:

- If there is a short interval between doses of the vaccine and a long risk interval, it would be necessary to avoid overlap of the risk interval of one dose with the risk and/or control intervals of a subsequent dose; depending on the length of the risk interval and the spacing between doses, it may be necessary for the control interval to be positioned after the risk interval of the final dose. For example, suppose the vaccine is administered in two doses approximately 28 days apart, and the outcome of interest has a risk interval of 1 to 42 days. Conducting a dose-level analysis (i.e., considering each dose to be a separate observation), with a risk interval of 1 to 42 days following each dose could potentially lead to confounding of the first dose by receipt of the second dose, and vice versa. To address this, a person-level analysis could be conducted combining the risk intervals following each exposure, for example:
  - For persons who receive two doses, define the risk interval as 1 to 42 days after the first dose plus 1 to 42 days after the second dose. The control interval could then be defined as 43 to 127 days after the second dose.
  - For persons who receive only one dose, define the risk and control intervals as 1 to 42 and 43 to 127 days after vaccination, respectively.
  - In the above scenarios, the control window could be placed even further in time from vaccination to incorporate a washout period between the risk and control intervals, as needed.
- If there is a short interval between doses of the vaccine but the risk interval is short, a dose-level analysis (treating each dose as a separate observation) could be conducted, but care must also be taken to ensure that the control interval does not overlap with the next dose. For example, suppose the vaccine is administered in two doses approximately 28 days apart, and the outcome of interest has a risk interval of 0 to 7 days. The control interval would need to end before 27 days after vaccination (e.g., 8-15 days) to ensure that there is no overlap of the control interval of the first dose with the risk interval of the second dose.

If the outcome affects the likelihood of a subsequent vaccination after the first dose, the impact of this potential bias could be explored in a sensitivity analysis using Farrington's pseudolikelihood method for perturbed, censored, or curtailed observation periods for postevent exposures [7].

CCO Design

If the CCO design is used, an exposure window preceding the event will be selected to reflect the period during which exposure to COVID-19 vaccination is hypothesised to trigger the adverse event of interest. A single comparison window preceding the risk window will be selected to reflect the baseline prevalence of exposure; the comparison window should be selected independently of exposure status. Multiple comparison windows per case may also be considered but are not recommended because they may increase the potential for bias due to time-varying confounding and temporal trends in

exposure. By convention, the exposure window will index on the date of the adverse event, which will be time = 0. A washout period between the exposure and comparison windows can be implemented to avoid any carryover effects of the vaccine between the two windows.

If multiple doses are given during the study, the comparison window should be selected such that the underlying propensity to be vaccinated is not correlated between the exposure and comparison window. This guidance is given because individuals who are vaccinated in both windows do not contribute to the analysis and excluding a large number of individuals due to this reason reduces statistical power and precision of risk estimates. As an example, suppose the vaccine dosing schedule calls for two doses approximately 28 days apart, and the risk window is 1 to 21 days prior to the event. If one were to select a control window of 22 to 42 days, we anticipate that many persons would be vaccinated in both windows and become uninformative to the study. To avoid this, the comparison window could be defined as 50 to 70 days before the event; the comparison window could be placed even further before the event to incorporate a washout period between the exposure and comparison window, as needed.

9.2.5.4 Vaccinated Case-Coverage Design

For the vaccinated case-coverage analysis, exposure and comparison windows will be defined using the same guidance and considerations as the CCO design, and cases that were vaccinated in either window will be informative to analysis. For each case, the observed odds of vaccination within the exposure window will be estimated and compared with an expected odds of vaccination inside the exposure window, which will be estimated in an external reference population. Data to estimate the expected odds of vaccination may come from population-based registers or surveys, or other secondary data sources that reflect temporal patterns in vaccination among the target population in the catchment areas for cases.

To calculate the expected odds of vaccination in the exposure window for each case, strata comprising all persons in the reference population who are similar to the case with respect to confounder status (e.g., age, sex, and risk factors) on the day of outcome onset will be created. Then the odds of vaccination in the same calendar period equating to the case's exposure window will be computed in the reference population. Reference population individuals in the stratum had to have received the same vaccine during the same calendar periods equating to the exposure or comparison windows before the onset of the case onset date and had to belong to the same groups as the case with regard to predefined confounding factors (e.g., age, sex, high-risk conditions). These predefined confounding factors will be selected on the basis that temporal patterns in vaccination are likely to be different across different levels of the confounder. Of note, this design requires information on vaccination in the reference population by risk factors and calendar date of vaccination. It is anticipated that these data will not be available for the catchment areas of most hospital sites.

Further Considerations for all Designs

For all designs, the risk window will depend on the severe adverse event under study and will be based on biological plausibility, expert input, clinical trials of COVID-19 vaccines, active and passive postmarketing surveillance of COVID-19 vaccines (including spontaneous reporting databases administered by pharmaceutical companies), and safety data from other vaccines (as applicable). Additionally, if the risk interval for an outcome is not well established (e.g., an emerging, unanticipated safety signal), then sensitivity analysis incorporating different definitions of the risk interval should be conducted.

9.2.5.5 Covariate Assessment

In this section, covariates of interest, operational definitions, and purpose for assessment will be described.

Descriptive Covariates

For descriptive purposes, sex, age, country, race/ethnicity (if available), and calendar month of vaccination will be output in the study population.

Confounders

Self-controlled Risk Interval and Case-Crossover Designs

While the SCRI and the CCO implicitly adjust for measured and unmeasured confounders that do not vary over time (e.g., chronic conditions and gender), covariates that vary over time may act as confounders if they affect the risk of the adverse event [4] or affect the timing of seeking care for the adverse event (e.g., provision of health care utilisation due to lockdown periods). Below are some possible time-varying confounders of relevance, though this list will need to be adapted based on the specific study population and outcomes of interest. It is anticipated that not all hospitals will have the ability to capture time-varying variables after hospital discharge.

Age may act as a time-varying confounder in children, depending on the outcome of interest. Age may be adjusted for in the SCRI by dividing person-time during follow-up into prespecified age groups (e.g., weeks or months).

Calendar time as a proxy for circulating wild-type SARS-CoV-2 and other respiratory infections and for health care utilisation (e.g., periods of lockdown) may also act as a time-varying confounder. Separate categorical variables for calendar time can be created by dividing up person-time into the relevant categories of calendar time; the categories should be selected based on the timing of changes in health care utilisation and rates of circulating infection (at the population level), rather than equally spaced categories such as calendar months. It is recommended that hospital site's internal administrative data be used to identify the specific timing of changes in health care utilisation in the population.

Both infections and receipt of other non-COVID-19 vaccines may act as confounders if they increase the risk of the adverse event of interest. Infections relevant to the adverse event of interest (e.g., SARS-CoV-2, influenza-like illness, upper respiratory infection, gastrointestinal infection) will be captured using diagnosis codes in hospital data and primary care data, if feasible. It is anticipated that not all hospitals will be able to collect information regarding individual-level infections for adjustment in the SCRI design because they will not be able to capture information after discharge, and any data obtained directly from primary care providers may require informed consent from patients. Vaccines relevant to the adverse event of interest will be captured in pharmacy dispensing records, general practice records, immunisation registers, medical records, vaccination cards, or other secondary data sources.

Both the SCRI and CCO can adjust for infections and receipt of other non-COVID-19 vaccines. In the SCRI, this is done by categorising the entirety of follow-up time into "exposed" and "unexposed" person-time with respect to infection or vaccination; each infection and non-COVID-19 vaccine will have its own risk window based on the temporal effect of the infection/vaccine on the outcome of interest. In the CCO, infection and vaccine status (yes vs. no) will be assessed separately during the risk and control windows for COVID-19 vaccination.

Vaccinated Case-Coverage Design

The vaccinated case-coverage design is not self-controlled and may be biased if time trends in exposure for calculating the expected odds of vaccination in the exposure window is not the same in cases and in the reference population. Adjustments for any such confounders will be made by matching cases to the reference population on the status of the confounder (e.g., age and sex), as of the case's index date. To do this, the risk stratum for calculating the expected odds of vaccination in the exposure window for each case will need to be defined accordingly.

[Investigator should add confounders relevant to specific adverse events in this section and provide operational definitions].

Effect Modifiers

In this section, any factors (e.g., age at vaccination, sex, race, chronic conditions, infections, concomitant vaccinations and medications, and dose number) that are hypothesised to modify the effect of COVID-19 vaccination on the adverse event of interest will be listed. Chronic conditions will be identified using diagnosis and procedure codes in inpatient data, outpatient specialist visits, medical records, and primary care data, as available. COVID-19 vaccination is given in multiple doses, dose number will be assessed as a potential effect modifier.

Additionally, health care workers and pregnant women may potentially be specific populations of interest and may be analysed as subgroups. Information on occupational

status may be obtained from administrative or medical records; availability of this information may be incomplete and may not be available in all study sites.

[Investigator should specify the effect modifiers and their operational definitions in this section].

9.3 Data Sources

A feasibility questionnaire (Annex 5) will be distributed to candidate hospital sites before the initiation of the study to identify suitable sites for the study. Data sources will include hospital discharge databases and other electronic data sources that capture diagnoses and treatments in the inpatient, emergency department and speciality ambulatory care settings at the participating hospital site, medical records, vaccination cards, immunisation registers, and other secondary data sources. To participate in this study, data sources must have the ability to capture data on COVID-19 vaccinations (including the ability to distinguish between individual products and identify the date of vaccination) and adverse events of interest as treated in the hospital. The ability to conduct follow-up on exposures, outcomes, and time-varying covariates after discharge will be assessed in the feasibility assessment for informational purposes, though it will not be a prerequisite to participate in the study if the vaccinated case-coverage or CCO design is used, or if the assumptions for the SCRI (described in Annex 3) are met. Data sources must also have the ability to conduct case adjudication to confirm cases and to assign onset dates if available in medical charts.

The data sources for the exposures, outcomes, and covariates will be listed in this section, including coding systems, data lag, and starting date of data availability. The size of the database and number of COVID-19 vaccinations by age and comorbidities of interest in the most recent data update will be included in this section. Validation data on relevant data elements will also be described if available.

9.4 Study Size

Statistical power is driven by the number of confirmed cases and the ratio between the duration of the risk and control periods. In Table 3, we provide the estimated number of cases (i.e., vaccinated cases with an event in the risk or control interval) needed for a SCRI design to have 80% power under a range of assumed effect sizes and the proportion of the observation period in the risk interval (number of days in the risk interval/[number of days in the risk interval + number of days in the control interval]) [8].

Additionally, based on the range of assumed relative incidences, durations of the risk and control intervals, background rate, and assumed vaccine uptake, one could estimate the total population size of the catchment areas for the hospital sites needed to achieve the necessary sample sizes. Other approaches may be acceptable to estimate study size.

Table 3. Sample Size Needed to Achieve 80% Power for the Self-controlled Risk Interval Design

Proportion of the Observation Period in the Risk Interval	Relative Incidence	Sample Size (Number of Cases)
25%	1.5	230
25%	2	74
25%	2.5	41
25%	3	28
25%	3.5	21
33%	1.5	203
33%	2	68
33%	2.5	38
33%	3	27
33%	3.5	21
50%	1.5	194
50%	2	69
50%	2.5	41
50%	3	29
50%	3.5	23

[To be completed by the study investigator(s) based on assumptions regarding length of the risk and control intervals and effect estimate size at the time of the full protocol development.]

9.5 Data Collection and Management

Each site will transform their local patient level data into the VAC4EU common data model (CDM). A distributed common programme will be run locally at each site using data from the CDM, which will create the study variables from the CDM, create the analytic data set, and conduct the analysis. Aggregate results and summary estimates will be returned to a single coordinating centre for pooled meta-analysis and reporting.

Routine procedures will include checking electronic files, maintaining security and data confidentiality, following analysis plans, and performing quality control checks of all programmes. Each research partner will maintain any patient-identifying information securely on site according to internal standard operating procedures or guidance documents.

Security processes will be in place to ensure the safety of all systems and data. Every effort will be made to ensure that data are kept secure so that they cannot be accessed by anyone except select study staff.

Appropriate data storage and archiving procedures will be followed in each research centre, with periodic backup as appropriate. Standard procedures will be in place at each research centre to restore files in the event of a hardware or software failure.

[Investigators should modify this section as needed for the specific study; if specific procedures of the identified hospital sites are known, they can be included here]

9.6 Data Analysis

9.6.1 Descriptive Analysis

The number and proportion of cases in the study population will be output according to descriptive characteristics for each AESI under study. Temporal graphs will be output showing the number of cases by time of vaccination to time of event (in days) for each AESI under study.

9.6.2 Measures of Association

If the SCRI is used, conditional Poisson regression (conditioned on the individual) will be used to estimate incidence rate ratios and 95% confidence intervals for each outcome, with logarithm of time in each interval as the offset. If the CCO is used, conditional logistic regression (conditioned on the individual) will be used to estimate odds ratios and 95% confidence intervals for each outcome.

For the SCRI and CCO, time-varying confounders will be adjusted for in regression models. If applicable, in the SCRI, age and calendar time may be categorised into several categories, or treated as polynomial functions, with or without the use of splines in regression models. Both unadjusted and adjusted incidence rate ratios, by site and pooled across all sites, will be reported.

If the vaccinated case-coverage design is used, a logistic regression model will be fit for each AESI under study using separate summarised data sets. The data set for each AESI under study will have one record per risk set (i.e., case), with the outcome indicating whether vaccination occurred in the case's exposure or comparison window. The logarithm of the expected odds (i.e., logit) of vaccination inside the exposure window will be entered into the model as an offset term. For each case, this expected probability of vaccination inside the exposure window will be obtained from the reference population, as described in Annex 3. The model will include only an intercept with no covariate, with the following general form.

$$\text{Logit}(p_1) = \text{logit}(p_0) + \beta_0,$$

where p_1 is the observed probability of vaccination inside the exposure window among cases, p_0 is the expected probability of vaccination inside the exposure window among cases (based on vaccination data in the reference population), β_0 is the intercept; by exponentiating this coefficient, one obtains an odds ratio describing the association between vaccination and the outcome of interest occurring inside the risk interval.

Of note, the logistic regression model drops all cases for whom the expected probability of vaccination inside the exposure window is 0 or 1 (i.e., either everyone or no one is vaccinated inside the risk interval amongst the reference population), as these cases are noninformative.

9.6.3 Data Integration

Results will be presented separately for each data source and pooled across data sources.

The method for pooling of results will depend on the data-sharing policies of each of the participating hospitals. If all sites are able to share individual-level data or aggregate data needed for the analysis (e.g., case counts by vaccination interval and covariate status), local investigators will transfer their site's individual-level data to the study coordinating centre to contribute to an analysis with one-stage pooling.

If some or all sites do not allow the necessary patient-level or aggregate data to be shared, then data analysis could be performed by data custodians at their sites behind firewalls. Counts and coefficients would be shared with the study coordinating centre, and overall results would be summarised using meta-analytic techniques.

Alternatively, if some institutions are able to share the necessary patient-level or aggregate data and others are not, a hybrid approach for pooling of data could be taken [9]. Depending on data-sharing restrictions, local investigators would either transfer aggregated data to the study coordinating centre for further analysis and pooling, or they would run the same analyses locally and transfer coefficients and counts to the coordinating centre. Both the pooled odds ratios/incidence rate ratios and individual odds ratios/incidence rate ratios from sites would then be summarised in a meta-analytic technique.

9.6.4 Subgroup Analysis

If relevant to specific adverse events, the presence of effect modification by relevant variables (dose number, age at vaccination, specific comorbidities, concomitant vaccinations) will be assessed by adding an interaction term between vaccination and the effect modifier of interest to regression models for the CCO and SCRI designs. Effect modification will be assessed in the vaccinated case-coverage design by adding the potential effect modifier as a covariate to the regression model.

Subgroup analysis will be performed by strata of effect modifiers of interest as relevant. For the vaccinated case-coverage design, subgroup analysis will require that the at-risk-stratum for calculating the expected odds of vaccination be redefined based on the different subgroups.

[The study investigator(s) should describe subgroups motivated by the current understanding of the study outcomes in this section.]

9.6.5 Sensitivity Analysis

Sensitivity analysis centred around the robustness of results to assumptions of the study design and availability of key data elements may include the following:

- If the risk window is not well known, conduct analyses with alternative risk intervals and/or washout periods between the risk and comparison windows
- Incorporate a more sensitive case definition by including both confirmed and probable cases
- If exact dates of events are unknown and some are imputed (e.g., if the onset of the event could be prior to date assigned by case validation), conduct analyses surrounding assumptions used to set the event date
- If time-varying confounders are not fully available in all sites, restrict the analysis to sites where data are available on these time-varying confounders
- If the outcome affects the likelihood of exposure and/or the no exposure information is collected after the hospital visit associated with the outcome, consider using Farrington et al's pseudolikelihood approach [7]

9.7 Quality Control

Standard operating procedures or internal process guidance at each research centre will be used to guide the conduct of the study. These procedures may include internal quality audits, rules for secure and confidential data storage, methods to maintain and archive project documents, quality control procedures for programming, and standards for writing analysis plans.

This section will describe the study-specific process for programming quality control (e.g., independent programming and/or review of summary output and programming logs by a second programmer), and procedures for data storage, archiving, and backup at each study centre. Also described will be processes for review and quality control of study documentation and reporting of pooled results across research centres.

9.8 Limitations of the Research Methods

The study is subject to limitations due to both the study design and use of clinical data and other data not collected for research purposes. The major limitation of self-controlled designs and their variants is that they are only suited to study outcomes with a short induction period and an abrupt onset. These designs are not appropriate for assessing outcomes with gradual onset or a long induction period.

Other limitations of self-controlled designs and their variants (including the vaccinated case-coverage design as proposed in this template) include the possibility that incorrectly specifying the risk window will lead to biased incidence rate ratio/odds ratio estimates. If the risk window is not well characterised based on prior data or studies, sensitivity analyses with alternative risk interval definitions should be undertaken. Other

study design approaches that are less susceptible to this source of bias (for example, a cohort design with historical comparators or a traditional cohort design) could also be used as complimentary approaches, as appropriate. Another limitation of the SCRI and CCO is that they are susceptible to bias due to time-varying confounders such as infections. While attempts to collect and adjust for time-varying confounders will be made, not all data sources will have information on them. A major limitation of the CCO is that it should not be used if there are temporal trends in exposure. While the vaccinated case-coverage design addresses potential bias due to time trends in exposure, it assumes that the temporal trends in exposure are the same in cases as they are in the reference population. Another limitation is that it requires information on the number of persons vaccinated on a daily basis, stratified by subgroups of important confounders; it is anticipated that this information will not be available for populations of interest for the catchment areas of all hospital sites. Finally, the vaccinated case-coverage design is that it may have less statistical power than the CCO and the SCRI designs, as cases for whom nearly everyone or no one is vaccinated during the risk window are uninformative for the analysis.

Data related limitations include that the study will depend on the accuracy of codes and algorithms to identify outcomes, and the availability of records to confirm outcomes. Misclassification of outcome (both events and dates of events) will be minimised by conducting validation. However, the use of medical record and other secondary data sources for validation purposes may limit the ability to apply Brighton Collaboration criteria and other standardised case definitions to confirm outcomes and to identify true onset of the outcomes.

Exposure ascertainment may be based on pharmacy dispensing records, general practice records, vaccination registers, medical records, vaccination cards, or other data sources. The validity of coding for COVID-19 vaccines and dates of vaccination are currently unknown. Additionally, it is unknown whether coding will distinguish between specific products of COVID-19 vaccines.

9.9 Other Aspects

This section, which is optional, will contain information on any other aspect of the research method not covered by previous sections, such as scientific advisory board or endpoint adjudication committees.

10 Protection of Human Subjects

This is a non-interventional study using secondary data collection and does not pose any risks for patients. All data collected in the study will be deidentified with no breach of confidentiality with regard to personal identifiers or health information. Each hospital research partner will apply for an independent ethics committee review according to local

regulations. Data protection and privacy regulations will be observed in collecting, forwarding, processing, and storing data from study participants.

11 Management and Reporting of Adverse Events/Adverse Reactions

For studies in which the research team uses data from automated health care databases only, according to the International Society for Pharmacoepidemiology (ISPE) [10] Guidelines for Good Pharmacoepidemiology Practices (GPP),

> *Aggregate analysis of database studies can identify an unexpected increase in risk associated with a particular exposure. Such studies may be reportable as study reports, but typically do not require reporting of individual cases. Moreover, access to automated databases does not confer a special obligation to assess and/or report any individual events contained in the databases. Formal studies conducted using these databases should adhere to these guidelines.*

For non-interventional study designs that are based on secondary use of data, such as studies based on medical chart reviews or electronic health care records, systematic reviews or meta-analyses, reporting of adverse events/adverse drug reactions is not required. Reports of adverse events/adverse drug reactions should only be summarised in the study report, where applicable [11].

According to the EMA Guideline on Good Pharmacovigilance Practices (GVP), Module VI – Management and Reporting of Adverse Reactions to Medicinal Products [11],

> *"All adverse events/reactions collected as part of [non-interventional post-authorisation studies with a design based on secondary use of data], the submission of suspected adverse reactions in the form of [individual case safety reports] is not required. All adverse events/reactions collected for the study should be recorded and summarised in the interim safety analysis and in the final study report."*

Module VIII – Post-Authorisation Safety Studies, echoes this approach [1]. The new legislation further states that for certain study designs such as retrospective cohort studies, particularly those involving electronic health care records, it may not be feasible to make a causality assessment at the individual case level.

12 Plans for Disseminating and Communicating Study Results

In its Guidelines for GPP, ISPE contends that "there is an ethical obligation to disseminate findings of potential scientific or public health importance" [10]; for example, results pertaining to the safety of a marketed medication. "…[T]he marketing

authorisation holder should communicate to the Agency and the competent authorities of the Member States in which the product is authorised the final manuscript of the article within 2 weeks after first acceptance for publication."

Study results will be published following guidelines, including those for authorship, established by the International Committee of Medical Journal Editors [12]. When reporting results of this study, the appropriate Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) checklist will be followed [13].

Communication via appropriate scientific venues will be considered.

[To be completed or modified by study investigator(s), as needed.]

13 Other Good Research Practice

This study will adhere to the *Guidelines for GPP* [10] and has been designed in line with the European Network of Centres for Pharmacoepidemiology and Pharmacovigilance (ENCePP) *Guide on Methodological Standards in Pharmacoepidemiology* [14]. The *ENCePP Checklist for Study Protocols* [15] will be completed (see Annex 2).

The study is a postauthorisation study of vaccine safety and will comply with the definition of the non-interventional (observational) study referred to in the International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use tripartite guideline *Pharmacovigilance Planning E2E* [16] and provided in the EMA *Guideline on Good Pharmacovigilance Practices (GVP) Module VIII: Post-Authorisation Safety Studies* [1], and with the 2012 European Union pharmacovigilance legislation, adopted 19 June 2012 [17]. The study will comply with the study reporting requirements specified in Module VIII section VIII.B.6.3.1. "Progress reports" and VIII.B.6.3.2. "Final Study Report" of the *Guideline of Good Pharmacovigilance Practices* [1].

The study will be registered in the European Union electronic register of post-authorisation studies (EU PAS Register) [18] before the study implementation commences.

The research team and study sponsor should adhere to the general principles of transparency and independence in the ENCePP Code of Conduct [19].

[If desired by the study investigators, the following may be included] The research team will apply for the ENCePP Study Seal [20].

[To be completed or modified by the study investigator(s), as needed. Country-specific study registration requirements may be discussed here, where required.]

14 References

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6. Madigan D, Fireman B, Maclure M, Simpson S, Hua W. Mini-Sentinel methods development: Case Based Methods Workgroup report. 4 October 2011. Available at: https://www.sentinelinitiative.org/sites/default/files/Methods/Mini-Sentinel_Methods_Case-Based-Report_0.pdf. Accessed 22 June 2020.

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Annex 1. List of Stand-Alone Documents

Number	Document Reference Number	Date	Title
1		*<<MM.DD.YYYY>>*	
2		*<<MM.DD.YYYY>>*	
3		*<<MM.DD.YYYY>>*	
4		*<<MM.DD.YYYY>>*	

Annex 2. ENCePP Checklist for Study Protocols

GVP. A copy of the ENCePP Checklist for Study protocols available at http://www.encepp.eu/standards_and_guidances/index.html completed and signed by the main author of the study protocol should be included in Annex 2.

The checklist will facilitate the review of the protocol and evaluation of whether investigators have considered important methodological aspects.

In question 9.5 of the Checklist, Revision 1:

"Study start" means "Start of data collection"

"Study progress" means "Progress report(s)"

"Study completion" means "End of data collection"

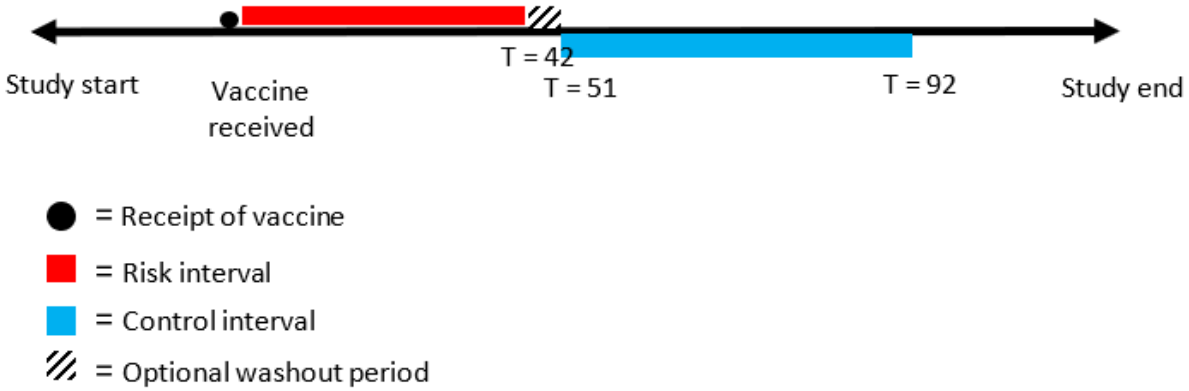
"Reporting" means "Final report of the study results"

Annex 3. Overview of Self-controlled Risk Interval Design, Case-Crossover Design, and Vaccinated Case-coverage Design

Self-controlled Risk Interval Design

The SCRI design (Figure 3-1) is a variant of the SCCS and builds upon the conceptual framework of the cohort study, with exposure history fixed and events random [3-5]. In the pandemic setting when providing timely results is key, a SCRI design is particularly helpful because it shortens the observation period, as compared with the traditional SCCS. The SCRI design uses information only from vaccinated persons identified during the study period and compares the incidence of adverse events within periods of time hypothesised to be at increased risk due to exposure ("risk window") with incidence during a self-matched control window [4] Although the study population includes all patients receiving vaccines, only vaccinees with events occurring during either the risk or control window are informative for the analysis.

Figure 3-1. Self-controlled Risk Interval Design



Note: In this example, the risk interval is 1 to 42 days after vaccination, and the control interval is 51 to 92 days after vaccination.

Control windows may be before or after vaccination and are typically a fixed length between individuals, although they are not required to be the same length as the risk window. This control period serves as an estimate of the baseline incidence. Unlike the traditional cohort study, the SCRI design does not censor follow-up at an event. These designs are well suited to study single or multiple exposures and independent recurrent events or rare non-recurrent events. However, if an event is recurrent but each occurrence is not independent of one another (e.g., stroke, myocardial infarction), then the analysis should be limited to the first event.

In a hospital-based study, the SCRI design would be operationalised by first identifying patients who have been treated and/or diagnosed with the outcomes of interest at hospital sites (regardless of vaccination status). Among the cases, vaccinations and date of vaccinations would then be identified. This approach has important study design and methodological implications because only exposures that occur before the outcome will be available for analysis, unless it is feasible to collect exposure information following hospital discharge. A SCRI design with a pre-vaccination control interval could be considered if it is feasible to collect exposure information following hospital discharge, as

this would enable the inclusion of outcomes that occur before exposure; to use this approach, the outcome should not be a contraindication to exposure. The use of a pre-vaccination control interval would provide more timely results than a postvaccination control window, as data must fully accrue through the end of follow-up for each dose before it can be included in analyses. However, it is anticipated that information on exposures may not be available after hospital discharge to the end of the study period, as was the case in a proof-of-concept study conducted by the World Health Organization (WHO) Global Vaccine Safety: Multi Country Collaboration [21]. Therefore, subsequent discussion of the SCRI in this document will describe the use of a postvaccination control interval, which would not require collection of exposure information following hospital discharge.

A key assumption of the SCRI design is that the occurrence of an event must not alter the duration of the observation period. In this study, both the anticipated lack of ability to collect vaccination information after hospital discharge and the potential for outcomes to prevent the likelihood of exposure may violate this key assumption. In the event of a single-dose vaccine, both sources of potential bias would be addressed by using a postvaccination control interval. In the case of a multidose vaccine, the use of a postvaccination control interval in of itself addresses this bias, and analytic and study design approaches could be used to address the bias while retaining the ability to study all vaccine doses. One possible approach would be to define the control interval for each dose such that vaccination would be very unlikely to occur, based on the vaccine dosing schedule. An analysis using a pseudolikelihood approach developed by Farrington et al. to account for perturbed, curtailed observation periods may also be considered to explore the potential impact of this bias on study results [7].

Another key assumption of the SCCS and, therefore, the SCRI is that data must be available on outcomes throughout the entirety of the risk and control intervals, with no loss to follow-up [3]. Acute outcomes may be studied with the SCRI if they meet other outcome-based criteria and the event is either non-recurrent (i.e., can only occur once during follow-up) or independently recurrent; any events subsequent to the event triggering initial inclusion in the study would be captured in the hospital. Alternatively, this assumption will be met if data on outcomes are available through other secondary data sources after hospital discharge.

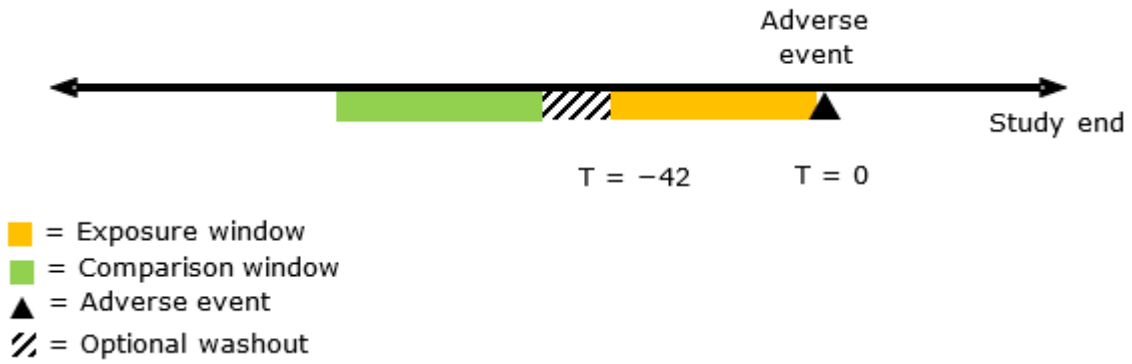
While the SCRI controls implicitly for time constant confounders, time-varying confounders can be adjusted for in analysis by dividing up observation time according to status of the time-varying confounder (e.g., age or calendar time categorised according to the timing of circulating SARS-CoV-2) over the course of follow-up. However, an important limitation of the use of the SCRI in hospital case-based studies is the anticipated lack of capture of confounder information following hospital discharge, unless the patient returns to the same hospital for treatment. Therefore, it is anticipated that beyond calendar time and age, not all hospitals would be able to provide information on time-varying confounders.

Case-Crossover Design

Similar to the SCRI, the CCO is a case-based study in which each person serves as his or her own control. However, the primary distinguishing feature of the two designs is that the CCO follows the conceptual framework of the case-control study, with events fixed and exposure random [4,22]. The design compares the odds of exposure in a window, during which it is hypothesised to trigger the adverse event to that in a control period, which represents the baseline odds of exposure. The study design is traditionally unidirectional, with the comparison window preceding the risk window in time, so as to avoid bias due to reverse causation (Figure 3-2). Only cases vaccinated in either the exposure or comparison window (not both windows) are informative for the analysis. Therefore, follow-up after events (i.e., hospital discharge) is not needed. The design is well suited to study single or multiple exposures as well as rare events.

Like the SCRI, the CCO can adjust for time-varying confounders if the appropriate data are available. However, unlike the SCRI, the CCO is biased if there are temporal trends in exposure. It is highly plausible that a person's likelihood of COVID-19 vaccination will change over time, as the vaccine will be new and likely highly desirable, and availability and vaccine recommendations may change over time. Additionally, the CCO may be subject to within-person protopathic bias and confounding by indication (or contraindication) if prodromal signs of the outcome prior to diagnosis of the event cause (or prevent) vaccination.

Figure 3-2. Case-Crossover Study Design



T = time in days.

Note: In this example, the risk window is 1 to 42 days before the adverse event.

Vaccinated Case-Coverage Design

A proposed variation of the case-coverage design, a vaccinated case-coverage design, is included as a candidate study design in this protocol template to adjust for temporal trends in exposure that may be present in a CCO design. The case-coverage design in its original form is analogous to logic of a case-control design and uses data from cases of the outcome under study and an external reference population, the latter of which is used to estimate the baseline odds of vaccination at the aggregate level. The case-coverage design can be matched on time to account for differences in vaccination coverage over time such that it compares the odds of vaccination in the exposure window for each case to the odds of vaccination during the same time period as the case's exposure window in an external reference population [23].

Similar to a traditional case-coverage design that is matched on calendar time, the vaccinated case-coverage design will compare the odds of vaccination in the exposure window for each case to the odds of vaccination during the same time period as the case's exposure window in an external reference population. However, unlike the traditional case-coverage design, the vaccinated case-coverage design will require that individuals be vaccinated during the observation period to be included. Like the CCO design, exposure and comparison windows preceding case onset date will be defined in cases; cases vaccinated in either the exposure or comparison window will be informative for analysis. To calculate the expected odds of vaccination in the exposure window for each case, the stratum comprising all individuals in the reference population who were similar to each case (e.g., of the same age, sex, and risk group) will be identified on the day of developing the outcome, and the odds of vaccination within the time period equating to the case's exposure window will be calculated. Individuals in the stratum of the reference population must have been vaccinated during calendar periods equating to the exposure or comparison windows before the onset of the case. Matching on calendar time accounts for differences in propensity to be vaccinated over time.

The vaccinated case-coverage design is predicated on the assumption that vaccination trends over time in the reference population reflect that of the cases. Bias due to the absence of this assumption should be minimised by matching cases to the reference population on important characteristics that are associated with the outcome and that may affect timing of vaccination (e.g., age or chronic conditions).

An anticipated challenge of the vaccinated case-coverage design in hospital-based studies is that it is likely to be difficult to identify appropriate data sources to estimate temporal trends in vaccination among groups of vaccinees defined by key confounders in catchment areas for participating hospitals; data on the number of vaccinations by calendar day and important risk factors are needed to implement this approach. Such data may come from population-based immunisation registers or other secondary data sources that capture vaccine coverage over time in samples representative of the target population.

Other Study Designs Considered but Excluded From This Template

The traditional SCCS was considered for inclusion in this template, but it has been excluded because it would require longitudinal data on vaccinations both before and after adverse events occur (i.e., both before and after hospital discharge) during the full study period. It is anticipated that this will not be possible without the use of immunisation registers, which are not available in many settings. Additionally, the SCCS provides less timely results than the SCRI because it requires a longer observation period in cases to accrue than the SCRI.

Annex 4. Preliminary Assessment of Suitability of the SCRI, CCO, and Vaccinated Case-Coverage Designs to Study AESIs

Table 4-1. Preliminary Assessment of the Suitability of the SCRI, CCO, and Vaccinated Case-Coverage Designs, by Study Outcome

Outcome	Suitability of SCRI (With Postvaccination Control Window)	Suitability of the CCO/Vaccinated Case-Coverage Design	Notes
Enhanced disease following immunisation	X	X	Requires unvaccinated comparator to identify whether disease is "enhanced" following vaccination
Multisystem inflammatory syndrome in children	✓	✓	
Acute respiratory distress syndrome	✓	✓	
Acute cardiovascular injury, including microangiopathy, heart failure, stress cardiomyopathy, coronary artery disease, arrhythmia	✓	✓	
Coagulation disorder, including deep vein thrombosis, pulmonary embolus, cerebrovascular stroke, limb ischaemia, haemorrhagic disease	✓	✓	
Generalised convulsion	✓	✓	
Guillain Barré Syndrome	✓	✓	
Diabetes (type 1 and unspecified type)	X	X	Has gradual onset and long latency
Acute kidney injury	✓	✓	
Acute liver injury	✓	✓	
Anosmia, ageusia	X	X	Not typically captured in hospital (unless accompanied by other illnesses requiring treatment in hospital)
Chilblain-like lesions	✓	✓	
Single organ cutaneous vasculitis	✓	✓	
Erythema multiforme	✓	✓	

Outcome	Suitability of SCRI (With Postvaccination Control Window)	Suitability of the CCO/Vaccinated Case-Coverage Design	Notes
Anaphylaxis	✓	✓	If the vaccine is given in more than one dose, the impact of bias in the SCRI design due to the potential interference of the outcome on subsequent vaccination could be explored using Farrington's pseudolikelihood method for censored, perturbed, or curtailed postevent exposures [7].
Death (any cause)	✓	✓	Bias due to the interference of the outcome on subsequent vaccination in the SCRI design should be accounted for using Farrington's pseudolikelihood method for censored, perturbed, or curtailed postevent exposures [7].
Sudden death	✓	✓	Bias due to the interference of the outcome on subsequent vaccination in the SCRI design should be accounted for using Farrington's pseudolikelihood method for censored, perturbed, or curtailed postevent exposures [7].
Acute aseptic arthritis	✓	✓	
Meningoencephalitis	✓	✓	
Acute disseminated encephalomyelitis	✓	✓	

Outcome	Suitability of SCRI (With Postvaccination Control Window)	Suitability of the CCO/Vaccinated Case-Coverage Design	Notes
Narcolepsy	X	X	Diagnosis may be delayed, and some symptoms may occur consecutively over a long time period, which makes the onset of symptoms difficult to determine retrospectively
Thrombocytopenia	✓	✓	
Transverse myelitis	✓	✓	
Preterm birth	X	X	Risk window cannot be defined
Major congenital anomalies	X	X	SCRI not feasible because date of onset is unknown; CCO/vaccinated case-coverage design is not recommended because there may be time trends in vaccination with respect to both calendar time and gestational age, and it is anticipated to be difficult to obtain vaccine coverage rates on both time scales concurrently
Microcephaly	X	X	SCRI not feasible because date of onset is unknown; CCO/vaccinated case-coverage design is not recommended because there may be time trends in vaccination with respect to both calendar time and gestational age, and it is anticipated to be difficult to obtain vaccine coverage rates on both time scales concurrently
Fetal growth restriction	X	X	Risk window is unknown

Outcome	Suitability of SCRI (With Postvaccination Control Window)	Suitability of the CCO/Vaccinated Case-Coverage Design	Notes
Gestational diabetes	X	X	Risk window is unknown and date of onset is unknown
Preeclampsia	X	X	Risk window is unknown
Spontaneous abortion	X	X	Risk window is unknown
Stillbirth	X	X	Risk window is unknown
Induced abortion	X	X	Risk window is unknown
Termination of pregnancy for fetal anomaly (TOPFA)	X	X	Risk window is unknown
Neonatal death	X	X	Risk window is unknown
Maternal death	X	X	Risk window is unknown

CCO = case-crossover; SCRI = self-controlled risk interval.

Annex 5. Feasibility Questionnaire

General Questions

1. Name of data source: _____
2. Contact person: _____

   Institution: _____

   E-mail address: _____

   Phone number: _____

Outcomes

3. Does your site have a hospital discharge database that captures diagnoses and procedures?

   ___ Yes

   ___ No → Stop, thank you for your time

4. Does your site distinguish primary diagnoses from the other diagnoses?

   ___ Yes

   ___ No

5. Number of patients treated by your hospital annually:

_____

6. Number of patients treated by your hospital annually for the following outcomes:

   a. *[Outcome A]*: _____

   b. *[Outcome B]*: _____

   c. *etc*

7. What is the geographic area covered in the catchment area for your hospital?

_____

8. What is the population coverage of your hospital?

   _____

9. How often are your hospitalisation data refreshed and made available for research?

   _____

10. How long is the data lag of the hospitalisation records, that is, how much time passes after hospitalisation before the data are available for research purposes?

    _____

11. What is the earliest date of data captured by your hospitalisation data?

    _____

12. Are the calendar dates of the hospitalisation available?

    ___ Yes, the admission and discharge date are available

    ___ Yes, the diagnosis date is available

    ___ Yes, other. Please specify: _____

13. Can your site identify diagnoses made in the hospital setting of the following outcomes?

    a. *[Outcome A]*? ___ Yes ___ No

    b. *[Outcome B]*? ___ Yes ___ No Etc.

14. What coding system does your site use for diagnosis in the hospital setting?

_____

15. Does your site have the ability to validate outcomes and dates of outcome onset through the use of medical record review, physician questionnaires, case notes, or other methods?

___ Yes

___ No

16. What method can you use to validate outcomes and date of onset?

___ Medical record review

___ Physician questionnaire

___ Case notes

___ Other, please specify: _____

Exposure

17. Can your site identify receipt of COVID-19 vaccines through linkage with other data?

    ___Yes

    ___No → Stop, thank you for your time.

    Note that for this study, primary data collection or other self-report information on vaccinations is not acceptable.

18. To what type of exposure data does your site have access (check all that apply)?

    ___ Vaccine registry

    ___ Primary care records

    ___ Pharmacy dispensing data

    ___ Patient vaccination cards

    ___ Hospital-based medical records

    ___ Other, please specify: _____

19. What is the population coverage of the vaccination data source?

    _____

20. What is the geographic area covered by the vaccination data source?

_____

21. How often is the database for vaccinations refreshed and made available for research?

    _____

22. How long is the data lag of the data source that captures COVID-19 vaccines?

    _____

23. Does your site have access to data on COVID-19 vaccines administered in all medical care settings?

    ___ Yes

    ___ No, please specify settings (e.g., primary care only)

    _____

24. What is the earliest date of COVID-19 vaccination captured by the data sources that you have access to? Is this the earliest date that vaccination was made available in the geographic region covered by your database?

    _____

25. Are the dates of vaccination captured?

    ___ Yes, exact dates are captured

    ___ Yes, dates are captured but some are imputed. Please specify: _____

    ___ No

26. Does your site have the ability to distinguish between different brands of COVID-19 vaccines?

    ___ Yes

    ___ No

27. If vaccination data are collected in an external immunisation register that you have access to, how many COVID-19 vaccines are currently observed in your hospital's catchment area? Please also specify the time period.

    _____

Other Variables

28. Does your site have the ability to capture the following variables?

    a. *[Covariate 1]*? ___ Yes___ No

       Specify data source: _____

    b. *[Covariate 2]*? ___ Yes ___ No

       Specify data source: _____

       Etc.

29. How often are the data sources for other variables refreshed and made available for research?

    _____

30. How long is the data lag for the data sources for other variables?

    _____

Thank you for completing this questionnaire!