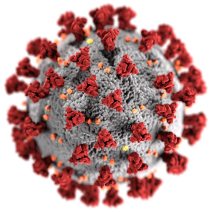
Safety evaluation of COVID-19 vaccines in electronic healthcare databases: a protocol template from the ACCESS project

ACCESS

vACCine covid-19  monitoring readinESS

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

Willame C, Dodd C. et al. Safety evaluation of COVID-19 vaccines in electronic healthcare databases: a protocol template from the ACCESS project.

DISCLAIMER

This 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 evaluation of COVID-19 vaccines in electronic healthcare databases: a protocol template from the ACCESS project
Protocol version identifier	0.2
Date of last version of protocol	3 December 2020
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Active substance	*List of pharmacotherapeutic group(s) (ATC codes) and active substance(s) subject to the study*
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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 evaluate the risk of specific events following <<COVID-19 vaccine product>>
Country(-ies) of study	Eligible data access providers based on ACCESS feasibility assessment.
Authors	Caitlin Dodd, University Medical Center Utrecht Corinne Willame, University Medical Center Utrecht
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Marketing authorisation holder(s)

Marketing authorisation holder(s)	*Name, address and contact details of the marketing authorisation holder(s).*
MAH contact person	*Contact person for this PASS protocol submission (if this a joint PASS, only one person should be mentioned)*

Trademarks

Brand Name	Generic Name	Trademark Holder

1 Table of Contents

2 List of Abbreviations

ADVANCE	Accelerated development of vaccine benefit-risk collaboration in Europe
AE	Adverse Event
AEFI	Adverse Event Following Immunization
AESI	Adverse Event of Special Interest
BC	Brighton Collaboration
CCO	Case-Crossover
CEPI	Coalition for Epidemic Preparedness Innovations
EC	European Commission
EMA	European Medicines Agency
EUPAS	European Union electronic Register of Post-Authorisation Studies
GBS	Guillain-Barré Syndrome
GDPR	General Data Protection Regulation
ICSR	Individual Case Safety Report
SCCS	Self-controlled Case Series
SCRI	Self-controlled Risk Interval
SPEAC	Safety Platform for Emergency vACcines
UMLS	Unified Medical Language System
VSD	Vaccine Safety Datalink

3 Responsible Parties

To be completed by study investigator(s) when they use the protocol

[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
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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:

Study size:

Data analysis:

Milestones:

5 Amendments and Updates

<<to be filled upon actual protocol>>

6 Milestones and Timeline

This section should be filled out with the following information, when the study is implemented.

Milestone	Date
Start of data collection	
End of data collection	
<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.

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) following what is likely to be an accelerated investigational and licensing procedure. Because the pre-licensure period is short and number of participants in clinical studies is limited, monitoring of the safety of vaccines in the post-introduction phase will be needed in an efficient manner, with the objective of identifying, assessing and evaluating as rapidly as possible any unintended side effects of vaccination.

As per EC communication in October 2020[1], Member States and public health authorities should prepare to undertake studies of vaccine effectiveness and safety via coordination by the European Medicines Agency and the European Centre for Disease Prevention and Control, and specifically to prepare for participation in large-scale EU-wide effectiveness and safety monitoring studies.

As part of the preparedness activities for safety surveillance of COVID-19 vaccines, this template protocol provides a template for quickly developing a full study protocol to perform vaccine safety evaluation studies to quantify potential risks through the secondary use of electronic healthcare databases. The ACCESS project has developed several template protocols, that address: vaccine coverage, vaccine effectiveness and vaccine safety.
To allow all countries to participate and to utilize maximum capacity in Europe, protocols are divided in those that use primary data collection (e.g. hospital based), and those that rely on the secondary use of available electronic health care data.

This template safety protocol is for the evaluation of safety of COVID-19 vaccine(s) using population based electronic health record databases in Europe. In order to use this specific protocol, electronic health care data on population, events and COVID-19 vaccine administration are required.
The potential designs for safety evaluation of vaccines studies inlcude the cohort, case-control, self-controlled case series (SCCS), self-controlled risk interval (SCRI), and case-crossover (CCO). Electronic health care data source requirements for the application of each study design are described in **Table 1**.

Table 1. Linkable electronic health care data elements for Cohort, Case-Control, SCCS, SCRI, and CCO designs

	Data Elements			
Design	Listing of all population members	Events	Covariates	Vaccine
Cohort	✓	✓	✓	✓
Case-Control	✓	✓	✓	✓
SCCS	X	✓	✓	✓

[1] https://ec.europa.eu/health/sites/health/files/vaccination/docs/2020_strategies_deployment_en.pdf

SCRI	X	✓	✓	✓
Case-Crossover	X	✓	✓	✓

Checkmark indicates design requires data element or feature; X indicates data element or feature is not required

As part of the harmonization of COVID-19 vaccine safety monitoring during the clinical development phase, the Coalition for Epidemic Preparedness Innovations (CEPI) has created a preliminary list of AESI for COVID-19 vaccine safety monitoring together with the Brighton Collaboration (SPEAC, 2020).

Within the ACCESS project, a list of AESI has been created which was approved by EMA *(EUPAS37273).* The listed AESI may not become real safety concerns but we should be ready to address them as they might potentially derail vaccination programs if they occur.
Although there will be readiness to address the AESI currently identified potential unexpected safety concerns related may arise during product development or after licensure; we aim that principles and designs in this protocol can also be applied to novel issues, which is why we created a decision framework to quickly assess which design may be most appropriate.

Each of the AESI listed in **Table 2** differs in terms of latency, acuity of onset, availability of empirical estimates for appropriate risk periods, and the effect of the event on subsequent likelihood of vaccination.
Criteria for determining the appropriate design for the event under study are described in **Annex 3.** Specific design recommendations for each AESI are provided in **Table 2** below.

Table 2. Assessment of the Suitability of Cohort, Case-Control, SCCS, SCRI and CCO designs for signal evaluation, by pre-identified AESI

Event	Cohort	Case-control	SCCS	SCRI	CCO
Enhanced disease following immunisation	X	✓	X	X	X
Multisystem inflammatory syndrome in children	✓	✓	✓[a]	✓[a]	✓
Acute respiratory distress syndrome	✓	✓	✓	✓	✓
Acute cardiovascular injury, including microangiopathy, heart failure, stress cardiomyopathy, coronary artery disease, arrhythmia, myocarditis	✓	✓	✓	✓	✓
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
Acute kidney injury	✓	✓	✓	✓	✓
Acute liver injury	✓	✓	✓	✓	✓
Anosmia, ageusia	✓	✓	✓	✓[a]	✓
Chilblain-like lesions	✓	✓	✓	✓	✓
Single organ cutaneous vasculitis	✓	✓	✓	✓[a]	✓

Event	Cohort	Case-control	SCCS	SCRI	CCO
Erythema multiforme	✓	✓	✓	✓[a]	✓
Anaphylaxis	✓	✓	✓	✓	✓
Death (any causes)	✓	✓	✓	X	✓
Sudden death	✓	✓	✓	X	✓
Acute aseptic arthritis	✓	✓	✓	✓	✓
Meningoencephalitis	✓	✓	✓	✓	✓
Acute disseminated encephalomyelitis	✓	✓	✓	✓[a]	✓
Narcolepsy	✓	✓	✓	X	X
Thrombocytopenia	✓	✓	✓	✓	✓
Transverse myelitis	✓	✓	✓	✓[a]	✓
Preterm birth	✓	✓	X	X	X
Major congenital anomalies	✓	✓	X	X	X
Microcephaly	✓	✓	X	X	X
Fetal growth restriction	✓	✓	X	X	X
Gestational diabetes	✓	✓	X	X	X
Preeclampsia	✓	✓	X	X	X
Spontaneous abortions	✓	✓	X	X	X
Stillbirth	✓	✓	X	X	X
Induced abortions	✓	✓	X	X	X
Termination of pregnancy for fetal anomaly (TOPFA)	✓	✓	X	X	X
Neonatal death	✓	✓	X	X	X
Maternal death	✓	✓	X	X	X

[a] Suitability of the self-controlled designs is dependent upon availability of a purported risk period, which for some AESI is as yet unknown.

8 Research Question and Objectives

Note to future investigators using this template to develop a full 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, <<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.

[For all designs, the secondary analysis of vaccine groups defined by vaccine platforms or components should be done if the products are hypothesized to have a similar safety profile across the grouped products. Also, if a safety concern for an adverse event has arisen around a specific vaccine product, then the analysis of all COVID-19 vaccine products combined should not be conducted for that event]

Primary objective: To determine whether there is an increased risk of pre-specified <<event>> following vaccination with specific <<COVID-19 vaccine product>> using study designs <<cohort, case-control, self-controlled, or case-crossover>> which allow for control of confounding.

Secondary objectives:
§ To determine whether there is an increased risk of pre-specified <<event>> in specific vaccine groups defined by platform and/or components (e.g. adjuvant)

§ To determine whether risk of <<event>> following vaccination with specific <<COVID-19 vaccine product>> differs by characteristics such as age, sex, comorbidities, infections, concomitant vaccinations, concomitant medications, and/or other characteristics.

9 Research Methods

9.1 Study Design

Note to future investigators: Feasibility assessment is a necessary step before implementing the actual signal evaluation study (Yih, 2012; Willame, 2016). For each of the study design, inclusion and/or exclusion criteria for subjects should be defined upfront.
Please choose the template description of the appropriate design you choose and delete other design descriptions

9.1.1 Cohort

Retrospective (multi)-database cohort study where index <<COVID-19 vaccinated>> subjects and reference (subjects not vaccinated with << COVID-19 vaccine>>: reference cohort) are compared for occurrence of << event>>.

The comparison cohort will be matched using as example frequency matching or propensity score matching for important covariates such as age, sex and comorbidities (including COVID-19 infection prior to reference date) and markers of health care utilization (Austin, 2011). The comparison cohort could be the following:

- A concurrent comparison cohort including subjects not vaccinated with <<COVID-19 vaccine>> at the time of study start, identified at the same date (+/- 7 days – eg. anchored on a healthcare visit or pharmacy dispensing) of the exposure date (1st vaccine dose in case of multi-dose vaccine) of the matched vaccinated subjects. This calendar date time matching will allow to control for the variation in the SARS-CoV2 circulation and will minimize the risk of immortal time bias given that the time period before vaccination is immortal. To test for the presence and magnitude of immortal time, the time

difference between cohort entry and the date of start of vaccine distribution should be calculated for each cohort member and the frequency distribution of immortal time compared between the vaccinated and unvaccinated cohorts.

  - If <<COVID-19 vaccine>> is distributed concurrently with the seasonal influenza vaccine, persons receiving both <<COVID-19 vaccine>> and the seasonal influenza vaccine could be compared with those receiving the influenza vaccine alone.

- A comparison cohort including subjects vaccinated with alternative <<COVID-19 vaccine>> in the same week as the matched index subjects. This time matching will allow to control for the variation in the SARS-CoV2 circulation.

- In the instance where the risk period of <<event>> is well known, the comparison cohort may be the same persons as the index cohort, with the comparison person time chosen after the ending of the risk window. Time trends in events cannot be controlled for in this manner.

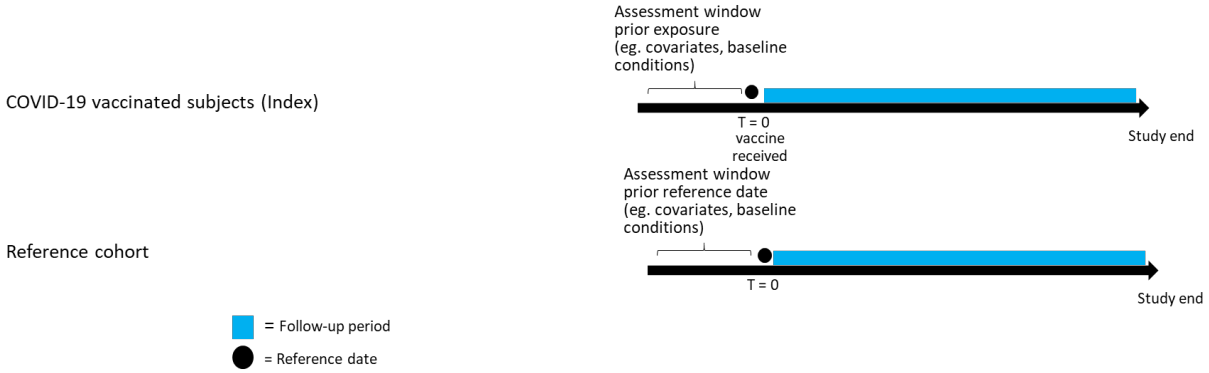
The incidence rate ratio of the <<event>> is calculated comparing the incidence rate in index with that in the comparison cohort. The required follow-up time will depend on the event under evaluation, this follow-up time should take into account the vaccination schedule (**Figure 1**).

For example, for the evaluation of Guillain Barre Syndrome (GBS), a follow-up time period of at least 42 days should be applied after vaccine dose 1. In case a second/third vaccine dose is recommended or inadvertently administered, the follow-up period should be classified by dose and be extended for an additional 42 days after dose 2/3.

As a second example, for the evaluation of anaphylaxis, a risk period of 48 hours should be considered after each vaccine dose.

Risk periods are not yet known for COVID-19 vaccines and may depend on the platform as well as latency time of the <<event>> and the time it takes to have a diagnosis of <<event>> in a specific health care system. General recommendations are to have at least 2 months of follow-up for events with short latency, and 3 years for events with long latency.

Figure 1. Cohort design



9.1.2 Matched case-control

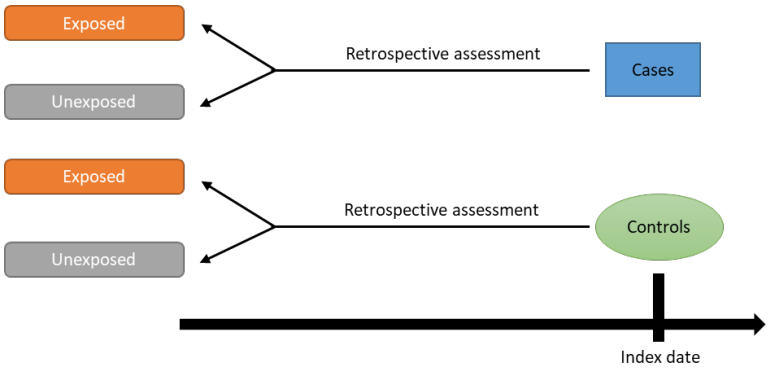
Retrospective (multi)-database case-control study where COVID-19 vaccination status is compared between cases (subjects who experienced << event>>) and controls (subjects who did not experience << event>>) in a specific time window.

Cases and controls should be matched on strong risk factors for the event and we recommend at least: age (year of birth), sex, and database (in case of multiple databases used) as well as calendar time. Controls should arise from a population where prior probability of exposure is the same as for the cases and be eligible to become and observed as a case if they develop the event of interest at a later date. As such persons may serve as control prior to becoming a case and may serve as a control for multiple cases (Richardson, 2004).

Index date for cases should be the disease date (preferably date of onset or first symptoms, otherwise diagnosis), the index date for the controls should be the index date of the corresponding cases. The calendar time matching, controls for confounding due to time related issues (e.g. circulation of SARS-Cov-2). Controls should be sampled using incidence density sampling (Lubin, 1984). For each subject in the database the start and end of follow-up is calculated, exclusion criteria are applied to all subjects and upon occurrence of an exclusion criterion, the follow-up time is censored. For each case, controls subjects who are actively registered in the data source at the index date of the case can be sampled or all eligible controls may be used (recommended if stratified analysis are conducted) (**Figure 2**).

In a case-control study, the aim is to compare the exposure during a specific time window between cases and controls. The time window prior to index date should be disease-specific plus the latency time period for the event under evaluation (e.g. for long latency events). For events with long latency, the risk window should be shortened or divided in small intervals to be able to assess the pattern of risk across different time windows. General recommendations are to have a time window of at least 2 months for events with short latency, and 3 years for events with long latency.

Figure 2. Case-control design



9.1.3 Self-Controlled Designs

The Self-Controlled designs use individuals who experienced the <<event>> in a pre-specified time window, which will be split into at-risk time and reference (control) time. Each subject serves as his/her own control, thus controlling for fixed potential confounders.

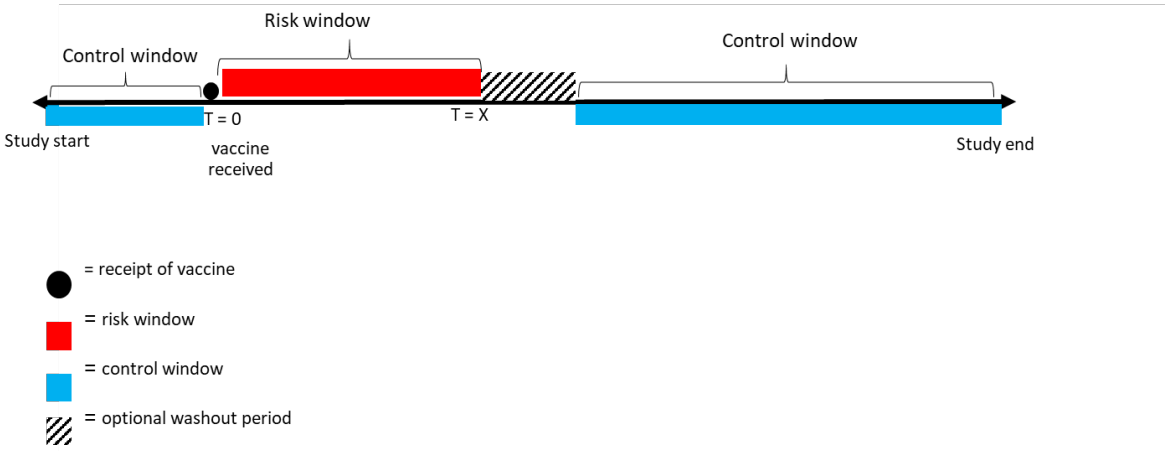
A pre-specified risk period will be required considered for each of the events under evaluation after any <<COVID-19 vaccine>> dose. The risk period depends on the type of event as specified above.

9.1.3.1 Self-controlled Case Series (SCCS)

Retrospective (multi)-database case-only study that includes subjects who were vaccinated with << COVID-19 vaccine>> and experienced << event>>.

The incidence rate ratio between a period of time hypothesized to be at increased risk due to exposure ("risk window") and control window (All other time within an individual's observation period, that does not fall within the risk period) is calculated (**Figure 3**).

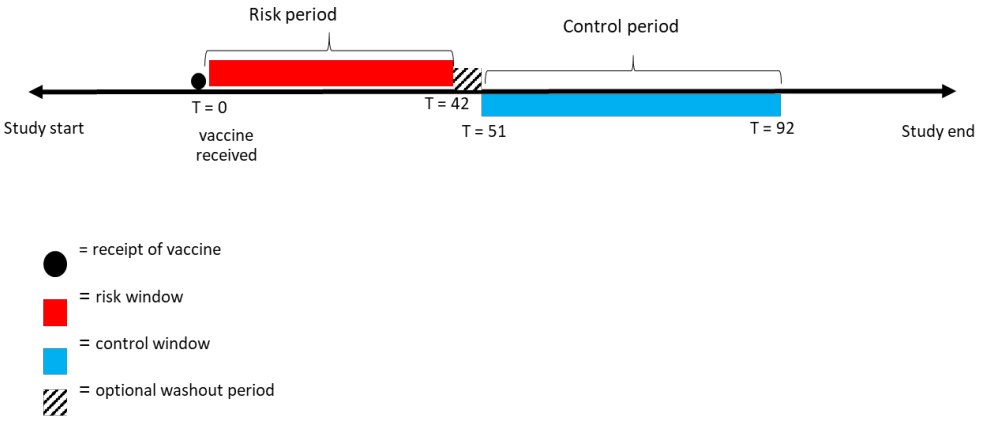
Figure 3. Self-Controlled Case Series



9.1.3.2 Self-Controlled Risk Interval (SCRI)

Retrospective (multi)-database case-only study including subjects who were vaccinated with <<COVID-19 vaccine>> and experienced << event>>.
The risk and control windows should be pre-specified. The incidence rate ratio between a period of time hypothesized to be at increased risk due to exposure ("risk window") and control window (a pre-specified time window occurring after the risk window) is calculated. The SCRI is a subtype of the SCCS design, with a pre-specified duration of the control period (**Figure 4**).

Figure 4. Self-Controlled Risk Interval design

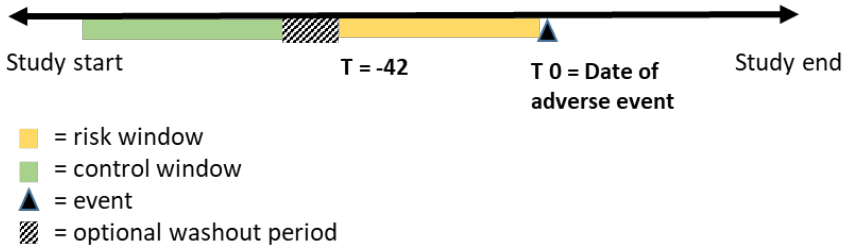


Note: Example with a risk period of 42 days and a control period of 42 days

9.1.4 Case-crossover (CCO)

Retrospective (multi)-database case-only study that includes subjects who experienced << event>>, independent of vaccination. The CCO design considers the occurrence of << event>> as fixed event and the <<COVID-19 vaccine>> exposure random. The design compares the odds of exposure in a specific time window retrospectively in time, where the odds of exposure is compared over these time periods. Index date for the case is the date of the event, index date for the control periods of the same person are distinct points in time prior to case occurrence. Index moment for the control window, should be distanced with at least the duration of the exposure window (**Figure 5**). It is likely that vaccinations will only be administered on weekdays therefore the index date for the control window should be matched on day of the week to have equal probability of exposure. Control periods should not extend in the period prior to launch of the vaccination since the probability of exposure would be zero. Due to unavoidable time trend in vaccination a case time control adaptation is required (Schneeweiss, 1997). The case-time-control design is an elaboration of the case-crossover design, which uses exposure history data from a traditional control group to estimate and adjust for the bias from temporal changes in prescribing.

Figure 5. Case-crossover design



9.2 Setting

9.2.1 Source Population

The source population for each of the study designs will comprise all individuals registered in the health care data source during the study period for that data instance.

9.2.2 Study Period, Population and Follow-up Period

The study population will comprise all persons in the source population that are eligible for the study according to specific inclusion and exclusion criteria (such as study period, design requirements and exclusion of prior events, see generic conditions in Table 3).

Eligible individuals should be identified in each of the database using a pre-specified selection process and/or by applying pre-specified algorithms. Attrition diagrams should be made. Follow-up time should start at the moment that the latest of the inclusion criteria is met, follow-up ends at the earliest of the occurrence of censoring conditions or the last data draw down/data availability.

Study period, study population and follow-up period for signal evaluation study designs are summarized in Table 3.

Note to future investigators: this section provides general information and should be adapted according to the type of safety study conducted.

Table 3. Study period, study population, and follow-up period by study design

Study design/Analysis Method	Study period	Study population[$]	Follow-up period
Cohort	Index cohort: from <<COVID-19 vaccine>> introduction until last data collected Comparison cohort: from <<COVID-19 vaccine>> introduction until last data collected	Index: all subjects who received at least 1-dose of COVID-19 vaccine Comparison: all subjects matched for covariates such as age, sex, comorbidities, identified from same data source(s) who did not receive COVID-19 vaccine or alternative vaccine.	Start: latest of fulfillment of inclusion criteria or start of study period End: earliest of end of study period or censoring conditions
Case-control	From <<COVID-19 vaccine>> introduction until date protocol is implemented or data is available	Cases: Subjects with a diagnosis of << event>> in the study period. Controls: Subjects matched on age, sex, database and/or region without << event>> diagnosis at the time of index	From start of follow-up until index date The length of risk period ('look back period') should be defined according to the event under evaluation

		date. Index date = index date of the corresponding cases	
SCCS	From <<COVID-19 vaccine>> introduction until latest data available	Subject who received at least 1-dose of COVID-19 vaccine and who experienced <<event>>	Start: latest of fulfillment of inclusion criteria or start of study period End: earliest of end of study period or censoring conditions
SCRI	From <<COVID-19 vaccine>> introduction	Subject who received at least 1-dose of COVID-19 vaccine and who experienced <<adverse event>>	Follow-up should begin on the day of vaccine exposure. Length of follow-up will be fixed and depend on the risk and control periods that may vary according to the event. Follow-up may be curtailed if censoring conditions are met.
CCO	From <<COVID-19 vaccine>> introduction	Subject who experienced << event>>	Start: after introduction of <<COVID vaccine>> in a country and other inclusion criteria and are met End: the index date of the event.

[$]Study population for pregnancy outcomes should be adapted and includes pregnant women only, specific inclusion criteria may be required.

Note to future investigators: this section provides guidance and should be adapted according to the type of study design implemented.

9.2.3 Variables

9.2.3.1 Event Assessment

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

Definitions, codes, and proposed algorithms for all AESI can be found at https://drive.google.com/drive/folders/1Y_3cuGRN1g-jBv2ec1fC0aYcpxEjtrY9. These AESI definition templates can serve as example for event definitions forms for non-anticipated events.

Note: The AESI event definitions forms documents will be evolving based on experience in the calculation of background rates in the ACCESS project (EUPAS37273).

<<Event>> should be identified in each participating database using diagnosis codes, where possible algorithms should be used to ascertain the event or for sensitivity analyses. Performance of algorithms should be benchmarked by comparing incidence rates with published rates and between databases as described in ADVANCE (Sturkenboom, 2020). The provenance of diagnosis codes (e.g. hospital vs. general practice) should be considered in development and application of event algorithms (Gini, 2019).

For signal evaluation studies event identification algorithms should be validated using chart abstraction or manual verification of electronic records while being blinded to the <<COVID-19 vaccine>> exposure.
If resources are restricted a sample may be validated initially to assess the positive predictive value (PPV). If the PPV is below 80% all cases should be validated.

Certainty of the diagnosis of an event should be classified against the existing and new Brighton Collaboration (BC) case definitions. SPEAC is providing a toolbox to those case definitions which is accessible from the Brighton Collaboration website or by writing to the bc-coordinator@brightoncollaboration.us. Analysis may be restricted to specific BC level cases for case-based analyses, whereas sensitivity analyses and cohort incidence estimations may focus on inclusion of lowest level of diagnostic certainty.

9.2.3.2 Exposure Assessment

In this section, operational definitions for identifying exposures to vaccines and medicines should be described, including the codes to identify them in the specific data sources.

In the primary analysis, exposure should be based on <<COVID-19 vaccine>>; a secondary analysis should be conducted grouping vaccines according to platform or other characteristics (e.g., adjuvant) if needed.

Vaccine information (eg. Date of vaccination, type of vaccine platform) should be obtained from all possible sources that capture COVID-19 vaccine and influenza vaccines such as pharmacy dispensing records, general practice records, immunisation registers, vaccination records, medical records, or other secondary data sources. Depending on the data source, vaccines should be identified via nationally used product codes including batch numbers where possible.

If the vaccine is administered in multiple doses, doses should be classified separately. 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 could be recording errors and/or medication errors. In that case, a censoring at subsequent doses will be applied.

In analyses utilizing a control vaccine exposure, care should be taken that salient features of subjects and/or healthcare systems do not pose a risk for differential recording of a specific COVID-19 vaccine product and the selected control exposure. Fit for purpose assessment should be used prior to selection of a data source.

9.2.3.3 Risk & Control periods

In this section, risk and control windows should be specified for each of the events under assessment for the specific design.

The duration of the risk periods should be specific for each of the outcomes and defined to establish an accurate relationship and patterns in that relationship. Risk windows should be subdivided in smaller periods of risk to allow for investigation of changes in the estimate of risk and doses. Control periods should be chosen in a manner that there is no misclassification of exposure/event occurrence.

As general reference for risk periods and opportunity to harmonize we recommend inspection of outputs of the SPEAC project as this is creating event definition, codes, risk factors and windows for many of the AESI which will be released on the Brighton Collaboration website in the coming year (https://brightoncollaboration.us).

9.2.3.4 Covariate Assessment

9.2.3.4.1 Descriptive Covariates

For descriptive purposes, sex, age, country, and calendar month of vaccination should be assessed in the study population (overall and/or by index and comparison cohort/ study groups), at the start of follow-up (for cohort, SCCS, SCRI) or at the index date (case-control).

9.2.3.4.2 Confounders

Important confounders are all factors that are known risk factors for the event and are associated with the COVID-19 vaccination. Since both conditions should be fulfilled, we recommend that a list is created of all risk factors associated with the event, which are better known, and the criteria for vaccination eligibility. Accurate assessment and control for confounders is required in signal evaluation studies. The effect of confounders may be minimised by applying matching, adjustment or restrictions. Methods for retaining relevant covariates/confounders in the statistical model may be diverse including stepwise regression or 'change-in-estimate' approach (Greenland, 2016).

Risk factors for events should be obtained from the literature and classified as stable or varying within one individual over the period of the study. Factors associated with vaccination should be obtained from national authorities and may include at-risk conditions or age.

Time varying confounders that should be considered are:

- Age may act as a time-varying confounder in children, depending on the event of interest. Age may be adjusted for the self-controlled designs by dividing person-time during follow-up into pre-specified age groups (e.g., weeks or months)
- Infections (in particular respiratory)
- non-COVID-19 vaccines (in particular influenza)

Special attention should be given to bias related to healthy vaccinee bias and confounding by indication (Remschmidt, 2015).

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

9.2.3.4.3 Effect Modifiers

In this section, any factors (e.g., age at vaccination, chronic conditions, infections, concomitant vaccinations and medications) that are hypothesised to modify the effect of <<COVID-19 vaccine>> on the event of interest should be listed.

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

9.3 Data Sources

The data sources for the exposures, events, 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 COVID-19 vaccination strategy should be included in this section. Validation data on relevant data elements should also be described.

9.4 Study Size

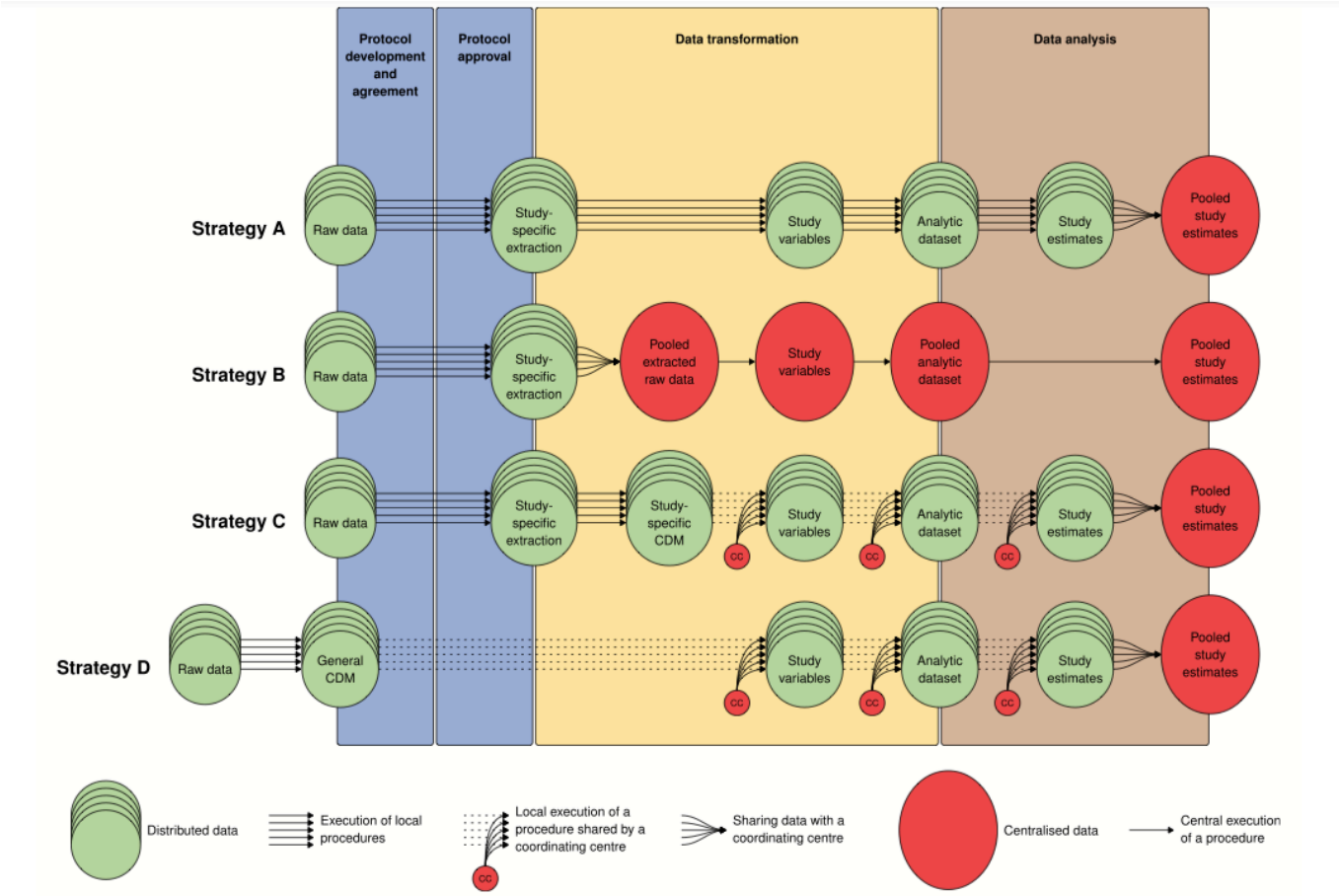
[*To be completed by the study investigator(s) based on assumptions of number of cases and effect estimate size at the time of the full protocol development*]

For signal evaluation studies sample size calculations should be conducted that would allow ability to detect risk with the highest precision. The sample size will be driven by the background rate of the event under evaluation and the size of the data source(s).

9.5 Data Collection and Management

This section assumes the approach of a distributed network of DAPs who agree to use a common protocol, common data model and common analytics. We recommend to prepare for a model where original data remain local, and are transformed in a common data model that will allow for study specific structural and semantic harmonization (model C, Figure 6) (Gini et al, 2020).

Figure 6. Options for multi-database studies in Europe



[*If other models are used this section should be adapted*]

In short, model C requires that each data access provider will extract the data required for the study and transform their local patient level data into a common data model (CDM). An example of a widely used common data model in Europe (currently 24 DAPs) is the ConcePTION CDM, which is publicly available[2]. Extract, transform and load (ETL) design and instructions are available, as well as tools to check the quality of the data for the AESI listed above as these are also utilized for the ACCESS background rate protocol.

A common program to run quality checks, data transformation, and analysis should be prepared and verified and be sent to all DAPs. Aggregate results and summary estimates resulting from the programs should be returned to a single coordinating centre for pooled meta-analysis and reporting.

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

[2] https://www.imi-conception.eu/wp-content/uploads/2020/10/ConcePTION-D7.5-Report-on-existing-common-data-models-and-proposals-for-ConcePTION.pdf

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

Appropriate data storage and archiving procedures should be followed by each DAP and the coordinating organization, with periodic backups. Standard procedures should 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 research partners are known, they can be included here*]

9.6 Data Analysis

9.6.1 Descriptive Analysis

Attrition diagrams demonstrating the loss of subjects applying inclusion and exclusion criteria should be provided.

For each study design, demographic characteristics of the study population (e.g. age at study entry, sex) and baseline characteristics (eg. co-morbidities) should be summarized for each data source using descriptive statistics. Description of <<COVID-19 vaccine>> type should be described and along with counts of exposure by calendar month to allow for inspection of time trends.

The distributions of the characteristics by study groups (index/comparison cohorts or cases/controls) should be presented in tables to demonstrate potential differences/or lack thereof between groups. For propensity matched cohorts the distribution and propensity scores should be plotted prior to the matching and balance after matching should be shown.

Counts and percentages should be presented for categorical variables (age at study entry in categories, sex, race/ethnicity, comorbidities). Mean, standard error, median and range should be presented for continuous variables (age at study entry). The missingness of variables should also be described.

Event counts should be provided categorized by level of severity/certainty. Appendices should provide code /algorithm counts for the events.

9.6.2 Measures of Association

Measures of association and statistical methods for each of the signal evaluation study designs are presented in **Table 4** below.

Null hypothesis for the study will be:

- **Cohort:** H_0: the incidence of << event>> in the index group is equal to the incidence of << event>> in the comparison group.

- **Case-Control:** H_0: the odds of cases exposed to <<COVID-19 vaccine >> is equal to the odds of controls exposed to <<COVID-19 vaccine>>.
- **Self-controlled:** H_0: the incidence of << event>> in the risk period is equal to the incidence of << event>> in the control period.

Table 4. Measures of association according to the type of study design

Study design	Events	Statistical method	Measures of association
Cohort	All events excluding pregnancy outcomes	Poisson regression or Cox regression (time-dependent covariates/exposure)	Rate ratio or Hazard ratio
	Pregnancy outcomes	Binomial or logistic regression	Prevalence or odds ratio
Case-Control/Case cross over	All	Conditional logistic regression	Odds ratio
Self-controlled	All	Conditional Poisson regression	Incidence Rate Ratio

9.6.3 Data Integration

Results should 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 data sources (see **Section 9.4**). We recommend for multi-site studies that aggregated data is shared and pooled. (Yoshida, 2018; Li, 2018; Shu, 2019).

If database access providers do not allow the necessary aggregate data to be shared, then data analysis will be performed by DAPs at their sites. Counts and coefficients would be shared with the study coordinating centre, and overall results would be summarised using meta-analytic techniques, such hybrid approaches were utilized previously to analyse narcolepsy data for the pandemic vaccine (Weibel, 2018).

Meta-analysis will be conducted using standard methods: heterogeneity should be tested and Forest plots be provided. Because of the size of data-sources we recommend random effect models (DerSimonian and Laird, 1986).

9.6.4 Subgroup Analysis

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

If relevant to specific events, the presence of effect modification by relevant variables (age at vaccination, specific comorbidities, concomitant vaccinations) should be assessed using stratification and statistically by testing for interaction.

9.6.5 Sensitivity Analysis

Sensitivity analysis should focus on the robustness of results to assumptions of the study design and availability of key data elements and should be conducted for the rapid assessment and signal evaluation studies and 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
- 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 lagging the event date.
- If time-varying confounders are not fully available in all data sources, restrict the analysis to sites where data are available on these time-varying confounders and assess at the impact of removing time-varying confounders

9.7 Quality Control

Standard operating procedures or internal process guidance at each research centre should be adhered to for the conduct of the study. These procedures should 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 should 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 should be processes for review and quality control of study documentation and reporting of pooled results across research centres.

Note to future investigators: The pandemic has led to changes in healthcare utilization and provision which are likely to extend into the vaccine roll-out period. This may be reflected in observational data as an excess of code counts for a subset of AESI and/or their proxies in the pandemic period, or as a deficit for others. In order to understand these changes to the data available for analysis, it is recommended that counts and rates of both individual codes utilized in any event case-identification algorithm as well as the set(s) of codes chosen to identify each event be described over time both within and between databases, taking into account the type of database and the type of healthcare encounters typically captured (general practice vs. hospitalization). These counts and rates should be compared graphically in order to aid interpretation of study results.

9.8 Limitations of the Research Methods

The different proposed study designs are subject to limitations due to both the study design and secondary use of health care data.

Data-related limitations include dependency on the accuracy of codes and algorithms to identify outcomes, and the opportunity to confirm events. Misclassification of events (both diagnosis and date of onset) may be minimised by conducting validation and assessing certainty by using BC event definitions. However, the

use of medical records 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, immunization registers, medical records, vaccination cards, or other data sources. The ability to identify specific COVID-19 vaccines and dates of vaccination are currently unknown as it is not clear how the vaccines will be rolled out and what level of detail will be recorded. ACCESS promotes the recording and identification of vaccine brands and batch numbers/ lot numbers. It is likely that subjects vaccinated outside of the healthcare system may not have a record of their vaccination. If brands cannot be distinguished, there may be misclassification of exposure which is of essence due to the differences in platforms and adjuvants. Inability to distinguish lots would misclassify exposure and would be important if any safety signal is related to vaccine production.

Cohort studies are usually less suitable to assess rare events. However, the use of secondary data collection allows for the inclusion of large sample size and increases the statistical power for small risk characterization. A main limitation relates to risk of immortal time bias when inclusion is based on the presence of a certain period of follow-up.
Unvaccinated subjects may become exposed to COVID-19 vaccine at any time over the course of study, censoring in the follow-up time may create an imbalance in the observation periods between vaccinated and unvaccinated groups, which is not random. Another important limitation relates to residual confounding due to unmeasured confounders as it is unlikely that the data sources will comprise information on all potential confounders.

Case -control studies using health care data sources have the advantage of having recorded vaccination prior to case occurrence. Matching and restriction should be applied to deal with confounding. Main sources of bias could be selection bias (e.g. validation cannot be performed for all cases) and is related to exposure, or if validation is conducted in an unblinded manner.

The main strengths of self-controlled designs are the adjustment for time-invariant covariates and their suitability to assess acute events. For less acute events and long latency events, a long washout period will be required and any uncertainty about risk periods will lead to misclassification and attenuation of risk estimates. A major limitation of the CCO is that it should not be used if there are temporal trends in exposure.

9.9 Other Aspects

This section, which is optional, should 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

The proposed studies are non-interventional studies re-using health care data. All data collected in the study will be de-identified with no breach of confidentiality with regard to personal identifiers or health information. Each data access provider should apply for an independent ethics committee review according to local regulations and the local DPIA should be informed. Data protection and privacy regulations (GDPR) should be respected in collecting, forwarding, processing, and storing data from study participants.

11 Management and Reporting of Adverse Events/Adverse Reactions

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 (EMA, 2017)

According to the EMA Guideline on Good Pharmacovigilance Practices (GVP), Module VI – Management and Reporting of Adverse Reactions to Medicinal Products (EMA, 2017),

"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 (EMA, 2020). 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" (ISPE, 2015); for example, results pertaining to the safety of a marketed medication. "…the 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 two weeks after first acceptance for publication."

Protocols should be registered at the EU PAS register and comply with ENCePP or ADVANCE code of conducts. According to both codes of conducts

Study results will be published following guidelines, including those for authorship, established by the International Committee of Medical Journal Editors (ICMJE, 2019). When reporting results of this study, the appropriate Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) checklist will be followed (STROBE, 2015), and recommendations on reproducible reporting of electronic health care data base studies should be followed (Wang, 2017)

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* and has been designed in line with the European Network of Centres for Pharmacoepidemiology and Pharmacovigilance (ENCePP) *Guide on Methodological Standards in Pharmacoepidemiology* (ENCePP, 2018). The *ENCePP Checklist for Study Protocols* (ENCePP, 2018) will be completed (see Annex 2).

The study is a post-authorisation 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* (ICH, 2019) and provided in the EMA *Guideline on Good Pharmacovigilance Practices (GVP) Module VIII: Post-Authorisation Safety Studies* (EMA, 2020), and with the 2012 European Union pharmacovigilance legislation, adopted June 19, 2012 (European Commission, 2019). 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* (EMA, 2020).

The study will be registered in the European Union Post-Authorisation Study Register (ENCePP, 2019) 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 (ENCePP, 2020) or the ADVANCE code of conduct (Kurz, 2017)

[If desired by the study investigators, the following may be included] The research team will apply for the ENCePP Study Seal (ENCePP, 2018).

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

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Annex 1. List of Stand-Alone Documents

Number	Document reference number	Date	Title
1	Annex 2	*<<MM.DD.YYYY>>*	ENCePP checklist for protocols

Annex 2. ENCePP Checklist for Study Protocols

The ENCePP Checklist for Study Protocols can be accessed and downloaded using the following link: http://www.encepp.eu/standards_and_guidances/checkListProtocols.shtml

Annex 3. Criteria to determine whether Cohort, Case-Control, Self-Controlled Case Series, Self-Controlled Risk Interval or Case-crossover Can Be Used for Signal Evaluation

Based on the assumptions and requirements of each design, we provide a decision framework for determining when Cohort, Case-Control, Self-Controlled Case Series (SCCS), Self-Controlled Risk Interval (SCRI), and Case-Crossover (CCO) designs can be used for signal evaluation.

The decision framework described below is based on event criteria. However, the identification of a suitable comparator group (active or unvaccinated) and the ability to identify major confounders should also be considered to determine the appropriate study design (see **section 9.1**). Cohort and case-control designs are suitable to assess a majority of events. In general, when the data is already available in electronic health care databases, cohort analysis should be conducted since it will provide absolute and relative risk measures. Case control design may be efficient if additional data needs to be collected or exposure patterns are difficult to track over follow-up time, also they allow for matching on calendar time, which is relevant with strong temporal trends. Because cohort and case control designs use other subjects as comparator, residual confounding due to factors that are not easily measurable in EHR data (such as genetics, habits, socio-economic status, ethnicity) can remain. If this is suspected self-controlled designs may be more suitable, but they require accurate estimation of the risk window and onset of the event.

Decision Framework for Determining Suitability of cohort, case-control, SCCS, SCRI, CCO for signal evaluation

Event criteria	Cohort	Case-control	SCCS	SCRI	CCO
Event latency					
Long latency	✓	✓	O[a]	X	X
Short latency	✓	✓	✓	✓	✓
Outcome onset					
Acute onset	✓	✓	✓	✓	✓
Gradual onset	✓	✓	O[a]	X	X
Ability to define risk period for outcome following exposure					
Can be clearly defined	✓	✓	✓	✓	✓
Cannot be clearly defined	✓	✓	O	X	X
Effect of event on likelihood of vaccination					
Event does not affect likelihood of vaccination	✓	✓	✓	✓	✓

Event temporarily decreases or increases likelihood of vaccination	✓	✓	✓	✓	✓
Event is a (permanent) contraindication to vaccination	O[b]	O[b]	O[b]	O[b]	✓
Event censors the period of observation for exposure (e.g., death or an outcome that increases the probability of death such as myocardial infarction)	✓	✓	X	X	✓
Event is independently recurrent	✓	✓	✓	✓	✓
Event is non-recurrent but rare	✓	✓	✓	✓	✓
Event is recurrent, and recurrent events are not independent (e.g., stroke)	✓	✓	O[c]	X	O
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	✓	✓	✓	✓	O

Checkmark indicates design is suitable; X indicates not suitable; O indicates that the study design is possible under certain circumstances.

[a] 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.
[b] Suitable if the vaccine is given in a single dose. If the vaccine is given in multiple doses, the design is not suitable unless special analytic techniques are applied to handle censored, perturbed, or curtailed post-event exposures.
[c] Suitable if appropriate adaptations to the self-controlled case series are applied (Farrington, 2010)