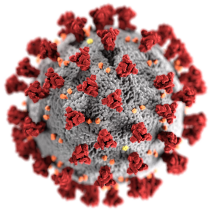
Rapid assessment of COVID-19 vaccines safety concerns through electronic health records: a protocol template from the ACCESS project

ACCESS

vACCine covid-19  monitoring readinESS

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

Dodd C, Willame C et al. Rapid safety assessment 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

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Medicinal product	*List of centrally authorised medicinal product(s) and/or, if possible, of nationally authorised products subject to the study*
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 rapidly assess the risk of specific severe adverse events following <<COVID-19 vaccine product>>
Country(-ies) of study	eligible data access providers based on ACCESS feasible assessment.
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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

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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
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
ITS	Interrupted Time Series
SCRI	Self-controlled Risk Interval
SPEAC	Safety Platform for Emergency vACcines
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
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:

Study size:

Data analysis:

Milestones:

5 Amendments and Updates

None to date.

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, 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 rapid safety assessment 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 rapid assessment 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 and events, as well as on COVID-19 vaccine administration for a subset of study designs, is required. The designs described here are intended for use in rapid (unadjusted) assessment of safety signals. Full evaluation studies are addressed in the companion ACCESS template protocol, *Safety evaluation of COVID-19 vaccines in electronic healthcare databases: a protocol template*. Rapidity of safety signal assessment will be dependent upon data lag times for the data sources utilized.

The potential designs for rapid safety assessment of vaccines studies include ecological designs, including interrupted time series (ITS) and the unadjusted self-controlled risk interval (SCRI) design. Electronic health care data source requirements for the application of each study design are described in **Table 1.**

Table 1. Assessment of the need for certain data elements for Ecological and Unadjusted SCRI designs to rapidly assess safety signals

	Data Elements			
Design	Listing of individuals in population	Events	Covariates	Vaccines
Ecological ITS	✓	✓	X	X

Unadjusted SCRI	X	✓	X	✓

Checkmark indicates design requires data element or feature; X indicates data element or feature is not required; O indicates that the data element or feature is required for some modifications of the design.

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)*. This list contains all of those identified by CEPI and SPEAC, with additional events based upon experience with other vaccines and potential target groups (for full details see *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, acuteness 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 rapid assessment of each AESI are provided in Table 2 below.

Table 2. Preliminary Assessment of the Suitability of the Ecological designs and Unadjusted SCRI for rapid assessment, by AESI

Outcome	Suitability of Ecological Designs*	Suitability of Unadjusted SCRI**	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, myocarditis	✓	✓	
Coagulation disorder, including deep vein thrombosis, pulmonary embolus, cerebrovascular stroke, limb ischaemia, haemorrhagic disease	✓	✓	
Generalised convulsion	✓	✓	
Guillain Barré Syndrome	✓	✓	

Outcome	Suitability of Ecological Designs*	Suitability of Unadjusted SCRI**	Notes
Diabetes (type 1), Diabetes (type 1 and unspecified type)	✓	X	
Acute kidney injury	✓	✓	
Acute liver injury	✓	✓	
Anosmia, ageusia	✓	✓	
Chilblain-like lesions	✓	✓	
Single organ cutaneous vasculitis	✓	✓	
Erythema multiforme	✓	✓	
Anaphylaxis	✓	X	Event is a permanent contraindication to vaccination
Death (any causes)	✓	X	
Sudden death	✓	X	
Acute aseptic arthritis	✓	✓	
Meningoencephalitis	✓	✓	
Acute disseminated encephalomyelitis	✓	✓	
Narcolepsy	✓	X	
Thrombocytopenia	✓	✓	
Transverse myelitis	✓	✓	
Preterm birth	✓	X	Risk window is unknown and could potentially be anytime during pregnancy
Major congenital anomalies	✓	X	SCRI not feasible because date of onset is unknown
Microcephaly	✓	X	SCRI not feasible because date of onset is unknown
Fetal growth restriction	✓	X	Risk window is unknown and could potentially be anytime during pregnancy following vaccination
Gestational diabetes	✓	X	Risk window is unknown and could potentially be anytime during pregnancy following vaccination; date of onset is unknown
Preeclampsia	✓	X	Risk window is unknown and could potentially be anytime during pregnancy following vaccination
Spontaneous abortions	✓	X	Risk window is unknown and could potentially be anytime during pregnancy following vaccination

Outcome	Suitability of Ecological Designs*	Suitability of Unadjusted SCRI**	Notes
Stillbirth	✓	X	Risk window is unknown and could potentially be anytime during pregnancy following vaccination
Induced abortions	✓	X	Risk window is unknown and could potentially be anytime during pregnancy following vaccination
Termination of pregnancy for fetal anomaly (TOPFA)	✓	X	Risk window is unknown and could potentially be anytime during pregnancy following vaccination
Neonatal death	✓	X	Risk window is unknown and could potentially be anytime during pregnancy following vaccination
Maternal death	✓	X	Risk window is unknown and could potentially be anytime during pregnancy following vaccination

*Ecological designs are likely to be better suited to those events not known to be associated with SARS-CoV-2 infection

**Suitability of the SCRI design is dependent upon availability of a purported risk period, which for some AESI is as yet unknown.

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.

8 Research Question and Objectives

[*Not all objectives may be possible in all data sources, depending on data availability. Investigators may adapt the objectives based on local settings and specific adverse events. This may include the option to study additional adverse events, as additional safety data become available]*

[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]

8.1 Ecological Methods

Primary objective: To assess whether there is increased incidence of pre-specified <<event>> following introduction of a specific <<COVID-19 vaccine product>> as compared to the period prior to introduction of a specific <<COVID-19 vaccine product>>

Secondary objective: To assess whether there is increased incidence of pre-specified <<event>> following introduction of a specific <<COVID-19 vaccine product>> as compared to the period prior to introduction of a specific <<COVID-19 vaccine product>> in groups defined by <<characteristic>> and/or <<characteristic>>.

8.2. Unadjusted Self-Controlled Risk Interval Analysis

Primary objectives: To determine whether there is increased incidence of pre-specified <<event>> following vaccination with specific <<COVID-19 vaccine product>> as compared to a pre-vaccination control period.

Secondary objectives:
§ To determine whether there is increased incidence of pre-specified <<event>> in specific vaccine groups defined by platform and/or components (e.g. adjuvant) as compared to a pre-vaccination control period.

§ To determine whether there is increased incidence of pre-specified <<event>> following vaccination with specific <<COVID-19 vaccine product>> as compared to a pre-vaccination control period in groups as defined by <<characteristic>> and/or <<characteristic>>.

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.

9.1.1 Ecological Methods

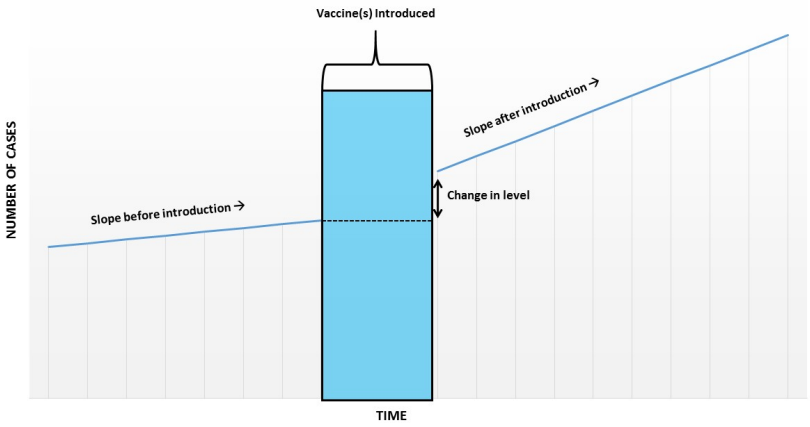
Retrospective, multi-database cohort study to assess changes in the incidence rate of <<event>> and to evaluate the impact of COVID-19 vaccine introduction on the occurrence of <<event>>.

Ecological analyses may employ a simple before/after comparison of incidence rates or may make use of multiple time points before and after an intervention in an interrupted time series (ITS) analysis to compare a pre-vaccine introduction period versus a post-vaccine introduction period. In this design there is no need to know vaccination status at an individual level, rather the country/regional introduction date is used. In an ITS analysis, which is one ecological design, slope and/or level in incidence trends over time can be compared in pre- vs. post-intervention time in a regression model (see **Figure 1**).

In an ITS analysis, incidence rates should be calculated at regularly spaced intervals (month, quarter) and the study period should include a sufficient number of time intervals prior to the vaccine introduction to

allow for assessment of temporal trends, independent of vaccination. Autocorrelation should be assessed and controlled for if present (Bernal, 2017). Power in ITS analyses is dependent not only upon the number of time points, but upon the sample size at each time point, so these should be taken into balanced consideration (Stratifications and restrictions may be conducted by <<characteristic>> when confounding or seasonal patterns are expected.

Figure 1. Interrupted Time Series Design adapted from Ramsey, 2013



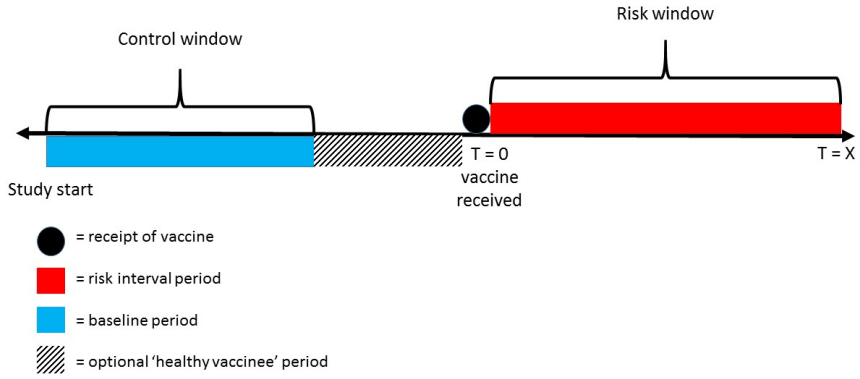
9.1.2 Unadjusted self-controlled risk interval (SCRI) Analysis

Retrospective (multi)-database case-only study that includes subjects who were vaccinated with COVID-19 vaccine and experienced an <<event>>. The incidence rate ratio of <<event>> between a period of time hypothesized to be at increased risk due to <<vaccine product>> ("risk window") and a pre-vaccination control window is calculated.

The SCRI design controls for non-time varying covariates, therefore it is particularly useful for quickly assessing signals detected using methods that are subject to between-person confounding.

In unadjusted SCRI analysis applied for rapid assessment, the risk and control periods are held constant across a number of <<events>>, and time-varying confounders are not controlled for. The absence of such adjustments for time-varying confounders, together with the use of a pre-vaccination control period only, allow for rapid assessment of events without the necessity for accumulation of observation time during post-exposure control windows. Care should be taken to select a pre-exposure control period that is short enough to avoid confounding by time-varying covariates, which are not controlled for in this design. If the event is considered to be a possible contraindication to vaccination, it may be appropriate to remove a 'healthy vaccinee' period from the control window prior to vaccination (Figure 2). In the case of a multiple dose vaccine, risk periods following the first dose should be censored at the date of the second dose if they extend beyond this date. Analyses limited to the first dose only, or to fully vaccinated individuals after the second dose only could be considered.

Figure 2. Unadjusted Self-controlled risk interval design



9.1.3 Criteria to determine whether Ecological Analysis or Unadjusted SCRI Can Be Used for Rapid Assessment

Based on the assumptions and requirements of each design, we provide a decision framework for determining when Ecological Analysis and Unadjusted SCRI can be used for rapid assessment.

The suitability of ecological analysis including the ITS design is dependent upon the nature of the intervention and the event (Bernal, 2017). The first requirement is for a clear differentiation between the pre- and post-intervention period in a group for whom uptake of the intervention (vaccination) is high. In the case of COVID-19 vaccines with recommended staged roll-out in health care works and risk groups, this time differentiation may not be clear in the population as a whole. In this situation, incidence in the risk group population rather than in the population as a whole should be studied if this population is readily identifiable. As described by Bernal et al, event data should be available both before and after the intervention, and events with short onset are best suited to ecological designs. Where possible, strata should be limited to groups with high vaccination coverage (Dodd, 2018). One important limitation of ecological designs including ITS is that they are subject to bias in the presence of another intervention which may impact occurrence or observation of the <<event>> of interest. This is an important limitation to consider in the context of COVID-19 and events, which may be impacted by wild-type virus circulation and behavioral changes including changes in healthcare provision and utilization.

Suitability criteria for application of the unadjusted self-controlled risk interval design for rapid assessment are equivalent to those for the self-controlled risk interval design (see companion protocol, *Safety evaluation of COVID-19 vaccines in electronic healthcare databases: a protocol template* and Annex 3) with the additional criteria that the pre-vaccination period should be suitable for use as a control window.

Fulfilling this requirement may necessitate the removal of a period prior to vaccination to control for the healthy vaccinee effect, or the reduced probability that a person experiencing the <<event>> will be vaccinated.

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 and attrition diagrams should be made. Follow-up time will 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 assessment 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

Ecological designs	Pre-vaccination period: sufficient period up to 31 December 2019 to accrue desired number of pre-intervention time intervals (dependent upon interval length) Post-vaccination period: from <<COVID-19 vaccine>> introduction until last available data The year 2020 should be kept separate in the analysis*	All eligible subjects according to inclusion criteria (e.g. with at least one day of follow-up in study period, or in specific risk groups)	Start: latest of fulfillment of inclusion criteria or start of pre-intervention period End: earliest of end of study period or censoring conditions. Time of follow-up is split in period prior to intervention and after intervention
Unadjusted SCRI	From <<COVID-19 vaccine>> introduction	Subjects who received at least 1-dose of COVID-19 vaccine and who experienced <<adverse event>>	Start: latest of fulfillment of inclusion criteria or start of study period End: earliest of end of study period or censoring conditions

[$]Study population for pregnancy outcomes should be adapted and includes pregnant women only, specific inclusion criteria may be required.
*The reporting of medical events might be impacted by the COVID-19 pandemic and the occurrence affected by SARS-Cov-2. Therefore, it is suggested to treat the year 2020 separate in the analysis.

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 Outcome 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 for the list of AESI provided by ACCESS, including code lists, were developed as part of the background rate protocol and can be found at https://drive.google.com/drive/folders/1Y_3cuGRN1g-jBv2ec1fC0aYcpxEjtrY9?usp=sharing

Note: These documents will be evolving based on experience in the calculation of background rates in the ACCESS project.

<<Event>> will 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 rapid assessment studies, validation of event identification algorithms using chart abstraction or manual verification of electronic records while being blinded to the <<COVID-19 vaccine>> exposure may be considered. However, validation of algorithms, if conducted, should be done prior to introduction of COVID-19 vaccine products so as not to delay rapid assessment analyses. If resources are restricted a sample may be validated initially to assess the positive predictive value. If the PPV is below 80% all cases should be validated.

Certainty of the diagnosis of an event may 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.

9.2.3.2 Exposure Assessment

In this section, operational definitions for identifying exposures to vaccines should be described, including the codes to identify them in the specific data sources. Individual-level exposure assessments described here are applicable only to analyses utilizing the unadjusted SCRI design.

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 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 may need to be identified via Anatomical Therapeutic Chemical codes, nationally used product codes, batch numbers, local codes, or free text. Data access providers should conduct quality assessment to assess whether vaccinations are adequately captured against external benchmarks using methods as described in ADVANCE system testing (Sturkenboom, 2020).

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.

9.2.3.4 Risk & Control periods

In this section, risk and control windows should be specified for each of the events under assessment for the specific design. Specification of risk and control periods described here are applicable only to analyses utilizing the unadjusted SCRI 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. Control periods and optional healthy vaccinee periods prior to exposure should be chosen in a manner to minimize 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 at the start of the study period and at the event date.

9.2.4.2 Confounders

Important confounders are all factors that are known risk factors for the event and are associated with the COVID_19 vaccination.

Ecological Designs (ITS)

Confounding in ecological designs may occur since comparisons are conducted at group level. These are inherent to the design and therefore such analyses will not provide causal evidence. Confounding due to additional interventions concurrent to the intervention of interest should be considered. This may be addressed through inclusion of a control time series if an appropriate control can be identified (Bernal, 2018). This control series may provide a counter-factual, estimating what the trends in incidence of the event of interest would have been in the absence of exposure, given exposure to other relevant time-varying events or interventions. The control series should be composed of a population observed during the same periods, exposed to other changes, but not exposed to the intervention. In the case of healthcare workers targeted in the initial roll-out of COVID-19 vaccines, an appropriate control series may be similarly aged adults who are not healthcare workers.

Unadjusted Self-Controlled Risk Interval Design

Within-person confounding is implicitly controlled for by design. Time-varying confounders will not be controlled for in unadjusted SCRI analyses.

9.2.4.3 Effect Modifiers

In this section, any factors (e.g., age at vaccination, chronic conditions, infections, concomitant vaccinations and medications) that are hypothesized 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 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

[*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. Sample size for ITS analyses may be calculated using the methodology of Hawley (Hawley, 2019). Sample size for SCRI analyses may be calculated using the methodology of Musonda (Musonda, 2006).*]

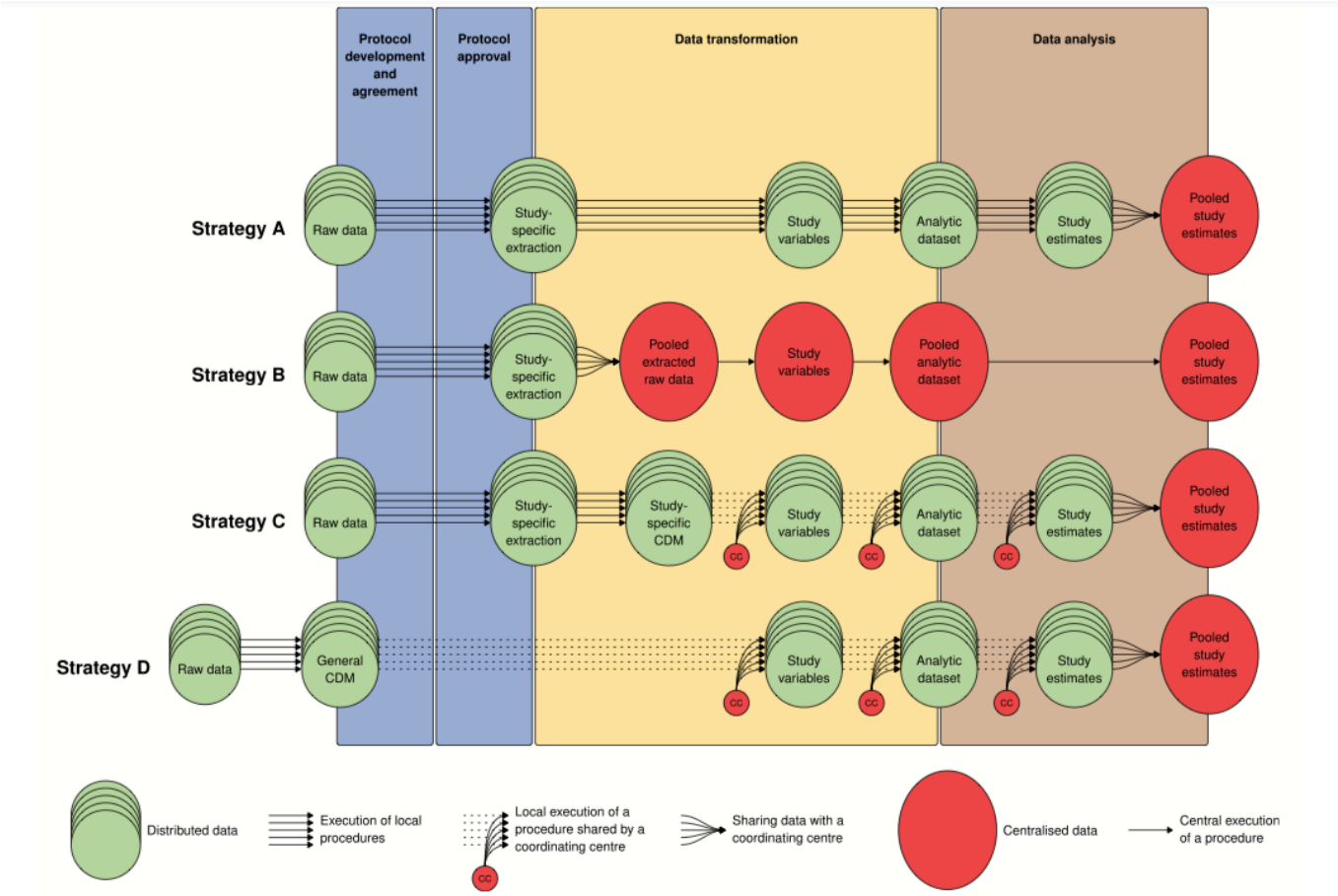
Rapid assessment

In rapid assessment the purpose is to quickly explore whether a potential safety signal can be confirmed, without doing proper adjustments for confounding. The null hypothesis is that the <<COVID-19 vaccine>> does not increase the risk of <<event>>. For this analysis, all available data that can be rapidly accessed should be utilized. When the null hypothesis cannot be accepted, the rapid assessment confirms the signal but does not show a causal relation as it may still be explained by confounding or bias; when the null hypothesis cannot be rejected, the existence of a true signal cannot be definitively refuted. The upper limit of the confidence interval will show what range of risk is compatible with the data.

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 3) (Gini et al, 2020).

Figure 3. 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[1]. 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.

[1] 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 (e.g. Co-morbidities) should be summarized for each data source using descriptive statistics where available. Note this may not be applicable to ecological designs. 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.

Counts and percentages should be presented for categorical variables (age at study entry in categories, sex). 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

Ecological Analysis or Unadjusted SCRI

For ecological analysis, incidence rates in different periods will be computed. The ratio between incidence rates in different periods should be computed using a Poisson regression model.
For interrupted time series analyses on incidence rates, a segmented Poisson regression model should be used to estimate changes in level and slope of pre- and post-intervention trends.

For Unadjusted SCRI, the ratio between the incidence rate in the risk period and the incidence rate in the control period (incidence rate ratio) should be computed using conditional Poisson regression.

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 in model C 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 expected variation in effect estimates of data-sources we recommend random effect models (Der Simonian and Laird, 1986).

9.6.4 Subgroup Analysis

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

[*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 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 studies and may include the following:

- For ecological analyses, a transition period after COVID-19 vaccine introduction should be applied to ensure a sufficient vaccine coverage and, consequently ensure to assess effect of vaccine.
- For ecological analyses of a population exposed to targeted vaccination (such as healthcare workers), consider use of a control series in an unexposed population to control for time trends concurrent with but unrelated to the intervention (Bernal, 2018)
- For unadjusted SCRI, if the risk window is not well known, conduct analyses with alternative risk intervals.
- For unadjusted SCRI analyses, 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.

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.

Ecological Analyses are limited in their utility and perform best when exposure to the intervention (vaccination in this case) is high and risk periods following exposure are short. Additionally, ecological analyses are subject to confounding in the presence of concurrently time-varying changes in the population which may impact rates of events. Ecological designs cannot be used to perform full evaluation studies and should only be used for rapid signal assessment.

The unadjusted SCRI method provides an opportunity to quickly assess suspected AESIs without the need to accrue post-risk period control time but is limited to acute events with short latency. Additionally, because only pre-vaccination control time is utilized, the approach is not appropriate for events which are a contraindication to vaccination. This can be somewhat ameliorated with inclusion of a pre-vaccination healthy vaccinee period if this period is known or can be accurately estimated.

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, any uncertainty about risk periods will lead to misclassification and attenuation of risk estimates.

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. Decision framework for determining suitability of rapid assessment designs

Table. Decision Framework for Determining Suitability of Ecological designs and Unadjusted SCRI for Rapid Assessment based on type of events and vaccination trends

Event criteria	Ecological Designs	Unadjusted SCRI
Event onset		
Acute onset	✓	✓
Gradual onset	O[a]	X
Ability to define risk period for event following exposure		
Can be clearly defined	✓	✓
Cannot be clearly defined	✓	X
Effect of event on likelihood of vaccination		
Event does not affect likelihood of vaccination	✓	✓
Event temporarily decreases or increases likelihood of vaccination	✓	O[b]
Event is a (permanent) contraindication to vaccination	✓	X
Event censors the period of observation for exposure (e.g., death or an outcome that increases the probability of death)	✓	✓
Event is independently recurrent	✓	✓
Event is non-recurrent but rare	✓	✓
Event is recurrent, and recurrent events are not independent (e.g., stroke)	✓	O[b]
Temporal trends in vaccination		
Temporal trends in vaccination are <u>not</u> present during the study period	O[c]	✓
Temporal trends in vaccination are present during the study period	O[c]	✓

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

[a] Requires sufficient accrual of post-intervention time for observation of events.

[b] May be used if a healthy vaccinee period to exclude from the pre-vaccination period can be defined.

[c] Requires that the start of the intervention be identifiable for the population under consideration. If timing of vaccination varies within the population under consideration, ecological designs may not be applicable, and the investigator may consider limiting the study population to those for whom the intervention period is identifiable.