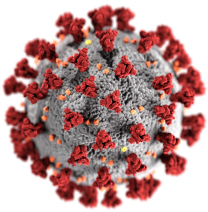
Real-world effectiveness of <<COVID 19 vaccine product>> in Europe: a protocol template for a cohort study based in existing health care data sources from the ACCESS project

ACCESS

vACCine covid-19  monitoring readinESS

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

Layton B, Garcia X. et al. Real-world effectiveness of <<COVID 19 vaccine product>> in Europe: a protocol template for a cohort study based in existing health care data sources 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	Real-world effectiveness of <<COVID-19 vaccine product>> in Europe: a protocol template for a cohort study based in existing health care data sources from the ACCESS project
Protocol version identifier	1.0
Date of last version of protocol	23 October 2020
EU PAS Register number	Study not yet registered
Active substance	[To be completed by study investigators]
Medicinal product	[To be completed by study investigators]
Product reference	[To be completed by study investigators]
Procedure number	[To be completed by study investigators]
Marketing authorisation holder(s)	[To be completed by study investigators]
Research question and objectives	To evaluate the effectiveness of <<COVID-19 vaccine product>> in preventing hospitalisations for COVID-19 and mortality due to COVID-19.
Country(-ies) of study	Participating electronic health care databases from ACCESS partners and associated partners where <<COVID-19 vaccine product>> is available. [To be completed by study investigators]
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Marketing authorisation holder(s)

Marketing authorisation holder(s)	[To be completed by study investigators]
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Contributions

Name & Organisation	Date	Contribution	Version of Document
Estel Plana, RTI Health Solutions	16 June 2020	Review of protocol template draft	0.1
	5 August 2020, 22 September 2020	Review of protocol template draft	0.2
	19 October 2020	Contribution of additional study size information	0.3
Alison Kawai, RTI Health Solutions	22 June 2020	Review of protocol template draft	0.1
	7 July 2020	Review of protocol template draft	0.2
	1 September 2020, 20 October 2020	Review of protocol template draft	0.3
Alejandro Arana, RTI Health Solutions	22 June 2020	Review of protocol template draft	0.1
Helle Vallach Kildemoes, University of Oslo	1 July 2020	Review of protocol template draft	0.1
	27 July 2020	Review of protocol template draft	0.2
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Vera Ehrenstein, Aarhus University	16 July 2020	Review of protocol template draft	0.2

Trademarks

[To be completed by study investigators]

Brand Name	Generic Name	Trademark Holder

1 Table of Contents

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2 List of Abbreviations

ATC	Anatomical Therapeutic Chemical (classification system)
CI	confidence interval
COVID-19	illness caused by the SARS-CoV-2 (severe acute respiratory syndrome coronavirus 2) virus
EHR	electronic health records
EMA	European Medicines Agency
ENCePP	European Network of Centres for Pharmacoepidemiology and Pharmacovigilance
EU PAS Register	European Union Electronic Register of Post-Authorisation Studies
GPP	Good Pharmacoepidemiology Practices
GVP	Good Pharmacovigilance Practices
HCU	health care utilisation
HR	hazard ratio
ICD-10	*International Classification of Diseases, 10th Revision*
ICU	intensive care unit
IRR	incidence rate ratio
ISPE	International Society for Pharmacoepidemiology
PASS	postauthorisation safety study
RD	risk difference
RR	risk ratio
STROBE	Strengthening the Reporting of Observational Studies in Epidemiology
VAC4EU	Vaccine Monitoring Collaboration for Europe

3 Responsible Parties

[To be completed by study investigators]

[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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name, degrees, job title	name, degrees, job title

Collaborating Institutions	**Study Sites**

4 Abstract

Title: Real-world effectiveness of <<COVID-19 vaccine product>> in Europe: a protocol template for a cohort study based in existing health care data sources

Version 1.0, 23 October 2020

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RTI Health Solutions

Rationale and background: Multiple vaccine candidates for COVID-19 are progressing through development and testing with anticipated widespread adoption and use after approval. The real-world effectiveness of these vaccines must be evaluated in European populations. This protocol template describes a general approach for a retrospective cohort study based in existing health data sources that may be modified or adapted to specific settings and research questions by future investigators.

Research question and objectives: To evaluate the effectiveness of <<COVID-19 vaccine product>> in reducing the burden of COVID-19, this protocol template addresses the following primary objective:

- To evaluate the effectiveness of <<COVID-19 vaccine product>> in preventing the following outcomes:
  - Hospitalisation for COVID-19
  - Mortality due to COVID-19

Secondary objectives of this protocol template are the following:

- To evaluate the effectiveness of <<COVID-19 vaccine product>> in preventing the following outcomes:
  - Intensive care unit (ICU) admissions for COVID-19
  - Medically attended diagnosis of COVID-19 in any setting
  - All-cause mortality
  - Hospitalisations for respiratory infections
- To evaluate if the effectiveness of <<COVID-19 vaccine product>> varies over clinically meaningful subgroups

Study design: This protocol template describes an observational cohort study of those vaccinated with <<COVID-19 vaccine product>> and those unexposed. The definition of the unexposed group may vary based on the actual use of <<COVID-19 vaccine product>> in the target population and the scientific question of interest.

This protocol template also describes a study feasibility stage, where the availability and validity of information needed to conduct the study will be evaluated, and the study design and analytic approach will be evaluated with a negative control outcome analysis.

Population: This study should be conducted in populations where <<COVID-19 vaccine product>> is approved and recommended for use. Due to rapidly changing COVID-19 incidence and testing/diagnosis capability and processes, exposed and unexposed groups should be drawn from the same time period. The study setting may include multiple existing health care data systems that contain information about vaccination status, hospitalisation records, mortality records, and comorbidity information.

The target population of interest should be consistent with the vaccine's approved indications, recommended use, and actual distribution. Recommendations and priority populations for vaccination may vary over time, and the study eligibility criteria should match.

Variables: <<COVID-19 vaccine product>> exposure status will be identified from vaccination records, as available in each data source. Eligibility criteria will be defined from enrolment, demographic, and clinical information in each data source. Outcomes will be defined in hospitalisation records, mortality records, and other records of diagnoses, as available in each data source. Covariates will consist of demographic and clinical variables necessary to describe differences between exposure groups and control confounding. Covariates will include demographic information, comorbidities, comedication use, health care utilisation, markers of current disease status at time zero, and markers of frailty.

Data sources[1]: [To be determined by the study investigators]

Study size: [To be determined by the study investigators]

Data analysis: Characteristics of the exposed and unexposed groups will be described. Incidence rates of COVID-19 outcomes will be calculated in the exposed and unexposed groups.

Incidence rates of COVID-19 outcomes will be compared between the exposed and unexposed groups, and vaccine effectiveness measures will be estimated. Additional absolute effect measures (e.g., risk difference) and time period–specific effect estimates (e.g., at 3, 6, or 12 months after vaccination) may also be estimated.

Subgroup analyses will separately estimate vaccine effectiveness in clinically meaningful subgroups. Sensitivity analyses will evaluate the robustness of the study approach across multiple variations of the study design.

[1] Database custodians and research partners will be contacted to explore interest in and availability to participate in the study. [To be included or modified as needed by the study investigators]

Milestones[1]: [To be determined by the study investigators]

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

5 Amendments and Updates

None to date.

6 Milestones and Timeline

[To be completed by study investigators]

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

EU PAS Register = European Union Electronic Register of Post-Authorisation Studies.

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

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

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

7 Rationale and Background

COVID-19, the disease caused by the novel coronavirus SARS-CoV-2, has become a global pandemic, affecting countries throughout Europe and the world. At the time of writing of this protocol template, multiple vaccine candidates are progressing through development and testing, with anticipated widespread adoption and use after approval and recommendation by health authorities. The real-world effectiveness of these vaccines must be evaluated in European populations.

To prepare for real-world evaluations of the effectiveness of potential COVID-19 vaccines in Europe, this protocol template has been developed as a guide for researchers who will implement studies comparing rates of COVID-19 outcomes between vaccinated and unvaccinated persons in existing health care data sources, such as population registers, electronic health records (EHRs), or billing claims data. At the time of the development of this protocol template, no vaccine candidate has yet been approved. Unknowns remain regarding many key factors that may influence the design and implementation of a study of COVID-19 vaccine effectiveness, including the following:

- Variation in COVID-19 incidence over time and geography during the study period
- Duration of person-level immunity from vaccination against COVID-19 or from SARS-CoV-2 natural infection
- <<COVID-19 vaccine product>>'s approved indications and/or contraindications
- Number of doses or dosing schedule for <<COVID-19 vaccine product>> (many current vaccine candidates in later-phase testing are multidose series)
- Recommendations for vaccination from public health authorities (including finalised priority populations for initial vaccination), and how the methods of vaccine distribution will affect the recording of vaccination status in existing health data
- Patterns of uptake (e.g., high-risk groups most likely to receive vaccination) of << COVID-19 vaccine product>>
- Number of approved COVID-19 vaccines being used concurrently in a population

Given the rapidly changing incidence of COVID-19 disease and testing/diagnosis capabilities and practices over time during the pandemic, ecological before-after approaches comparing COVID-19 incidence before and after the introduction of <<COVID-19 vaccine product>>, such as uncontrolled pre-post designs or interrupted time series designs, are less likely to be feasible [2], and time-varying exposure approaches that compare unvaccinated person-time before vaccination early in the study period with vaccinated person-time later in the study period or self-controlled designs that compare vaccinated and unvaccinated time within an individual may be subject to time-varying confounding. Additionally, in the event that multiple vaccines are available concurrently in a population, differentiation and evaluation of an individual COVID-19 vaccine product may be of interest; therefore, an approach that considers individual-

level exposure to <<COVID-19 vaccine product>> versus patients unexposed to <<COVID-19 vaccine product>> is warranted.

This protocol template provides an outline of a cohort study, but it also describes an evaluation to determine whether a study of vaccine effectiveness is feasible, with guidance to address the following key issues regarding the validity of a potential effectiveness study:

- Availability of required data elements in the database(s) involved in the study
- Coding validity of COVID-19 outcomes and vaccine exposure
- Identification of vaccinated and unvaccinated patients for comparison and defining the beginning of follow-up (time zero)
- Confounding of vaccine receipt and COVID-19-associated outcomes

Studies of vaccinated versus unvaccinated patients are highly subject to confounding by difficult-to-measure characteristics such as health care–seeking behaviour, access to health care, lifestyle factors, short-term health status, and frailty. Comparisons of older vaccinated versus unvaccinated persons have reported spurious, implausible protective associations, even after sophisticated attempts to control for confounding [3-9]. As receipt of a newly licenced vaccine may be strongly associated with risk status (e.g., health care workers or essential workers), health status (e.g., at high risk for complications), or lifestyle factors (e.g., adherence to recommendations regarding vaccination, hygiene, self-quarantine, social distancing, and/or mask-wearing), confounding is likely the strongest threat to the validity of a potential cohort study of <<COVID-19 vaccine product>> effectiveness. This confounding can be addressed through study design (e.g., identifying an exchangeable comparison group) and analysis (e.g., statistical adjustment). Suggested adjustment variables include not only clinically relevant characteristics such as comorbid conditions, but also markers of frailty and indicators of preventive health care–seeking behaviour, such as receipt of other vaccinations or screening tests.

The following template outlines a general approach to designing and implementing a comparative study of the effectiveness of a newly approved COVID-19 vaccine using existing health care databases. Modifications or local adaptations may be necessary depending on the country(ies) participating in the study, the data availability and structure, the characteristics of the vaccine and vaccine recipients, and additional understanding of COVID-19 disease and the vaccine at the time of the study. The template will indicate tools to determine if such a study is feasible, identify areas where adaptations to specific data sources or settings may be necessary, and address potential pitfalls to aid researchers who implement a study in existing health care data.

Note to investigators using this template to develop a full study protocol: As multiple potential COVID-19 vaccine products are under development, this protocol template refers generically to a <<COVID-19 vaccine product>>, which may be replaced with the name of the specific vaccine being investigated. The wording of some sections of this protocol can be retained or modified as appropriate in a final study protocol. Notes directly to the investigators in these sections are indicated in square brackets []. However, the language in some sections describes general principles, issues, and considerations for the investigators and will require the investigators to develop those sections with study-specific content, as appropriate for the specific study being considered.

8 Research Question and Objectives

This protocol templates addresses the research question of whether a newly licenced COVID-19 vaccine, <<COVID-19 vaccine product>>, is effective in reducing the burden of COVID-19 in countries in Europe where it is used. To address this research question, this protocol template addresses the following primary objectives:

- To evaluate the effectiveness of <<COVID-19 vaccine product>> in preventing hospitalisations for COVID-19 and mortality due to COVID-19 using existing health care databases
- To evaluate the effectiveness of <<COVID-19 vaccine product>> in preventing the following outcomes:
  - Hospitalisations for COVID-19
  - Mortality due to COVID-19

Secondary objectives of this protocol template are the following:

- To evaluate the effectiveness of <<COVID-19 vaccine product>> in preventing the following outcomes:
  - Intensive care unit (ICU) admissions for COVID-19
  - Medically attended diagnosis of COVID-19 in any setting
  - All-cause mortality
  - Hospitalisations for respiratory infections
- To evaluate if the effectiveness of <<COVID-19 vaccine product>> varies over clinically meaningful subgroups

A feasibility evaluation should be conducted before the start of the study to evaluate the availability of key data elements and appropriateness of the study design.

[Not all objectives may be possible in all data sources, depending on data availability. Investigators may adapt based on local settings. This may include the option to study

additional outcomes that are not currently listed, as clinical sequelae of COVID-19 become known.]

[The study investigators should specify here the choice of the unexposed group against which the <<COVID-19 vaccine product>> group is to be compared]

9 Research Methods

9.1 Study Design

An observational cohort study of those vaccinated with <<COVID-19 vaccine product>> and those unexposed will be implemented to allow for the estimation of effect measures on the absolute scale (e.g., time point–specific difference) [10] and relative scale (e.g., time point–specific risk ratios, hazard ratios, and vaccine effectiveness measures). This protocol template primarily describes a retrospective approach to using health care data sources after the necessary data have accumulated.

This study will compare individuals receiving <<COVID-19 vaccine product>> ("exposed") to a group of individuals not receiving <<COVID-19 vaccine product>> ("unexposed"). The choice of an exchangeable comparator group is a key factor in ensuring a valid study design and addressing confounding. However, at the time of writing this protocol template, the necessary information to select an exchangeable unexposed group is unknown. Potential choices of comparison groups include the following, in order of least to most likely to result in an exchangeable unexposed group:

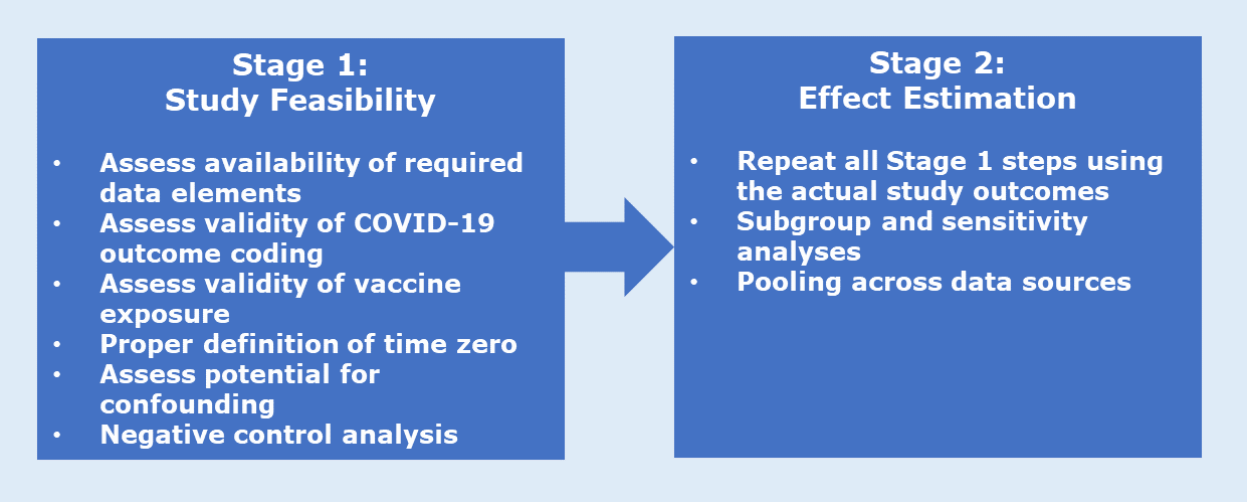
- Individuals not receiving <<COVID-19 vaccine product>>, identified at a randomly selected date or matched on the vaccination day of a person in the <<COVID-19 vaccine product>> group
- Individuals not receiving <<COVID-19 vaccine product>>, matched in some way on health care utilisation (e.g., identified at receipt of a different vaccine such as influenza or during a general practitioner visit)
- Individuals receiving a different COVID-19 vaccine product, if multiple vaccines are available in the study country(ies) simultaneously
  - This active-comparator design would minimise confounding but would answer a comparative effectiveness question that may be of different scientific or regulatory interest than comparing receipt of <<COVID-19 vaccine product>> to being unvaccinated.

Some of these options for the unexposed group may not be possible in each setting. The study investigators should select and justify the choice of an unexposed group to be used based on the conditions present during the study period. Additional considerations to inform the choice of an unexposed group are discussed in Section 9.1.1.5. The inclusion and exclusion criteria for both the <<COVID-19 vaccine product>> and unexposed groups are described in Sections 9.2 and 9.3.2. The unexposed group should

not be restricted to "never users" of <<COVID-19 vaccine product>> (i.e., individuals who never receive vaccination at any point in their available records, both before or after time zero), as use of future information to define exposure status at the start of follow-up fails to align the evaluation of eligibility criteria, exposure assignment, and beginning of follow-up and may introduce bias [11].

Because of the challenges outlined in the Background (Section 7), the study should be conducted in two stages (Figure 1). The first stage, the study feasibility stage, should evaluate the availability of all required data elements, assess the validity of the capture of COVID-19 outcomes in the included data source(s), and implement all the design features aimed at dealing with the proper definition of time zero and the potential for unmeasured confounding. Once these elements have been addressed and implemented, the second stage, estimating the effectiveness of the <<COVID-19 vaccine product>>, can be undertaken.

Figure 1. Study Implementation Stages



COVID-19 = illness caused by the SARS-CoV-2 (severe acute respiratory syndrome coronavirus 2) virus.

9.1.1 Study Feasibility Stage

The feasibility of conducting a vaccine effectiveness study in existing health care databases should be evaluated based on the conditions of the pandemic and the vaccine at the time of study implementation. It is likely that a valid study may not be possible in some settings. Future researchers applying this study protocol template should carefully evaluate the appropriateness of the setting and available data sources and should consider whether these issues can be adequately addressed and mitigated in the selected data source(s) before proceeding to study implementation. The aspects of feasibility regarding data availability and data validity (Sections 9.1.1.1, 9.1.1.2, and 9.1.1.3) can be evaluated before conducting the vaccine effectiveness study. The aspects of feasibility regarding valid study design (Section 9.1.1.4) should be addressed during final protocol development. The negative control analysis (Section 9.1.1.5) would

need to be conducted within the study data after protocol development has been finalised.

9.1.1.1 Availability of Required Data Elements

As part of the study feasibility stage, researchers should determine that all data elements for the implementation of the study (see Section 9.3) are available. Also, appropriate ascertainment of the inclusion and exclusion criteria (Section 9.2), exposure, outcomes, and rich information on potential confounders (Sections 9.1.1.5 and 9.3.4) will be needed. If the study is to be implemented in multiple data sources, data availability should be assessed in all proposed data sources.

9.1.1.2 Validity of COVID-19 Outcome Coding

In this study based in existing data sources, COVID-19 outcomes will be identified from recorded diagnoses arising from health care delivery. COVID-19 diagnosis coding has been introduced recently into the *International Classification of Diseases, 10th Revision* (ICD-10) as code U07, with subcodes for confirmed or suspected cases [12]. Variation in the development of COVID-19 diagnosis coding may continue in other coding systems. If the validity of COVID-19 data capture is unknown at the time of the study implementation, the validity of the outcomes should be ascertained through case adjudication, linkage to COVID-19 testing results (where available), or some other method. Sensitivity analyses varying the outcome definitions (e.g., altering the setting of care, identifying cases based on treatments or symptoms) may be implemented (Section 9.7.4.2).

9.1.1.3 Validity of Vaccine Exposure

As COVID-19 vaccines are not currently used in clinical practice, the validity of COVID-19 vaccine records in health care databases or vaccination registers is not known at the time of writing this protocol template, and it may vary across countries and data systems depending the approaches to vaccination campaigns. The data source(s) selected for the study should be evaluated to ensure that accurate recording of vaccination status is available, whether vaccinations were given in physician offices or hospital clinics (and thus may be routinely recorded in EHR systems) or in public health vaccination campaigns (and thus may be recorded in vaccination registers). If multiple COVID-19 vaccines are available concurrently, and the intent of the study is to evaluate a specific COVID-19 vaccine product, then the ability to differentiate vaccine brands should be considered a prerequisite for inclusion of a data source in the study.

The initial priority population for vaccination will likely include health care workers and other essential personnel. If these personnel are vaccinated outside of the mechanisms used for the general population (e.g., if health care workers are vaccinated by their employers rather than by the primary care clinicians), the availability of these vaccinations in EHR or other accessible research data should be evaluated. If employer-based vaccinations are not available and linkable to the necessary study data, then

separate approaches may be needed to evaluate vaccine effectiveness among these priority groups, and the EHR-based study may be restricted to populations where vaccination status can be accurately identified.

If the unexposed group is identified through some recorded event in EHR systems (e.g., receipt of influenza vaccine, general practitioner office visit), the validity of the index event in the unexposed group should also be evaluated.

9.1.1.4 Proper Definition of Time Zero

In studies of vaccinated versus unvaccinated persons, researchers must determine the appropriate time point at which to identify patients and begin follow-up. Aligning the evaluation of eligibility criteria, covariate assessment, exposure assignment, and beginning of follow-up (time zero) avoids selection bias and immortal person-time bias and addresses a well-defined study question [13]. Time zero is the time when the exposure status is assigned; all eligibility criteria must be fulfilled at that point, and study outcomes must start to be counted at that point [14]. Deviating from this principle can introduce bias due to selection (e.g., immortal time bias) [13,15-17].

Among the study population, time zero in the exposed group receiving <<COVID-19 vaccine product>> should be the time when <<COVID-19 vaccine product>> is administered. If <<COVID-19 vaccine product>> is a multidose vaccine series, investigators should specify whether the exposure of interest is receipt of a first dose only without concern for receipt or timing of subsequent doses (analogous to the "intent-to-treat" approach), or whether completion (and timing) of the full series is of interest. If the completion and timing of the vaccine series are of interest, additional considerations are necessary to define exposure groups based on the observed vaccination strategy (e.g., fully completed vaccine series, partially completed vaccine series, delayed completion of vaccine series) (Annex 3), but follow-up for all treatment strategies should begin at time zero (Section 9.3.1).

If the unexposed comparator group is composed of individuals receiving another medical intervention (e.g., influenza vaccine, a different COVID-19 vaccine product, or another preventive health intervention), time zero for the comparator group may be identified as the day of receipt of the other intervention.

If the unexposed comparator group consists of individuals not receiving any vaccine or medical intervention, patients in this unexposed group may meet the eligibility criteria at multiple time points, and multiple options may be available for choosing time zero. For example, consider a hypothetical study comparing patients with diabetes who received <<COVID-19 vaccine product>> during the summer months (June-August), with patients with diabetes who did not receive the vaccination. An individual with a diagnosis of diabetes in May can meet the eligibility criteria for the unexposed group at any time he or she is not vaccinated (i.e., should his or her time zero be June 1, June 15, July

15?). The following two unbiased options exist for selecting time zero for an unexposed group [14]:

1. Choosing a single eligible time as time zero (e.g., a random calendar date or a calendar date matched to the time zero of a vaccinated individual).
2. Choosing every eligible date. If this approach is selected, several nested cohorts can be created to increase efficiency [15] via the following approaches:
   - Choosing health care interactions as the time zero for each nested cohort [18]. One example could be every primary care physician visit when the patient could plausibly be offered <<COVID-19 vaccine product>> [19].
   - Choosing a fixed time unit to create a series of nested cohorts, each starting at each new time unit [20,21]. The time unit can be months, weeks, or any other convenient interval as appropriate for the study question; in this setting, shorter periods such as weeks may be appropriate.

Although both of these unbiased options are equally valid, the first will be easier to implement, but will result in less precise estimates. For the second option, the variance estimation will need to be adjusted accordingly (e.g., by bootstrapping) because individuals are allowed to contribute to multiple study cohorts [22].

9.1.1.5 Assess Potential for Unmeasured Confounding

As elaborated in Section 7, unmeasured confounding is a serious threat to the estimation of vaccine effectiveness using observational data [3-9].

Of note, there may be situations where the initial recommendations for vaccination, the vaccine distribution strategy, and the uptake of the vaccine may heavily influence the magnitude and direction of confounding. Examples include the following potential scenarios (in order from potentially introducing the most to the least confounding):

- If the vaccine is initially administered only to those at highest risk for contracting COVID-19 (e.g., health care workers or nursing home residents) or for complications of COVID-19 (e.g., older adults or those with serious comorbidities), comparisons between vaccine recipients and non-recipients during this time period may be strongly confounded by the differences in risk or health status between the two groups. Comparisons within more restricted populations (such as vaccinated health care workers versus unvaccinated health care workers) may be less confounded than comparisons between more disparate groups (e.g., vaccinated health care workers versus unvaccinated general population).

- If adoption of the vaccine is nearly universal in the entire population (or within a priority population of interest, such as health care workers), the minority of patients not receiving the vaccine may differ fundamentally from those who do receive it (e.g., those with limited life expectancy, thus having preventive care withheld; contraindications to vaccination; or antivaccination beliefs coupled with other lifestyle factors).
- If the vaccine is initially burdensome to obtain or highly priced for the recipient, those initially receiving the vaccine may be those with better access to health care, higher personal motivation for preventive health care, higher socioeconomic status, or healthier lifestyles.
- If the vaccine is initially in short or sporadic supply, and only a fraction of eligible patients receive it, but the factors related to receipt are less dependent on individual factors (e.g., it is available only in some clinics or geographic areas; frequent disruptions in supply lead to not everyone who desires it receiving it), then confounding between unexposed and exposed individuals by clinical characteristics may be minimal.
- If <<COVID-19 vaccine product>> is distributed concurrently with the seasonal influenza vaccine, persons receiving both <<COVID-19 vaccine product>> and the seasonal influenza vaccine could be compared with those receiving the influenza vaccine alone, with the dates of the vaccination serving as time zero in both groups. This would constitute an active comparator and may reduce unmeasured confounding by health-seeking behaviour.
- If multiple COVID-19 vaccine products are available concurrently in a population, recipients of different COVID-19 vaccines could be compared in a head-to-head fashion. This choice would greatly diminish, if not eliminate, confounding by indication. However, if differences in access, price, or other characteristics exist, residual confounding may be present.

The study investigators should weigh how vaccine recommendations, availability, distribution, and uptake may impact the amount and direction of confounding. Ideally, the feasibility stage should show that adequate adjustment for confounding is possible and planned. For that purpose, the protocol should address the following:

- List all the potential confounders based on subject-matter knowledge at the time of the conduct of the study (initial recommendations in Section 9.3.4)
- Determine that measures of all the potential confounders are available in the data source(s)
- Specify the method(s) to be used for adjustment of confounding (see Sections 9.7.3.2 and 9.7.3.3 for context)
- Implement a negative control outcome analysis [23]

Negative Control Outcome Analysis

Due to concerns of unmeasured confounding, we recommend the inclusion of negative control outcome analyses to evaluate the potential risk of unmeasured confounding (Section 9.1.1.5). For example, influenza prevention studies have frequently evaluated the association of influenza vaccination with mortality during the preinfluenza period (the time between vaccine receipt and the onset of circulating influenza in the community when no biological effect of the influenza vaccine would be expected) as a negative control to illustrate residual confounding [3-6,24]. Of note, many of these analyses demonstrated evidence of intractable unmeasured confounding. Presently, COVID-19 has not adopted a well-defined seasonality similar to influenza; thus, this specific negative control may not be feasible in this setting.

A negative control outcome analysis to explore the presence of residual confounding is one that fulfils the following criteria:

- The set of common causes of receiving <<COVID-19 vaccine product>> and hospitalisation for COVID-19 should be as identical as possible to the set of common causes of receiving <<COVID-19 vaccine product>> and the negative control (e.g., the negative control and hospitalisation for COVID-19 are approximately "U-comparable" outcomes) [23]
- <<COVID-19 vaccine product>> cannot cause the negative control outcome.

The investigators should implement a properly reasoned, comparative negative control outcome analysis that supports an appropriate adjustment for confounding before proceeding to the next stage, where the causal effect will be estimated. Potential negative control outcomes may include the following:

- An unrelated outcome that may also be influenced by personal adherence to preventive measures (e.g., accidents)
- COVID-19 outcomes within the first 10 or 14 days after COVID-19 vaccination, as the vaccine is unlikely to have any preventive effect before a patient's immune response to the vaccine
- COVID-19 outcomes in areas where or during times when SARS-CoV-2 is not actively circulating if <<COVID-19 vaccine product>> is distributed in any of these times or places

If evaluation of the association of <<COVID-19 vaccine product>> with the negative control outcome results in a non-null effect measure estimate as assessed by the magnitude of effect measure estimate and its 95% confidence interval (CI), then the presence of residual confounding should be assumed. Investigators should not proceed to the primary analysis stage without addressing the residual bias; previous examples from influenza studies in older adults have demonstrated residual confounding by functional status [5], frailty [6,9], health care utilisation [25], and short-term health

status [9,26]. Modifications to the study design or analysis may be warranted to improve control of residual confounding, potentially including the following:

- Inclusion of additional covariates for statistical adjustment, if available [6]
- Modifications of inclusion or exclusion criteria to restrict analyses to more comparable groups [9,25] and align more closely with the recommended population for <<COVID-19 product>> receipt
- Modifications to the unexposed group (e.g., using an active comparator, if available) [24]

After making modifications, the negative control outcome analysis should be repeated to demonstrate that appropriate control of confounding has been achieved.

The use of quantitative bias analysis [27] cannot be a substitute for the use of negative controls in this setting because if the magnitude of the unmeasured confounding is unknown, the magnitude of the confounding bias is also unknown. Plus, these methods assume that residual confounding can be summarised by a single dichotomous, time-fixed variable that is unassociated with all measured variables that were adjusted for in the main analysis. Such an assumption is untenable in the setting of vaccine effectiveness research because potential unmeasured confounders like functional status, frailty, or health consciousness obviously violate such an assumption.

9.1.2 Vaccine Effectiveness Estimation Stage

Researchers should proceed to this stage only when a negative control outcome analysis has shown an appropriate control of confounding. The analysis for the effect estimate stage should then be the same as in Section 9.1.1, but using the actual study outcome(s).

9.2 Setting

This study should be conducted in countries and jurisdictions where <<COVID-19 vaccine product>> is approved and recommended for use. Due to the potentially changing incidence of COVID-19 over time, the study period should align with periods of availability of the COVID-19 vaccine in order to compare vaccinated persons with unexposed individuals during the same time periods. The study period should begin at the time of availability and use of <<COVID-19 vaccine product>> until the end of data availability or the end of the pandemic in each country.

The target population of interest should be described clearly by the investigators implementing the study, and it should be consistent with the approved indication of the vaccine and public health recommendations for the vaccine. For example, if the vaccine is approved only for certain age groups (e.g., adults aged ≥ 65 years; adults aged ≥ 18 years; or adults and children aged ≥ 1 year) or for those with certain comorbidities, the study eligibility criteria should reflect those same indications.

Additionally, if the distribution of the vaccine varies from the approved indication in practice due to prioritisation of certain populations (e.g., the vaccine is indicated and recommended for all adults, but is distributed only to health care workers or other high-risk groups during the study period), the study population should be matched to the actual distribution of the vaccine. As recommendations for vaccination and patterns of uptake of the vaccine may change over time (e.g., if the vaccine is only offered to older individuals during the first year, but then offered to the general population afterward), the eligibility criteria may be altered flexibly over time to match. It appears increasingly likely that the initial priority vaccination groups will be determined by employment status (e.g., health care worker, essential worker) rather than demographic or clinical characteristics. Health care workers and other priority groups may be at higher risk of COVID-19 infection than the general population, introducing increased risk of confounding in comparisons between vaccinated health care workers and unvaccinated individuals in the general population; comparisons of vaccinated to unvaccinated health care workers during narrow time intervals may be most appropriate. However, details of individuals' employment or essential worker status may not be recorded in health care databases, and vaccines administered through employers may not be captured in population registers or EHR systems. If the initial priority groups or their vaccination status cannot be identified in health care databases, the study period may be altered to begin when the vaccine is recommended for use in a broader population that can be identified using accessible health care information.

Individuals will be selected for inclusion into the study cohort at time zero for both the <<COVID-19 vaccine product>> and unexposed groups, as described in Section 9.1.1.4.

Inclusion criteria based on previous enrolment or observation in the data source(s) before time zero (Figure 2) may vary, as appropriate for each setting. A minimum of one year of history before time zero (Section 9.1.1.4) is recommended in order to properly characterise baseline variables; all available data before time zero may be appropriate to define chronic conditions, while shorter windows may be used to define acute events, short-term health status, or comedications.

Exclusion criteria may be defined, such as contraindications for vaccination. Exclusion criteria should be justified as either necessary to define the indicated study population of interest or to reduce confounding.

Considerations for specific exclusion criteria may include the following:

- Exclusion criteria based on previous COVID-19 diagnosis, positive viral or antibody testing, ventilator use, or COVID-19 treatment (e.g., remdesivir) may be considered, but should be implemented only if consistent with the approved indication or actual use of the vaccine in clinical practice. COVID-19 test results or diagnoses may be missing from EHR systems or prone to misclassification, and criteria based on such results should be implemented with caution.

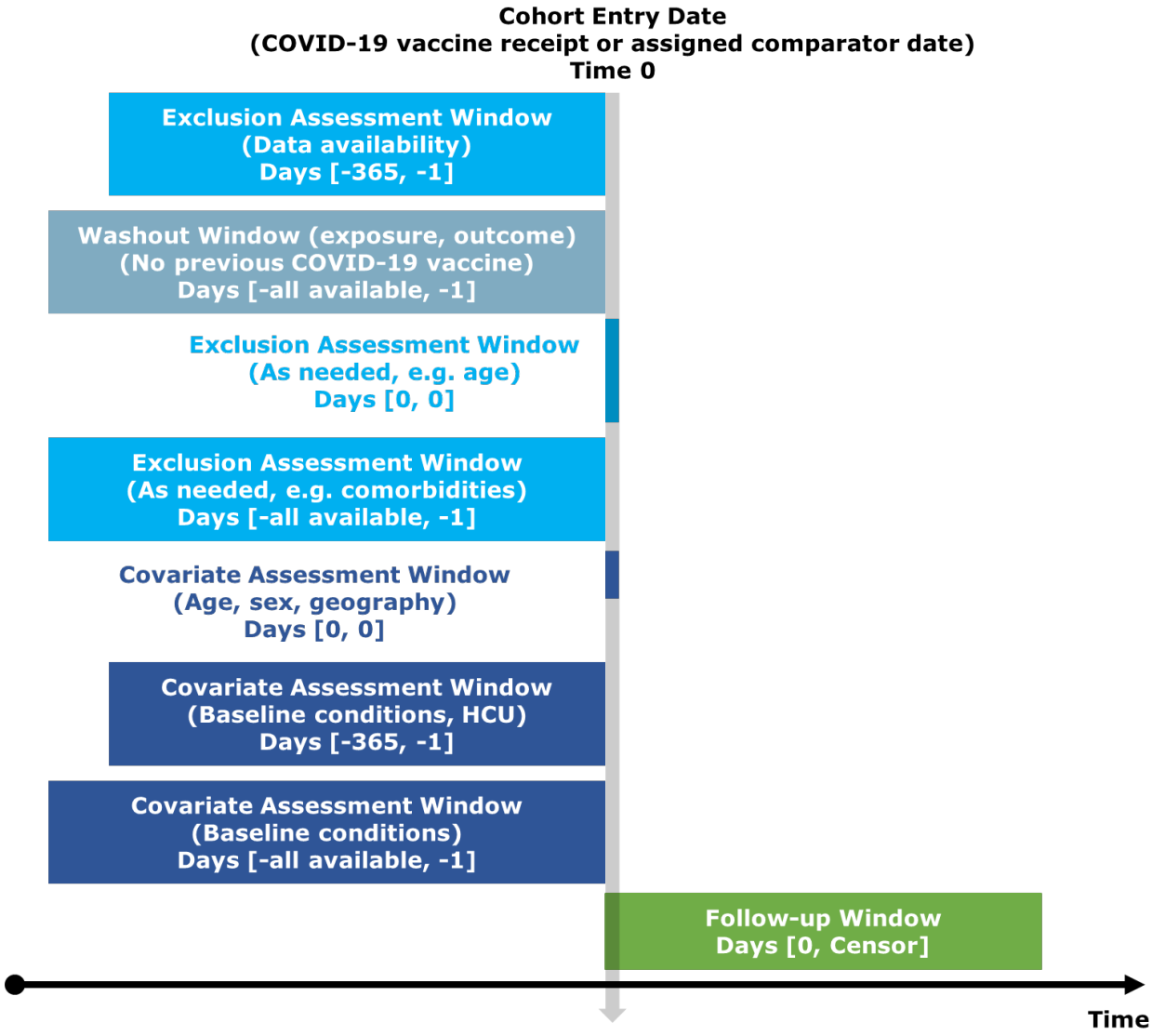
- If multiple COVID-19 vaccine products are available and used in a population, previous receipt of a different COVID-19 vaccine product may be considered an exclusion criterion for the present study of <<COVID-19 vaccine product>>.
- If the unexposed group consists of individuals not receiving any vaccination (neither <<COVID-19 vaccine product>> or an active comparator such as influenza vaccine), then some exclusions based on current, short-term health status at time zero may be considered. For example, those who are currently sick with a fever generally do not receive vaccinations until the current illness has resolved. Therefore, if general practice visits or screening tests are used to identify the unexposed group, visits where an individual has a fever may be excluded from the pool of potential eligible visits.
- Exclusion criteria should not be based on future events occurring after time zero (e.g., future vaccination with <<COVID-19 vaccine product>> among the unexposed group; future vaccination with a different COVID-19 vaccine among either group). These future events may be considered as events that would end follow-up (together with appropriate methods to adjust for such potential informative censoring), but they should not result in exclusions at time zero.
- Exclusion criteria for real-world studies need not match those used in preapproval clinical trials of the vaccine.

The cohort will also be stratified by key demographic and clinical characteristics in secondary analyses to evaluate the potential for heterogeneity of vaccine effectiveness across subgroups.

9.3 Variables

The measurement of exposure status, eligibility criteria, outcomes, and covariates will be defined in the data source(s) and subsequently used in analysis.

Figure 2. Example Study Design Schematic Illustrating the Relationship of Variable Assessment Windows to the Cohort Entry Date



HCU = health care utilisation.

Figure template available at www.repeatinitiative.org.

9.3.1 Exposure Assessment and Time At Risk

Receipt of an individual vaccine dose is a point exposure, and proper exposure assessment relies on accurate recording of the specific COVID-19 vaccine product and date of receipt.

The important elements of this exposure measurement include receipt of <<COVID-19 vaccine product>> and the date of vaccination. These data elements may be ascertained from pharmacy dispensing records, general practice records, vaccination register data, or other data sources (as appropriate in each participating country) with the granularity to differentiate between COVID-19 vaccine products, if multiple vaccine products are available concurrently. The initial vaccine exposure identified at time zero should

represent the first vaccination of the patient with <<COVID-19 vaccine product>>, with a necessary washout period required to identify new use (e.g., using all available baseline history to identify first-ever use). Investigators should identify options for dealing with implausibly closely spaced vaccination records to address either vaccination contrary to recommendations (e.g., unrecommended multiple doses in a year, see Section 9.7.3.3) or potential data entry errors (e.g., two vaccination records within 7 days may have both resulted from the same vaccination event, so the second is ignored).

Currently, whether the vaccine will be recommended as a single dose or a multidose series is unknown (many vaccine candidates currently in late-phase testing are being evaluated as two-dose vaccine series). If <<COVID-19 vaccine product>> is indicated as a multidose series, it may be of interest to define exposure and time at risk based on adherence to the recommended vaccination schedule (e.g., fully completed on-time vaccination, partially completed, delayed completion) and compare different vaccination strategies to receipt of no vaccine or to each other. Vaccination strategy groups should be defined without utilising future information in the data after time zero to appropriately assign person-time without introducing immortal person-time bias. Additional considerations are discussed in Annex 3.

As described in Sections 9.1 and 9.1.1.4, multiple options exist for identifying the unexposed comparator group and assigning time zero for the comparators. The study investigators should specify how the unexposed group will be defined and how the event(s) that will be used to define time zero (e.g., influenza vaccination, receipt of screening test, general practitioner visit) will be identified in the data source.

However, in any study, regardless of the selected unexposed comparators, receipt of <<COVID-19 vaccine product>> after time zero among the comparators or receipt of a different COVID-19 vaccine in either group would need to be handled analytically rather than by exclusion of the patient at baseline based on the future vaccination status (Section 9.7.3.3).

Individuals in the <<COVID-19 vaccine product>> and unexposed groups will be followed from the day of time zero (inclusive) until the first occurrence of the following:

- Administrative end of study
  - End of data availability
  - End of study period
  - End of the pandemic (if SARS-CoV-2 is no longer circulating)
- Patient disenrollment from the data source or emigration from the country or catchment area of the data source
- Death

- First occurrence of a prespecified study outcome (a patient may have different follow-up periods for different outcomes)
- If the vaccine is intended to give protection for a fixed period of time, then the follow-up period for effectiveness should be truncated at the end of that time period
- Deviation from the vaccination strategy assigned at time zero (e.g., an unexposed patient receiving <<COVID-19 vaccine product>>; in the case of a multidose vaccine series, a vaccinated patient assigned to the fully vaccinated group missing the second dose; see Annex 3, Figure 3-1)

Some analyses may restrict follow-up to certain time points (e.g., 3, 6, 9, and 12 months) to evaluate vaccine effectiveness during set time periods (Sections 9.7.2 and 9.7.3.1).

9.3.2 Eligibility Criteria

If additional eligibility criteria are needed to define the cohort as described in Section 9.2 (e.g., health care worker status, comorbidities, previous COVID-19 infection or testing, short-term health status before time zero), the process for defining the needed variables should be described here.

9.3.3 Outcome Assessment

Outcomes will be assessed during the follow-up window (Section 9.3.1). Multiple effectiveness outcomes associated with vaccination for COVID-19 are proposed in this protocol template, as the severity of COVID-19 and its complications may vary widely. Laboratory-confirmed infection status is not recommended at this time as an outcome for studies conducted in the general population. The severity of COVID-19 illness has been shown to vary from asymptomatic to life-threatening, and a patient's test-seeking behaviour may be associated with both severity of infection symptoms and personal health-seeking behaviour, which may introduce selection bias or confounding [28,29]. Additionally, testing capacity and practice may vary widely across countries and locales (from widespread population testing to testing only symptomatic, suspected cases), and availability of test results may vary. In certain settings (e.g., among health care workers), COVID-19 testing may be widespread and routine, and an evaluation of laboratory-confirmed illness may be appropriate if the study population is restricted to those with routine screening. However, in the general population, this is unlikely to be the situation unless COVID-19 testing becomes near universal and repeated with individuals. Thus, in this protocol template, hospitalisation for COVID-19 and COVID-19–specific mortality outcomes are proposed as primary outcomes to define more severe COVID-19 cases most likely to be identified and recorded.

Formal validation studies are critical to correct for outcome misclassification, a substantial source of systematic error in observational epidemiologic studies using routinely collected health care data. If no validation studies are available at the time of

study implementation, then outcome validation work may be undertaken as part of the project. If a formal validation study or outcome adjudication component is to be employed as part of the study, the investigators should specify the approach used for ascertaining the gold standard case status of patients and adjudication (e.g., hospital chart extraction and review). If the outcomes cases are to be sampled from the overall population, the sampling frame should be described.

Estimation of validation measures, likely the positive predictive value, should be described.

9.3.3.1 Hospitalisation for COVID-19

The primary outcome of hospital admission for COVID-19 will be defined as an inpatient record with an admission or discharge diagnosis of COVID-19. The date of the outcome will be the hospital admission date.

9.3.3.2 COVID-19–Specific Mortality

The primary outcome of COVID-19–specific mortality will be defined as one of the following:

- A recorded death with COVID-19 listed as an underlying cause of death on cause-of-death registers
- Death during a hospitalisation, with COVID-19 as a listed diagnosis
- Death within a specified time period (e.g., 28 days) after a diagnosis or hospitalisation for COVID-19

This definition may require modification based on the data availability in each data source. The date of the outcome will be the date of death.

9.3.3.3 ICU Admission for COVID-19

The secondary outcome of ICU admission for COVID-19 will be defined as an inpatient record with an admission or discharge diagnosis consisting of COVID-19 with a specific notation of ICU as the setting of care. The date of the outcome will be the ICU admission date. If the exact date of ICU admission is not available, admission date of the hospitalisation may be considered.

9.3.3.4 Medically Attended Diagnosis of COVID-19

As the other primary and secondary outcomes consist of more severe hospitalised or mortality outcomes, it may be desirable to include a non-hospitalised outcome including those with less severe disease. However, due to limited testing in the general population, the infection status of many individuals will never be determined. Additionally, not all infected individuals will become symptomatic, seek treatment, be tested, or receive a diagnosis. Researchers may desire to use symptomatic COVID-19 disease as a potential outcome, but that may not be feasible in a study based in existing health care data

sources; those with mild disease may never seek care, and many EHR systems may lack the necessary granularity to identify symptomology. Therefore, a surrogate outcome that includes less severe disease may be diagnosis of COVID-19 by a health care provider in any setting, including hospitalised and non-hospitalised settings. However, if an individual's personal health beliefs and behaviours increase the likelihood of both <<COVID-19 vaccine product>> receipt and seeking health care for milder disease, then the analysis of this outcome may be particularly subject to confounding by health care–seeking behaviour.

The secondary outcome of a medically attended diagnosis of COVID-19 diagnosis will be defined as an inpatient record, emergency department visit, outpatient clinic, or general practitioner encounter with a recorded diagnosis of COVID-19. The date of the outcome will be the hospital or emergency department admission date or the date of the clinic or general practitioner encounter.

9.3.3.5 All-Cause Mortality

Cause-of-death information in EHR systems is often lacking; therefore, all-cause mortality will be used as a secondary outcome. All-cause mortality will be defined as a recorded patient death during the outcome ascertainment period. Depending on the data source, this may be ascertained through national or local cause-of-death registers, health care system enrolment data, hospital discharge status, etc. The date of the outcome will be the date of death.

9.3.3.6 Hospitalisation for Respiratory Infection

The outcome definition for hospitalisation for respiratory infection will be defined as a documented inpatient admission during the outcome ascertainment period with a diagnosis code for respiratory infection listed as the admission or discharge diagnosis. The date of the outcome will be the admission date.

9.3.4 Covariate Assessment

Substantial confounding may exist depending on the unexposed comparator group selected and characteristics of the vaccine distribution process, and every effort should be taken to control for measurable confounders in the analysis. Measured confounders will include demographics, lifestyle characteristics, comorbidities, comedications, and health care utilisation prior to or at time zero at the patient level. Given that risk factors for COVID-19 infection are not currently well understood [30], the measurement and inclusion of particular covariates will need to be flexible and responsive to emerging science and conditions. Thus, this protocol focuses on measurable covariates that are classically controlled for in pharmacoepidemiologic research and leaves room for the inclusion of risk factors yet to be determined.

The following demographic variables will all be assessed at time zero:

- Age
- Sex
- Race and/or ethnicity, as appropriate in each country
- Geographic region, as appropriate in each country
  - Geographic region, where available, will be of importance given that prevalence of COVID-19 in the population can vary substantially within a given country, and this may influence both the decision to be vaccinated and the probability of becoming infected with SARS-CoV-2.
- Socioeconomic status, as available in each country (including housing, employment, and income, if available)
- Health care worker or essential worker status, if available
- Date of vaccination (categorised as appropriate, e.g., by year or month)

Personal lifestyle characteristics may be associated with COVID-19 outcomes, including the following:

- Smoking status
- Body mass index (as available)

Comorbidities may be assessed through either recorded diagnoses or medication use, depending on the data source(s) used in the analysis and the condition being measured. The following comorbidities (and others that may be shown to be associated with COVID-19 prognosis) will be assessed using all available lookback in the data source before time zero:

- Diabetes mellitus (types 1 and 2)
- Hypertension
- Cardiovascular disease
- Cerebrovascular disease
- Chronic respiratory disease
- Chronic kidney disease
- Chronic liver disease
- Cancer
- Immunodeficiencies
- Autoimmune disorders
- Human immunodeficiency virus and other immunosuppressing conditions
- Charlson Comorbidity index (may be included as the composite scale, or the scale components may be included as individual terms)

Comedication use may be assessed through pharmacy dispensing or physician prescribing records, as available in each data source. Considered comedications may be indicative of comorbidities placing patients at higher risk or markers of health care–seeking behaviour and utilisation and may serve as markers of patients' history of other infections or be risk factors for severe COVID-19 disease themselves. The capture of over-the-counter medications potentially indicative of short-term disease status (e.g., painkillers, cough medicines, and fever reducers) are not likely to not be captured reliably. The following comedications, and others as deemed relevant by the study investigators, may be assessed during the year before time zero.

- Analgesics
- Antibiotics
- Antiviral medications
- Corticosteroids
- Non-steroidal anti-inflammatory drugs
- Psychotropics
- Statins
- Immunosuppressant medication use

Health care utilisation in the year before time zero will be evaluated as measures of health care–seeking behaviour, overall health status, and access to health care. Additionally, short-term health care utilisation in the 2 weeks before and including time zero will be recorded separately, as short-term markers of current health status may influence individuals' vaccination decisions. Considered variables may include the following, as available in each data source:

- Number of hospitalisations
- Number of emergency department visits
- Skilled nursing facility, nursing home, or extended care facility stay
- Primary care utilisation
- Influenza vaccination
- Pneumococcal vaccination
- Cancer screening
- Other preventive health services, as appropriate
- COVID-19 tests

Frailty has been demonstrated as a confounder of vaccine-outcome associations in older adults [5,6,9]. Additional personal characteristics demonstrated to be associated with frailty [6,31,32] should be included as confounding factors, and may include the following:

- Wheelchair use
- Home hospital bed
- Paralysis
- Parkinson's disease
- Skin ulcer
- Weakness
- Stroke/brain injury
- Ambulance transport
- Dementia
- Difficulty walking
- Home oxygen
- Rehabilitation care
- Psychiatric illness
- Sepsis
- Heart failure
- Podiatric care
- Bladder continence
- Diabetes complications
- Arthritis
- Coagulation deficiencies
- Vertigo
- Lipid abnormalities

9.4 Data Sources

The data source(s) used for the implementation of the study should be described. Depending on the selected country(ies) or institutions, data sources may vary and may include general practice–based record systems, population vaccination registries, hospital system records, mortality and/or cause-of-death registries and other health registries, payer-based claims systems, and others. Data sources selected for the study must contain reliable information on vaccination receipt, hospitalisation, and mortality and should also contain rich information on potential confounders. The sources for the included variables should be described, as well as any available information about the validity of the recording or coding of data in these data sources. If linkage between data sources will be performed, the methods for data linkage should be described.

[Study investigators to complete based on study-specific circumstances]

Data source custodians and research partners <<will be/have been>> contacted to explore interest in and availability to participate in the study. A summary of potential populations and automated data sources in which the study can be implemented is shown in Table 1. Contacts with data source custodians/research partners to explore interest in conducting and availability to participate in this study <<have/have not>> been initiated.

[Study investigators may complete the following table for the data sources participating in the study at the completion of the final study protocol].

Table 1. Main Features of Selected European Data Sources

Feature	<<Country, Data source>> (N = <<country population>>)	<<Country, Data source>> (N = << country population>>)	<<Country, Data source>> (N = << country population>>)
Database type			
Database population			
Proportion of the country's population covered by the data source			
Potential <<COVID-19 vaccine product>> users in <<study period>>			
Year 20XX			
Year 20XX			
Representativeness of patients			
Data on administered vaccines			
Vaccine brand available			
Vaccination date available			
Drug dictionary codes/ therapeutic classification			
Outpatient diagnosis			
Hospital diagnosis			
Mortality and cause of death			
Disease and procedure codes			
Comedication use			
Lifestyle risk factors			
Years of data availability			
Approximate time lag (updates) and frequency of updates			
Approval process for database research			

COVID-19 = illness caused by the SARS-CoV-2 (severe acute respiratory syndrome coronavirus 2) virus.

Note: The information in this table is provided as background on the data sources being investigated for this study. Data source custodians and research partners will be contacted to explore interest in and availability to participate in the study.

9.5 Study Size

Study size in observational research is usually driven by the available data. All patients meeting the eligibility criteria in the participating data source(s) will be included in the study. The researchers can use the expected sample size together with the expected distribution of the exposure and the outcome risk in the control group to estimate the precision of the effect measure estimates under different assumptions of the strength of the effect [33]. Other approaches can also be used, e.g., by solving for the minimum detectable vaccine effect under specific assumptions of power, two-sided alpha, sample size, risk of the outcome in the unexposed and ratio of vaccine unexposed to exposed.

For example, Table 2 displays the probabilities that the upper limit of the 95% CI of the risk ratio (RR) being below 1.00 (a correlate of the lower bound of the vaccine effectiveness estimate being above 0.00 [Section 9.7.3.1] demonstrating a protective effect of vaccination) under varying assumptions of levels of vaccination, risk of the COVID-19 outcomes, and anticipated sample sizes [33].

Table 2. Example Study Size Precision Estimates

Expected Vaccine Effectiveness[a]	Expected Ratio of Vaccine Unexposed to Exposed	Expected Sample Size (Exposed + Unexposed)	Expected Risk of the Outcome in the Unexposed[b]	Probability of the Upper Limit of the 95% CI to Be Below 1.00
50% (IRR = 0.50)	1:1	40,000	0.001	0.43
50% (IRR = 0.50)	1:1	100,000	0.001	0.80
80% (IRR = 0.20)	1:1	40,000	0.001	0.84
80% (IRR = 0.20)	1:1	40,000	0.0005	0.55
80% (IRR = 0.20)	1:1	50,000	0.001	0.91
80% (IRR = 0.20)	1:1	73,000	0.0005	0.80
80% (IRR = 0.20)	2:1	40,000	0.001	0.71
80% (IRR = 0.20)	2:1	50,000	0.001	0.80

CI = confidence interval; IRR = incidence rate ratio.

Source: Rothman, K. Episheet: spreadsheets for the analysis of epidemiologic data. 2015. Available at: http://www.krothman.org/episheet.xls. Accessed 22 October 2020.

[a] Vaccine effectiveness measured as 1 minus the IRR, where the IRR compared the risk of the outcome in vaccine-exposed versus that in unexposed individuals (i.e., an IRR below 1 indicates a protective effect of the vaccine, corresponding to positive vaccine effectiveness).

[b] Rate expressed as cases per person in population without scaling.

[To be completed by the study investigators based on assumptions of outcome incidence, vaccine coverage, and size of the effect measure estimate at the time of full protocol development. Calculations may be made using the "Study Size" calculator within Episheet (http://www.krothman.org/episheet.xls).]

9.6 Data Management

The necessary data to implement this study from each included data source will be extracted locally and transformed into the VAC4EU (Vaccine monitoring Collaboration for Europe) common data model [34]. All individual-level data will be held at the local research sites. Common analytic programs, which can be run on the commonly structured analytic data from each site to create an analytic data set and run the necessary analysis locally, will be developed. Aggregate study results will be transferred to the coordinating centre or primary study investigator for potential pooling and reporting [35].

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

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

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

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

9.7 Data Analysis

9.7.1 Descriptive Characteristics

The distributions of baseline characteristics by exposure group will be calculated to describe the study cohort and illustrate differences between the groups. For continuous variables, means, standard deviations, medians, and interquartile ranges will be estimated. For categorical variables, counts and proportions will be estimated. The missingness of variables will also be described.

To describe the relative imbalance of characteristics between exposure groups, absolute standardised differences will be calculated for each baseline characteristic [36,37]. Multilevel categorical variables will calculate one, overall standardised difference across all levels [37]. The larger the absolute standardised difference values, the greater the imbalance between baseline characteristics.

If a matching or weighting method is employed to account for measured confounding (Section 9.7.3.2), an additional table of characteristics in the matched/weighted sample with accompanying absolute standardised differences can be calculated to observe the improvement in the covariate balance after matching/weighting.

9.7.2 Incidence Analysis

The crude incidence rates of the COVID-19 outcomes will be estimated in the <<COVID-19 vaccine product>> and unexposed groups; if different vaccination strategy groups are used (e.g., fully completed on time, partially completed, delayed completion; see Section 9.3.1 and Annex 3), each vaccination strategy can be considered a separate exposure group. Crude incidence rates will be estimated using the number of outcome events as the numerator and the number of person-years of follow-up as the denominator; 95% CIs can be derived using exact or approximated/modelled approaches, as appropriate based on the sample size.

Additionally, cumulative incidence for outcomes will be estimated to visualise the occurrence of COVID-19 outcomes over time since time zero [38].

9.7.3 Comparative Analysis

9.7.3.1 Estimation of Vaccine Effectiveness

Unadjusted estimates of vaccine effectiveness will be estimated using the group-specific incidence rates described in Section 9.7.2. Vaccine effectiveness is a measure of the reduction in cases of the outcome that is attributable to vaccination and is calculated as follows:

$$VE = \frac{I_u - I_v}{I_u}$$

Where VE is vaccine effectiveness, I_u is the incidence rate (attack rate) in the unexposed group, and I_v is incidence rate (attack rate) in the <<COVID-19 vaccine product>> group [39]. However, incidence rates make the potentially strong assumption of a constant event rate over the period of outcome assessment. In settings such as changing COVID-19 incidence during a rapidly evolving pandemic or if vaccine effectiveness wanes over time since vaccination, this assumption may be violated, prompting the need to consider flexible methods for estimating vaccine effectiveness over time.

Vaccine effectiveness can also be calculated as 1 minus the incidence rate ratio (IRR) of the <<COVID-19 vaccine product>> group (or vaccination status group) to the unexposed group [39]. The following time-flexible methods may be considered to estimate or approximate the IRR or RR in order to calculate vaccine effectiveness:

- Cox proportional hazards regression, yielding a hazard ratio (HR), accounting for censoring, changing incidence over time, and competing risks (Section 9.7.3.4). The assumption of proportionality of the survival curves in the <<COVID-19

vaccine product>> and unexposed groups should be evaluated. Vaccine effectiveness could be calculated as 1 minus HR. Similar to the IRR approach, this method calculates a single vaccine effectiveness measure for the duration of follow-up.

- Cumulative incidence estimation (estimated using as 1 minus the Kaplan-Meier survival estimate or with parametric survival curves [38]), which yields risks at each time point of follow-up. Risks of the outcome could be compared at any time point (e.g., 3, 6, 9, and 12 months) to yield the time point–specific risk differences (RDs) or RR. Thus, the calculation of vaccine effectiveness could be done at any time point of interest over follow-up using the time period–specific RR at that time point; the 95% CI can be estimated via bootstrapping.

Crude, unadjusted vaccine effectiveness effect measure estimates will be estimated for all included outcomes.

9.7.3.2 Adjustment for Potential Baseline Confounding

Several techniques to adjust for the potential confounding by measured baseline covariates can be used, such as multivariable adjustment and propensity score matching or weighting. These are widely used in comparative effectiveness research and will not be reviewed here. The authors can choose any and should justify the choice. Note that different methods may be answering different research questions (e.g., the treatment effect in the treated or the average treatment effect in the population) and can yield different results if the effect of the vaccine is not uniform [40]. Further details on the statistical methods should be included in a statistical analysis plan.

Adjusted HRs or RRs will be calculated using the approach(es) described in Section 9.7.3.1 with the selected adjustment method applied. The adjusted vaccine effectiveness will be estimated as 1 minus the adjusted HR or time period–specific RR.

Adjusted time-specific RDs (e.g., RD at 3, 6, 9, 12 months after time zero) will also be calculated [38]

9.7.3.3 Adjustment for Potential Time-Varying Confounding

If study patients do not deviate from the <<COVID-19 vaccine product>> vaccination strategy and there are no losses to follow-up (i.e., the outcome can be ascertained in every participant), the researchers do not need to account for time-varying confounding.

If study patients deviate from their assigned vaccination exposure group (Section 9.3.1), and the researchers want to estimate the effect of full adherence to the vaccination strategy, appropriate methods should be used [22]. The following are examples of deviation from the vaccination strategies assigned at time zero:

- After time zero, patients in the unexposed group receive the <<COVID-19 vaccine product>>.

- After time zero, patients in the exposed group receive an unrecommended additional dose of <<COVID-19 vaccine product>> or another COVID-19 product that is not the one under study.
- The vaccine is multidose, and, in the absence of toxicity, patients in the exposed group fail to complete the whole vaccination course.

Different vaccination strategies and different causal contrasts can have different definitions of non-compliance.

Estimating the effect of the different vaccination strategies under full compliance requires the use of a specific set of methods (g-methods) [22]. For example, researchers can censor study patients when they deviate from the vaccination strategy under study. Because such censoring can be informative, researchers should consider measuring time-varying confounders and using inverse probability weighting to adjust for it [41]. The authors should justify their choice of methods.

Regardless of the causal contrast, if there are losses to follow-up, this can introduce bias if such losses can be affected by the <<COVID-19 vaccine product>> and by unmeasured factors also affecting the outcome [16]. The investigators should consider the possibility that such informative censoring will be present in the study and propose appropriate methods for adjustment [41].

9.7.3.4 Competing Risk Analysis

Events (e.g., death due to causes other than COVID-19) that may make it impossible for the event of interest to occur (e.g., hospitalisations for COVID-19) act as competing events in the analysis of certain outcomes. The relevance of competing events increases when the study population is old or sick (a plausible target population of the COVID-19 vaccine) or when the follow-up is long. The use of specific methodology to handle competing events can help in the accurate interpretation of the study results.

Different estimands of the risk of the event of interest can be used:

- The risk under elimination of competing events [42], which has been termed "marginal cumulative incidence" or "net risk" in the statistical literature [43]
- The risk without elimination of competing events [42], which has been termed "subdistribution function, cause-specific cumulative incidence" or "crude risk" in the statistical literature [43].

The authors should weigh the relevance of competing events for the study and plan the analysis accordingly. These analytic choices may also be informed by earlier selection of methods to measure the IRR and either HR or time-specific RR.

9.7.4 Subgroup, Sensitivity, and Exploratory Analyses

9.7.4.1 Conducting Subgroup Analyses

If possible, the primary analyses should be stratified by clinically meaningful subgroups, which may include the following:

- Age group (particularly among older ages at higher risk for COVID-19–related complications)
- Comorbidities
- Geographic region (if large variation in COVID-19 incidence or seroprevalence exist across study centres)

[The study investigators may modify or add additional subgroups motivated by the current understanding of COVID-19 at the time of full protocol development.]

9.7.4.2 Varying Outcome Definitions

As the validity of COVID-19 diagnosis coding is currently unknown, additional variations of the outcome definitions may be considered to evaluate the effect of case definitions that are looser (e.g., including those with signs and/or symptoms of COVID-19 but without COVID-19 diagnoses or identifying outcomes based on treatments such as remdesivir or ventilator use) or stricter (e.g., requiring multiple diagnoses or requiring a diagnosis plus a laboratory test).

9.7.4.3 Restricting to Receivers of Influenza Vaccines

A sensitivity analysis, restricted to only patients who received an influenza vaccine during the year before the time zero, is proposed. By restricting on recent vaccination receipt, this sensitivity analysis seeks to reduce unmeasured confounding by health care access, adherence to recommendations, and preventive health care behaviours [9,25].

9.7.4.4 Delaying the Beginning of the Study Period

If there is concern of channelling of atypical patients to receive <<COVID-19 vaccine product>> in the period immediately following its approval [44], the study period may be delayed by some period of time after vaccine introduction in the study populations (e.g., 6 months), excluding the initial recipients and including a time period after the vaccine is used more widely among the general population.

9.7.4.5 Considering All COVID-19 Vaccines or Similar Vaccines Together

This protocol template describes a study considering only a single COVID-19 vaccine product of interest. If multiple COVID-19 vaccine products are available and used in the data source(s) during the study period, they may be combined into one exposure group if that would address a relevant scientific or regulatory question (e.g., if the vaccines share the same platform).

9.7.4.6 Correcting for Differential Outcome Misclassification

If a formal adjudication of the COVID-19 outcome(s) has been performed as part of the study or if results of a validation study are available, quantitative bias analyses can be performed to evaluate the potential impact of differential misclassification of the outcome on the observed study estimate. Validation studies yield bias parameters of sensitivity, specificity, positive predictive value, and/or negative predictive value, which can be used to correct the observed exposure-outcome association to more accurately reflect the true association [45,46]. If formal adjudications of the outcomes have not been performed, a range of potential differential misclassification scenarios may be considered. Thus, quantitative bias analysis of potential outcome misclassification is highly encouraged to examine the sensitivity of results to differential outcome classification.

9.7.5 Pooling Across Data Sources

If the study is to be performed in multiple data sources, the appropriateness of pooling the final data source–specific effect measure estimates should be evaluated with statistical measures of heterogeneity and qualitative assessments of the differences in the contributing data sources. The pooling approach may vary depending on the governance and privacy regulations of the participating study sites. If numbers of cases and person-years per exposure group can be shared across sites, pooled unadjusted incidence rates and IRRs can be estimated from the overall count and person-years, accounting for confounding in each data source [47]. Two-step pooling may be considered if some data sources can share individual-level data while others cannot [48]. If individual-level data cannot be shared across data sources, the data source–specific aggregated unadjusted and adjusted HR or time period–specific RR estimates can be meta-analysed to generate an overall HR or RR that can be used to estimate an overall vaccine effectiveness as 1 minus the pooled HR or pooled time period–specific RR.

A pooling analysis plan should be developed based on the selected data sources and study methodology, considering the data structure and coding systems employed in the participating centres, and formal tests of statistical heterogeneity should be considered.

9.7.6 Missing Data

The researchers should specify the expected amount of missing data and propose an analytic approach accordingly. Ideally, as part of the study feasibility stage, the researchers should estimate the amount of missing data and state which assumption for the pattern of missingness (missing completely at random, missing at random, not missing at random) is most appropriate. The authors should propose and justify a methodological approach (e.g., complete-subject analysis, multiple imputation, inverse probability weighting) to handle the occurrence of missing data [49].

As discussed in Section 9.1.1.3, vaccine brand information may not be recorded in all data sources, or it may be missing in some cases. If multiple COVID-19 vaccines are

available simultaneously, then differentiating between COVID-19 vaccine products is essential for a study of a specific COVID-19 vaccine product. The degree of missing data on brand information should be evaluated as part of the feasibility assessment to determine if a given data source may contribute to the study.

9.8 Quality Control

The conduct of this study should be guided by the ADVANCE Code of Conduct for collaborative vaccine studies [50], and individual research centres will adhere to their standard operating procedures or internal process guidance. These procedures may include internal quality audits, rules for secure and confidential data storage, methods to maintain and archive project documents, quality-control procedures for programming, standards for writing analysis plans, and requirements for senior scientific review.

[Describe study-specific process for programming quality control, including double independent programming, oversight, etc. at each study centre.]

[Describe processes for review and quality control of study documentation and reporting across research centres.]

[Describe procedures for data storage, archiving, and backup at each study centre.]

[To be completed or modified by study investigators, as appropriate for the participating research centres.]

9.9 Limitations of the Research Methods

This protocol template provides a guide for researchers to implement a real-world study of the effectiveness of future COVID-19 vaccines during routine use in Europe. Although it addresses many design considerations to avoid common biases of vaccine effectiveness research, future studies of COVID-19 vaccines may be subject to many of the limitations common to non-randomised studies based in existing health care data.

As discussed previously, confounding of the relationship between vaccine receipt and COVID-19 outcomes may be very likely, and spurious relationships between vaccine receipt and implausible outcomes have been noted in other studies comparing vaccine recipients to non-recipients. The use of eligibility criteria to define comparable exposure groups, active comparators (where available), covariates based on updated subject-matter knowledge, and negative control outcomes may allow investigators to adequately address confounding through the design and analysis.

The validity of coding for future COVID-19 vaccines—including the ability to distinguish between separate products (if available)—or COVID-19 outcomes is unknown at this time, and the likelihood of missing data on specific vaccine brand (important if multiple COVID-19 vaccine products are used in an area) is high. Misclassification of vaccine exposure, outcome status, or covariates is possible in existing health care data not

collected for research purposes. Information about COVID-19 infection and immunity, such as the presence of naturally acquired infection and the results of COVID-19 infection or antibody tests, may not be captured reliably in databases. Additionally, COVID-19 testing is not systematic in most populations, and laboratory confirmation of case status may not be available for many patients. Researchers should evaluate data validity prior to conducting a study.

If multiple data sources are included in the analysis, there may be variation in the capture and recording of various clinical elements. Additionally, if different types of data sources are used (e.g., records from general practice and population registers) or if different coding systems are used, then variables defined in different data sources may not exactly represent the same concept across data sources. Thus, heterogeneity of vaccine effectiveness estimates across data sources may be due to the underlying heterogeneity of confounding control, misclassification, or other data source factors rather than true differences in vaccine effectiveness.

Patterns of routine health care delivery and utilisation may be disrupted in many countries during the COVID-19 pandemic as patients and providers forgo or delay routine preventive, elective, or non-emergency care. These disruptions in health care may result in under-ascertainment of important patient comorbidities in existing health care databases during periods of disruption.

In order to conduct a valid study and address potential confounding, the eligibility criteria of the study may be restricted relative to the approved indications of the vaccines. Therefore, the results of this study may not be generalisable to the general population.

With the introduction of a new vaccine, there is the potential for rapidly changing herd immunity in the population. This study is not designed to assess overall and indirect effects of vaccination with <<COVID-19 vaccine product>>.

Comparative analyses may not be possible in every setting if confounding is deemed to be insurmountable. However, descriptive information about vaccine recipients and crude incidence rates may still be informative and meaningful, even without calculation of vaccine effectiveness measures.

[Additional limitations specific to the study setting to be completed or modified by the study investigators.]

9.10 Other Aspects

[To be completed by study investigators, if needed. For example, scientific advisory board, endpoint adjudication committee.]

10 Protection of Human Subjects

This is a non-interventional study using secondary data collection and does not pose any risks for patients. Each data source research partner will apply for an independent ethics committee review according to local regulations.

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

[To be completed or modified by study investigators, as needed.]

11 Management and Reporting of Adverse Events/Adverse Reactions

For studies in which the research team uses only data from automated health care databases, according to the International Society for Pharmacoepidemiology (ISPE) [51] *Guidelines for Good Pharmacoepidemiology Practices (GPP*),

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

For non-interventional study designs that are based on secondary use of data, such as studies based on medical chart reviews or electronic health care records, systematic reviews or meta-analyses, reporting of adverse events/adverse drug reactions is not required. Reports of adverse events/adverse drug reactions should only be summarised in the study report, where applicable [52].

According to the European Medicines Agency (EMA) *Guideline on Good Pharmacovigilance Practices (GVP), Module VI – Management and Reporting of Adverse Reactions to Medicinal Products* [52],

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

Module VIII – Post-Authorisation Safety Studies, echoes this approach [1]. European Union 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 Good Pharmacoepidemiology Practices (GPP)*, ISPE contends that "there is an ethical obligation to disseminate findings of potential scientific or public health importance" [51]; 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."

Study results will be published following guidelines, including those for authorship, established by the International Committee of Medical Journal Editors [53]. When reporting results of this study, the appropriate Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) checklist will be followed [54].

Communication via appropriate scientific venues will be considered.

[To be completed or modified by study investigators, as needed.]

13 Other Good Research Practice

This study will adhere to the *Guidelines for Good Pharmacoepidemiology Practices (GPP)* [51] and has been designed in line with the European Network of Centres for Pharmacoepidemiology and Pharmacovigilance (ENCePP) *Guide on Methodological Standards in Pharmacoepidemiology* [55]. The *ENCePP Checklist for Study Protocols* [56] will be completed (see Annex 2).

The study is a postauthorisation study of vaccine effectiveness and will comply with the definition of the non-interventional (observational) study referred to in the International Conference on Harmonisation tripartite guideline *Pharmacovigilance Planning E2E* [57] and provided in the EMA *Guideline on Good Pharmacovigilance Practices (GVP) Module VIII: Post-Authorisation Safety Studies* [1], and with the 2012 European Union pharmacovigilance legislation, adopted 19 June 2012 [58]. The study will comply with the study reporting requirements specified in Module VIII section VIII.B.6.3.1. "Progress reports" and VIII.B.6.3.2. "Final study report" of the *Guideline of Good Pharmacovigilance Practices* [1].

The study will be registered in the EU PAS Register[1] [59] before study implementation commences.

[1] EU PAS Register = European Union electronic register of post-authorisation studies.

The research team and study sponsor should adhere to the general principles of transparency and independence in the ENCePP Code of Conduct [60] and the ADVANCE Code of Conduct [50].

[If desired by the study investigators, the following may be included.] The research team will apply for the ENCePP Study Seal [61].

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

14 References

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Annex 1.
List of Stand-Alone Documents

None.

Annex 2. ENCePP Checklist for Study Protocols

[The study investigators should include a completed copy of the most current revision of the ENCePP Checklist for Study Protocols at the time of protocol finalisation, available here: http://www.encepp.eu/standards_and_guidances/checkListProtocols.shtml]

Annex 3. Defining Vaccination Strategies at Time Zero

In the event that <<COVID-19 vaccine product>> is approved and recommended as a multidose vaccination series, it may be of interest to define vaccination exposure status or time at risk based on a patient's adherence to the recommended number of doses and timing of doses. In actual clinical and public health practice, there is likely to be large variation in adherence to these recommended schedules (e.g., due to missed or delayed second doses), resulting in multiple observed vaccination strategies (e.g., fully completed on-time vaccine series, partially completed vaccine series, delayed completion of vaccine series). If it of interest to the investigators, multiple potential comparisons are possible, including comparisons of each of the vaccination strategies with being unvaccinated, or comparisons of the vaccination strategies with each other.

Comparisons based on vaccination strategies require appropriately assigning patients' person-time to the strategies with which their vaccination behaviour is compatible without using future information; a patient may concurrently contribute to multiple strategies. A patient's adherence to the vaccine series is not known at the receipt of the first dose, and it would be inappropriate to use future information available in the data to assign patients to an exposure state based on adherence (e.g., fully completed on-time vaccine series, partially completed vaccine series, delayed vaccine series) at time zero without introducing immortal person-time bias.

At the time a patient is identified for the unvaccinated comparator group, the patient's exposure status is known, as the patient did not receive <<COVID-19 vaccine product>>, and the patient is assigned to the "no vaccine" comparator group at the defined time zero.

However, for exposed patients identified at the patient's first dose of <<COVID-19 vaccine product>> (time zero), the patient's behaviour is consistent with multiple different vaccination strategies (as fully completed on-time, partially completed, and delayed completion vaccination strategies all originate with receipt of the first dose). Thus, the patient may be assigned to and contribute person-time to all the vaccination strategy groups starting at time zero [14,62,63]. For example, if the treatment comparison of interest was "fully completed on-time vaccine series" vs. "no vaccine," it would be inappropriate to exclude patients who received only one dose of the series because excluding these patients at time zero would use future information to inform a baseline exclusion and would introduce immortal person-time bias. These patients may contribute person-time to the "fully completed on-time vaccine series" from time zero until their behaviour is no longer compatible with the definition of the vaccination strategy (e.g., they fail to receive the second dose on time).

Once patients deviate from their assigned vaccination strategies, their follow-up should be censored from that vaccination strategy group (Figure 3-1) with appropriate

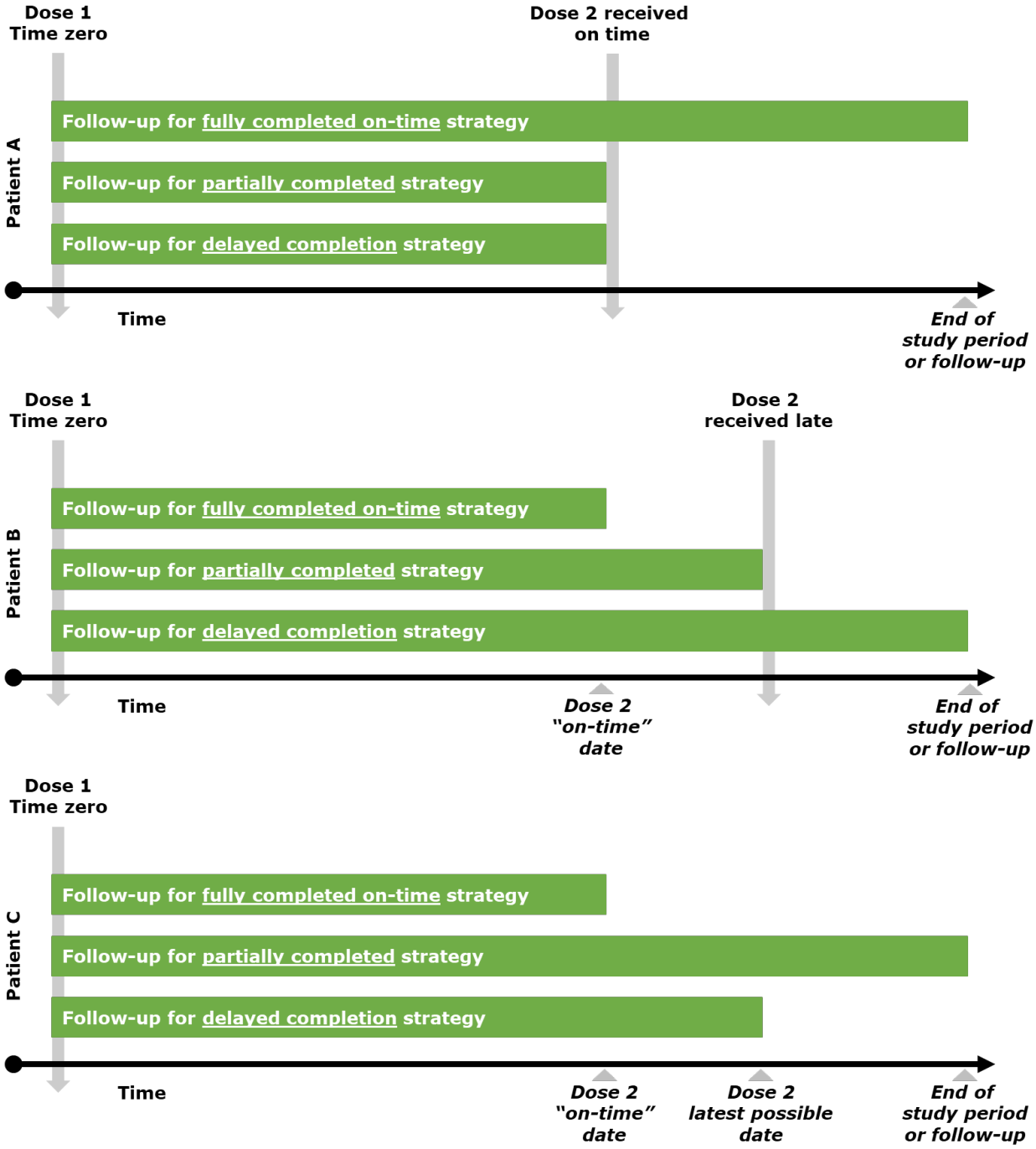
accounting for the censoring (Section 9.7.3.3) using inverse probability weighting [64]. Examples of deviations from assigned vaccination strategy include the following:

- A patient in the fully completed on-time vaccination strategy group failed to receive the second dose of the vaccine in the recommended time period
- A patient in the partially completed vaccination strategy group received the second (final) dose of the series
- A patient in the delayed completion vaccination strategy group received the second dose on time
- A patient in the "no vaccine" group received a dose of the vaccine

Using this approach, each patient contributes person-time to each vaccination strategy group with which his or her behaviour is compatible without utilising future information to make the exposure assignment, and follow-up for each vaccination strategy group begins at time zero.

Additional analytical considerations for multidose series are discussed in Section 9.7.3.3).

Figure 3-1. Assignment of Person-time From Three Hypothetical Patients to Vaccination Strategy Groups for a Two-Dose Vaccine When Initial Vaccination Receipt is Consistent With Multiple Potential Vaccination Strategies



Note: Follow-up for each vaccination strategy group begins at time zero. Each patient contributes person-time to each of the vaccination strategies with which his or her behaviour is compatible, regardless of future vaccination behaviour. When the patient's behaviour is no longer compatible with the assigned vaccination strategy, the patient's person-time is censored from that group.

[Other annexes may be added as needed; this template uses Word's captioning feature to number annexes.]