PASS INFORMATION

Title	VAC4EU Postauthorisation Safety Study of BIMERVAX® Vaccine in Europe
Protocol version identifier	Final Protocol Version 1.1
Date	12 January 2024
EU PAS Register number	Study will be registered before start of data collection
Active substance	SARS-CoV-2 virus recombinant spike (S) protein receptor binding domain (RBD) fusion heterodimer – B.1.351 – B.1.1.7 strains (Anatomical Therapeutic Chemical (ATC) Code J07BN)
Medicinal product	BIMERVAX® emulsion for injection COVID-19 vaccine, recombinant, adjuvanted
Product reference	EU number: EU/1/22/1709
Procedure number	EMA number: EMEA/H/C/006058/0000
Marketing authorisation holder (MAH)	HIPRA Human Health, S.L.U. Avda. la Selva, 135, 17170 Amer (Girona) Spain
Joint PASS	No
Research question and objectives	The research question is: Is there a difference in the risk of selected adverse events of special interest (AESIs) after vaccination with BIMERVAX® as a booster compared with vaccination with other vaccines for the same indication? The primary study objectives are as follows: • To characterise recipients of BIMERVAX® in relation to demographics and clinical characteristics at the time of vaccination, including the following: pregnancy status, age of childbearing potential, immunocompromised status, comorbidities, presence of autoimmune and inflammatory disorders, and interaction with other vaccines (influenza). • To estimate the risk ratio and risk difference of prespecified AESIs comparing recipients of BIMERVAX® with recipients of other coronavirus disease 2019 (COVID-19) vaccines authorised for the booster indication, using a cohort design. • To estimate the incidence rate ratio of selected AESIs comparing a prespecified risk period following BIMERVAX® vaccination with a later post-risk interval, using a self-controlled risk interval design.

	The secondary objectives (study size allowing) are: • To estimate the risk ratio and risk difference of prespecified AESIs comparing recipients of BIMERVAX® with recipients of other COVID-19 vaccines authorised for the booster indication, using a cohort design in subgroups defined by the following baseline variables: pregnancy status, immunocompromised status, frailty due to comorbidities, presence of autoimmune or inflammatory disorders, prior use of influenza vaccine and calendar time. • To estimate the incidence rate ratio of selected AESIs comparing a prespecified risk period following BIMERVAX® vaccination with a later post-risk interval, using a self-controlled risk interval (SCRI) design in subgroups defined by the following baseline variables: immunocompromised status, frailty due to comorbidities, presence of autoimmune or inflammatory disorders, prior use of influenza vaccine and calendar time.
Country(-ies) of study	List of countries pending confirmation. Currently planned countries are Spain (ES), France (FR), and Great Britain in the United Kingdom (UK). Other European countries are under evaluation.
Authors	[redacted]

Marketing Authorisation Holder

Marketing authorisation holder	HIPRA Human Health, S.L.U. Avda. la Selva 135, 17170 Amer (Girona), Spain
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Approval Page: RTI Health Solutions on behalf of the research team

Project Title: VAC4EU Postauthorisation Safety Study of BIMERVAX® Vaccine in Europe

Protocol ID Number: HIPRA-HH-12

Effective Date:

Authors [redacted]

Version and Date: 1.1, 12 January 2024

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Date

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Approval Page: HIPRA Human Health S.L.U.

Project Title: VAC4EU Postauthorisation Safety Study of BIMERVAX® Vaccine in Europe

Protocol ID Number: HIPRA-HH-12

Effective Date:

Authors [redacted]

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2. LIST OF ABBREVIATIONS

Abbreviation	Definition
ACCESS	vACCine covid-19 monitoring readinESS
AESI	adverse event of special interest
BMI	body mass index
BPE	Bordeaux PharmacoEpi
CDM	common data model
CESREES	Comité éthique et scientifique pour les recherches, les études et les évaluations dans le domaine de la santé (France)
CI	confidence interval
CNAM	Caisse Nationale de l'Assurance Maladie (France)
CNIL	Commission Nationale de l'Informatique et des Libertés (France)
CONSORT	Consolidated Standards of Reporting Trials
COVID-19	coronavirus disease 2019
CPRD	Clinical Practice Research Datalink
DPT	diphtheria, tetanus, pertussis
DRE	digital research environment
DVT	deep vein thrombosis
EHR	Electronic health records
EMA	European Medicines Agency
ENCePP	European Network of Centres for Pharmacoepidemiology and Pharmacovigilance
ES	Spain
ETL	extraction, transformation, and loading
EU	European Union
EU PAS Register	European Union Electronic Register of Post-Authorisation Studies
FDA	Food and Drug Administration
FISABIO	Foundation for the Promotion of Health and Biomedical Research of Valencia Region
FR	France
GDPR	General Data Protection Regulation
GPP	Good Pharmacoepidemiology Practices
GVP	Guidelines on Good Pharmacovigilance Practices
ICD-10	*International Statistical Classification of Diseases, Tenth Revision*
ICD-9	*International Classification of Diseases, Ninth Revision*
IRB	institutional review board
ISPE	International Society for Pharmacoepidemiology
MAH	marketing authorisation holder
MBDS	Minimum Basic Data Set at Hospital Discharge [VID]
MMR	measles-mumps-rubella vaccine
mRNA	messenger RNA
NA	not applicable

Abbreviation	Definition
OQ	Office of Quality
PASS	postauthorisation safety study
PRAC	Pharmacovigilance Risk Assessment Committee
Q*n yyyy*	quarter of the calendar year
QC	quality control
RMP	risk management plan
RTI	RTI International
RTI-HS	RTI Health Solutions
RT-PCR	reverse transcription polymerase chain reaction
SAP	statistical analysis plan
SARS-CoV-2	severe acute respiratory syndrome coronavirus 2
SCRI	self-controlled risk interval
SES	socioeconomic status
SI-DEP	National Population Screening Information System
SIDIAP	Information System for Research in Primary Care (Sistema d'Informació per al Desenvolupament de la Investigació en Atenció Primària) Spain
SNDS	French Administrative Healthcare Database (Système National des Données de Santé)
SNOMED-CT	Systemized Nomenclature of Medicine-Clinical Terms
SOP	standard operating procedure
STROBE	Strengthening the Reporting of Observational Studies in Epidemiology
UK	United Kingdom
UMCU	University Medical Center Utrecht
VAC4EU	Vaccine Monitoring Collaboration for Europe (study network)
VID	Valencia Health System Integrated Database (Spain)
VIS	Vaccine Information System

3. RESPONSIBLE PARTIES

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4. ABSTRACT

Title: VAC4EU Postauthorisation Safety Study of BIMERVAX® Vaccine in Europe

Rationale and background: The coronavirus disease 2019 (COVID-19) HIPRA vaccine BIMERVAX® is a recombinant protein-based bivalent variant vaccine intended for use as a booster in individuals 16 years of age and older who have previously received a messenger RNA (mRNA) COVID-19 vaccine. In March 2023, the European Commission granted marketing authorisation of BIMERVAX® vaccine for use in the European Union [1]. Efficient and timely monitoring of the safety of the vaccine and its subsequent adaptations is needed in European countries; hence, a postauthorisation safety study (PASS) is a postauthorisation measure to the European Medicines Agency (EMA).

Research question and objectives:

Research question: Is there a difference in the risk of selected adverse events of special interest (AESIs) after vaccination with BIMERVAX® as a booster compared with vaccination by other vaccines for the same indication?

Primary objectives:

- To characterise recipients of BIMERVAX® in relation to demographics and clinical characteristics at the time of vaccination, including the following: pregnancy status, age of childbearing potential, immunocompromised status, comorbidities, presence of autoimmune and inflammatory disorders, and interaction with other vaccines (influenza).
- To estimate the risk ratio and risk difference of prespecified AESIs comparing recipients of BIMERVAX® with recipients of other COVID-19 vaccines authorised for the booster indication, using a cohort design.
- To estimate the incidence rate ratio of selected AESIs comparing a prespecified risk period following BIMERVAX® vaccination with a later post-risk interval, using a self-controlled risk interval (SCRI) design.

Secondary objectives (study size allowing):
- To estimate the risk ratio and risk difference of prespecified AESIs comparing recipients of BIMERVAX® with recipients of other COVID-19 vaccines authorised for the booster indication, using a cohort design in subgroups defined by the following baseline variables: pregnancy status, immunocompromised status, frailty due to comorbidities, presence of autoimmune or inflammatory disorders, prior use of influenza vaccine and calendar time.
- To estimate the incidence rate ratio of selected AESIs comparing a prespecified risk period following BIMERVAX® vaccination with a later post-risk interval, using an SCRI design in subgroups defined by the following baseline variables: immunocompromised status, frailty due to comorbidities, presence of autoimmune or inflammatory disorders, prior use of influenza vaccine and calendar time.

Study design:

The study will comprise:

- A vaccine utilisation study component, which will use a descriptive study design to characterise individuals at the time of vaccination
- A component on comparative safety studies, including:
  - A cohort design to estimate the incidence of AESIs after receiving a BIMERVAX® vaccine booster dose compared with the incidence in a comparator group vaccinated by other COVID-19 boosters.
  - A self-controlled risk interval design to evaluate the risk of AESIs in a time interval following the receipt of a BIMERVAX® booster vaccine (the risk interval) compared with the risk of the same AESI during a subsequent post-risk time interval (the control interval).

Population: The eligible population for the vaccine utilisation study will be all individuals actively enrolled in each of the selected European health data sources for at least 12 months before receiving a booster dose of the BIMERVAX® vaccine within the study period. For the comparative safety studies, the main eligibility criterion will be having received a COVID-19 vaccine in the past. The study period will be from the date of availability of BIMERVAX® vaccine in each participant country to 2 to 3 years past that date (4 years for pregnancy outcomes), pending the timing and potential seasonality of booster administration campaigns.

Variables:

- In the vaccine utilisation study, the following variables will be measured at the time of vaccination: demographics; pregnancy status and trimester of pregnancy, as feasible; immunocompromised status; comorbidities that may determine frailty; autoimmunity, and inflammatory conditions; prior COVID-19 vaccination (brand, doses); prior use of other vaccines (influenza); comedications; and COVID-19 history.
- In the comparative safety studies, exposures will be based on recorded prescription, dispensing, or administration of COVID-19 vaccines as booster during the study period. The outcomes will be based on the BIMERVAX® risk management plan that included AESIs proposed by the ACCESS project for a cohort and an SCRI study design. Key confounders will include demographics, COVID-19 history, vaccinations, personal lifestyle characteristics, comorbidities, comedications, immunocompromising conditions, and others. Subgroups will be defined by baseline variables, such as immunocompromised status, vaccinations, and others.

Data sources: The planned data sources for this study, pending confirmation of vaccine rollout, are EpiChron (Spain), Information System for Research in Primary Care (SIDIAP) (Spain), Valencia Health System Integrated Database (VID) (Spain), Clinical Practice Research Datalink (CPRD) (United Kingdom [UK]), and French Administrative Healthcare Database (SNDS) (France). Rollout in other European countries will be monitored to evaluate other potential data sources.

Study size: The study size for both the vaccine utilisation study and the comparative safety studies will be determined by the uptake of BIMERVAX® booster in the participating data sources during the study period.

Data analysis: The vaccine utilisation study will summarise the variables of interest at the time of vaccination using standard measures of central tendency and of dispersion for continuous variables as well as counts and percentages for categorical variables.

The comparative safety cohort study will use matching and inverse probability weighting to adjust for the measured baseline confounders. Outcomes will be treated as time-to-event variables and will be analysed accordingly. Effect estimates will be provided as risk ratios and as risk differences scales.

The SCRI study will compare the risk of each AESI during a prespecified period following the index date (the "risk interval" during which there is a hypothesised increased risk of the outcome) with that of a self-matched "control interval," used to assess the baseline risk of the outcome.

Milestones:

Key milestones are:

- Protocol submission: 14 August 2023
- Regulatory endorsement: estimated Q1 2024
- Progress report: 3 months after protocol endorsement, estimated Q2 2024
- Final study report: 36 months after administration of at least 4,000 BIMERVAX® doses

5. AMENDMENTS AND UPDATES

The following amendments have been made to the protocol:

Version number	Date	Protocol section changed	Summary of amendment/ update	Reason
1.1	12 Jan 2024	4. Abstract 8. Research Question and Objectives	Wording of primary study objectives edited	Requested by PRAC
1.1	12 Jan 2024	4. Abstract 8. Research Question and Objectives	Listed the subgroup analyses as secondary study objectives	Requested by PRAC
1.1	12 Jan 2024	4. Abstract 8. Research Question and Objectives 9.7.3.3 Subgroup Analysis	Removed pregnancy status from list of subgroup analyses in the SCRI study	Removed because one of the assumptions behind the SCRI design is likely untenable in a pregnancy subgroup
1.1	12 Jan 2024	4. Abstract 6. Milestones and Timeline 9.7 Data Analysis	Estimated dates of protocol regulatory endorsement, progress report, interim reports, end of data collection and final report, updated	Updated to align with current estimated timelines following the updated start of data collection date requested by PRAC

Version number	Date	Protocol section changed	Summary of amendment/ update	Reason
1.1	12 Jan 2024	6.Milestones and Timeline 9.7.2 Matched Cohort Design	Start of data collection milestone updated, to be dependent on vaccine rollout and administration of a minimum number of doses of the original and adapted vaccine	Requested by PRAC to ensure study generates informative evidence (at least more informative than the evidence generated in the clinical trials)
1.1	12 Jan 2024	9.1.2 Matched cohort design 9.1.3 Self-controlled risk interval design 9.2.2.2. Matched cohort design 9.2.2.3 Self-controlled risk interval design	Updated inclusion criteria to "Have received the last administration of a COVID-19 vaccine at least 6 months ago" instead of 3 months	Requested by PRAC to align with the EMA's BIMERVAX® administration recommendations
1.1	12 Jan 2024	9.1.3 Self-controlled risk interval design 9.7.3.5. Sensitivity analysis	Extended length of control interval in sensitivity analysis from 84 to 127 days	Requested by PRAC
1.1	12 Jan 2024	9.2.2.1 Vaccine utilisation study	Added justification for not excluding individuals aged < 16 years in the vaccine utilisation study	Requested by PRAC to clarify the rationale of describing potential off-label use of the vaccine
1.1	12 Jan 2024	9.3.2.1 Outcome identification, by data source	Added more detailed description on the outcome identification process	Requested by PRAC for clarification of the process by data source
1.1	12 Jan 2024	9.7.2.2 Descriptive statistics	Added descriptive statistics to describe the receipt of subsequent COVID-19 vaccines in the matched cohort design	Requested by PRAC, for completion

COVID-19 = coronavirus disease 2019; EMA = European Medicines Agency; PRAC = Pharmacovigilance Risk Assessment Committee; SCRI = self-controlled risk interval;

6. MILESTONES AND TIMELINE

The start of data collection (i.e., the date from which data extraction starts [2]) will occur once a total of 4,000 BIMERVAX® vaccinees is reached across the participating data sources. A total of 4,000 BIMERVAX® vaccinees is a threshold where observational data will start generating informative and complementary evidence to existing randomised clinical trials, which analysed a total of 3,480 individuals. Therefore, the start of the data collection and the consecutive milestones will be anchored to this threshold.

Milestone	Date
Protocol submission to EMA PRAC (v1.0)	14 August 2023
Protocol regulatory endorsement (v1.1)	Estimated Q1 2024
Registration in the EU PAS Register	After regulatory endorsement and prior to start of data collection
Start of data collection[a]	Estimated Q4 2024. Will be anchored on the administration of at least 4,000 doses of BIMERVAX®[b]
Study progress report	Estimated Q2 2024 (3 months after protocol endorsement)
Interim report 1	Estimated Q4 2025 (12 months after start of data collection)
Interim report 2	Estimated Q4 2026 (24 months after start of data collection)
Data extraction for the final report (before pregnancy outcomes update)	Estimated Q1 2027
Final report of study results (before pregnancy outcomes update)	Estimated Q4 2027 (36 months after start of data collection)
End of data collection[c]	Estimated Q1 2028
Final report of study results (with pregnancy outcomes update)	Estimated Q4 2028 (48 months after start of data collection)

EMA = European Medicines Agency; EU PAS Register = European Union Electronic Register of Post-Authorisation Studies; PRAC = Pharmacovigilance Risk Assessment Committee; Q*n* yyyy = quarter of the calendar year.

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

[a] Start of data collection is "the date from which information on the first study subject is first recorded in the study data set or, in the case of secondary use of data, the date from which data extraction starts" [2].

[b] Refers to doses from the adapted and original vaccines. First rollout of the adapted vaccine is expected by the end of Q1 2024. First use of the original vaccine in Spain occurred during 2023.

[c] End of data collection is "the date from which the analytical data set is completely available" [2].

7. RATIONALE AND BACKGROUND

The severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), the cause of coronavirus disease 2019 (COVID-19), has led to a global pandemic. BIMERVAX® is a recombinant protein-based bivalent variant vaccine developed by HIPRA and is intended for use as a booster for active immunisation against COVID-19.

In March 2023, the European Commission granted marketing authorisation of BIMERVAX® for use in the European Union (EU) as a booster vaccine in people aged 16 years and older who have previously been vaccinated with a messenger RNA (mRNA) COVID-19 vaccine [1].

The results of laboratory-based and clinical studies [3,4] showed that a BIMERVAX® booster dose triggered the production of higher levels of antibodies against the Beta and Omicron variants of SARS-CoV-2 and comparable levels against the Delta variant, when compared with a Comirnaty (Pfizer-BioNTech) booster dose. Therefore, BIMERVAX® is expected to be at least as effective as Comirnaty at restoring protection against COVID-19 [1]. The BIMERVAX® safety profile also was comparable to that of other COVID-19 vaccines. Based on these results, the Committee for Medicinal Products for Human Use concluded that sufficiently robust data on the quality and safety of the vaccine were available and recommended its marketing authorisation in the EU [1]. To gain a more complete understanding, safety monitoring of the BIMERVAX® booster vaccine is needed in European countries.

This protocol was prepared based on the EU risk management plan (RMP) Version 1.0 reviewed by European Medicines Agency (EMA)/Pharmacovigilance Risk Assessment Committee (PRAC). According to the EU RMP, the safety concerns that are of special concern for BIMERVAX® include pericarditis, myocarditis, and vaccine-associated enhanced disease, including vaccine-associated enhanced respiratory disease. Areas of missing information include the use of BIMERVAX® in pregnancy and while breastfeeding; use in immunocompromised individuals, frail individuals with comorbidities, and individuals with autoimmune or inflammatory disorders; interaction with other vaccines; and long-term safety. These areas of missing information will be addressed by analysing the corresponding population subgroups and by estimating the risk of adverse events of special interest (AESIs) up to 365 days of follow-up to assess long-term safety.

As part of the RMP, this protocol describes the postauthorisation safety study (PASS) to be conducted within the Vaccine Monitoring Collaboration for Europe (VAC4EU) study network. This PASS will evaluate the risk of safety concerns and AESIs, as defined in the approved EU RMP, following immunisation in the real-world setting. The PASS has 2 components—a vaccine utilisation study and a comparative safety study—that will be conducted in a staggered-phase approach. The vaccine utilisation study will characterise individuals receiving BIMERVAX® vaccine. The comparative safety study will comprise 2 sub-studies: a cohort study and a self-controlled risk interval (SCRI) study (a subtype of the self-controlled case series design). The cohort study will evaluate the risk of adverse events due to use of BIMERVAX® vaccine booster compared with that of other COVID-19 vaccines with the same indication, whereas the SCRI study will evaluate the risk of adverse events following receipt of a BIMERVAX® vaccine booster compared with the risk of AESIs in a later period not preceded by any COVID-19 vaccination booster. Given the evolving nature of the SARS-CoV-2 virus, the vaccine's composition may periodically be updated. This will be addressed via subgroup analyses (Section 9.3.4).

This PASS is a commitment to the EMA and complies with the European Network of Centres for Pharmacoepidemiology and Pharmacovigilance (ENCePP) code of conduct [5]. This protocol follows the structure and contents as included in the EMA's *Guidelines on Good Pharmacovigilance Practices (GVP), Module VIII—Post-Authorisation Safety Studies* [2].

8. RESEARCH QUESTION AND OBJECTIVES

To evaluate the safety of the BIMERVAX® booster vaccine, this study will address the following research question: Is there a difference in the risk of selected AESIs after vaccination with BIMERVAX® as a booster compared with vaccination by other vaccines for the same indication?

The primary study objectives are as follows:

- To characterise recipients of BIMERVAX® in relation to demographics and clinical characteristics at the time of vaccination, including the following: pregnancy status, age of childbearing potential, immunocompromised status, comorbidities, presence of autoimmune and inflammatory disorders, and interaction with other vaccines (influenza)
- To estimate the risk ratio and risk difference of prespecified AESIs comparing recipients of BIMERVAX® with recipients of other COVID-19 vaccines authorised for the booster indication, using a cohort design
- To estimate the incidence rate ratio of selected AESIs comparing a prespecified risk period following BIMERVAX® vaccination with a later post-risk interval, using an SCRI design

The secondary objectives (study size allowing) are:

- To estimate the risk ratio and risk difference of prespecified AESIs comparing recipients of BIMERVAX® with recipients of other COVID-19 vaccines authorised for the booster indication, using a cohort design in subgroups defined by the following baseline variables: pregnancy status, immunocompromised status, frailty due to comorbidities, presence of autoimmune or inflammatory disorders, prior use of influenza vaccine and calendar time
- To estimate the incidence rate ratio of selected AESIs comparing a prespecified risk period following BIMERVAX® vaccination with a later post-risk interval, using an SCRI design in subgroups defined by the following baseline variables: immunocompromised status, frailty due to comorbidities, presence of autoimmune or inflammatory disorders, prior use of influenza vaccine and calendar time

9. RESEARCH METHODS

9.1. Study Design

This will be a non-interventional, multi-database study based on the secondary use of healthcare data from different European countries within the VAC4EU network. The comparative safety study will have 2 components: a matched cohort design and an SCRI design, which will be implemented for specific outcomes (specified in Table 1). Both designs will follow vACCine covid-19 monitoring readinESS (ACCESS) specifications for vaccine safety studies [6]. The study period will be from the date of launch of BIMERVAX® until 36 months later for all AESIs, except pregnancy outcomes, which will be assessed until 48 months later (Section 9.2.4); the lookback period for selected covariates will be all available data history.

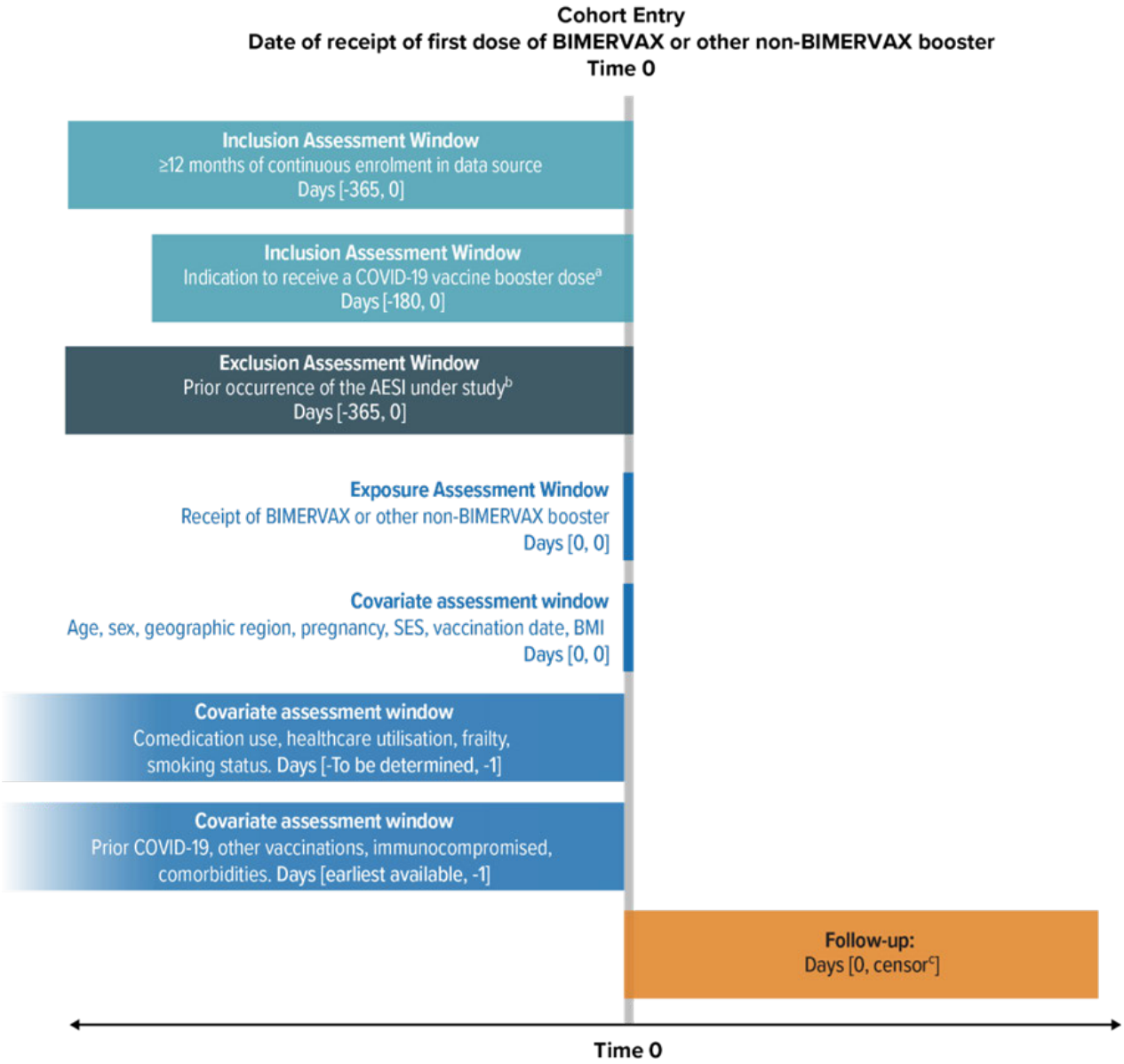
9.1.1. Vaccine Utilisation Study

The vaccine utilisation study will be a descriptive exercise [7]. All subjects receiving BIMERVAX® will be characterised at the time of the first BIMERVAX® vaccination recorded in the study databases within the study period, and their subsequent vaccination trajectories will be described.

9.1.2. Matched Cohort Design

The matched cohort design (Figure 1) will be a causal inference exercise [7]. It will estimate the risk of all listed AESIs (Section 9.3.2) after receipt of BIMERVAX® as a booster (exposed group) and will compare it with the risk of those AESIs in individuals who received non-BIMERVAX® COVID-19 boosters (comparator group).

Figure 1 Matched Cohort Study Design



AESI = adverse event of special interest; BMI = body mass index; COVID-19 = coronavirus disease 2019; SES = socioeconomic status.

[a] Individuals are indicated to receive a booster vaccine if they are 16 years and older and have previously been vaccinated with an mRNA COVID-19 vaccine. Individuals will be included in the study if at least 6 months have elapsed after a prior COVID-19 vaccination.

[b] Prior occurrence of the AESI under study within the past year will be an exclusion criterion for all AESIs except type 1 diabetes, which will be an exclusion if occurring at any time before time zero.

[c] Censoring will happen at the end of study period, occurrence of the AESI under analysis, death, or disenrolment from the data source, whichever is first. Additionally, individuals will be censored as per the strategies described in Section 9.7.2.6.

Figure template source: Schneeweiss et al. [8].

9.1.2.1. Causal Contrast or Estimand

The causal contrast will be the observational analogue of a per-protocol effect, i.e., the effect under complete adherence to the following vaccination strategies and under no infection by SARS-CoV-2:

- Receive 1 dose of BIMERVAX® vaccine. Individuals can subsequently receive other COVID-19 vaccinations as per local policies
- Receive 1 dose of another COVID-19 vaccine authorised for booster use. Individuals subsequently can receive other COVID-19 vaccinations as per local policies, using any brand but BIMERVAX.

9.1.2.2. Time Zero or Baseline

Time zero (baseline) will be defined as the time at which the exposure status is assigned, when inclusion and exclusion criteria are applied and when follow-up for study outcomes will start [9-12], and will be operationalised as follows:

- BIMERVAX® group: date of BIMERVAX® administration
- Non-BIMERVAX® vaccine group: date of booster dose of a non-BIMERVAX® vaccine, matched to date of BIMERVAX® booster in the corresponding match

9.1.2.3. Matching Process

The matching process will aim at being similar to those of prior applications of observational studies comparing head-to-head vaccines for COVID-19 [13-15]. The cohort study will match persons vaccinated with BIMERVAX® to persons vaccinated with non-BIMERVAX® vaccines in a 1:1 ratio, using the following variables:

- Calendar date of booster dose (time zero); granularity (e.g., week, month, trimester) to be defined in the statistical analysis plan (SAP)
- Age, in 3-year groups
- Sex, exact matching
- Geographic location, as available in the data source, exact matching; level of granularity to be defined in the SAP
- Having received an mRNA vaccine in the past (received any mRNA vaccine, did not receive any mRNA vaccine), exact matching

Matching variables will be assessed at time zero (i.e., age, geographic location at time zero). The selection of variables will be tailored based on the availability of the variable in each data source and their distribution in the boosted population.

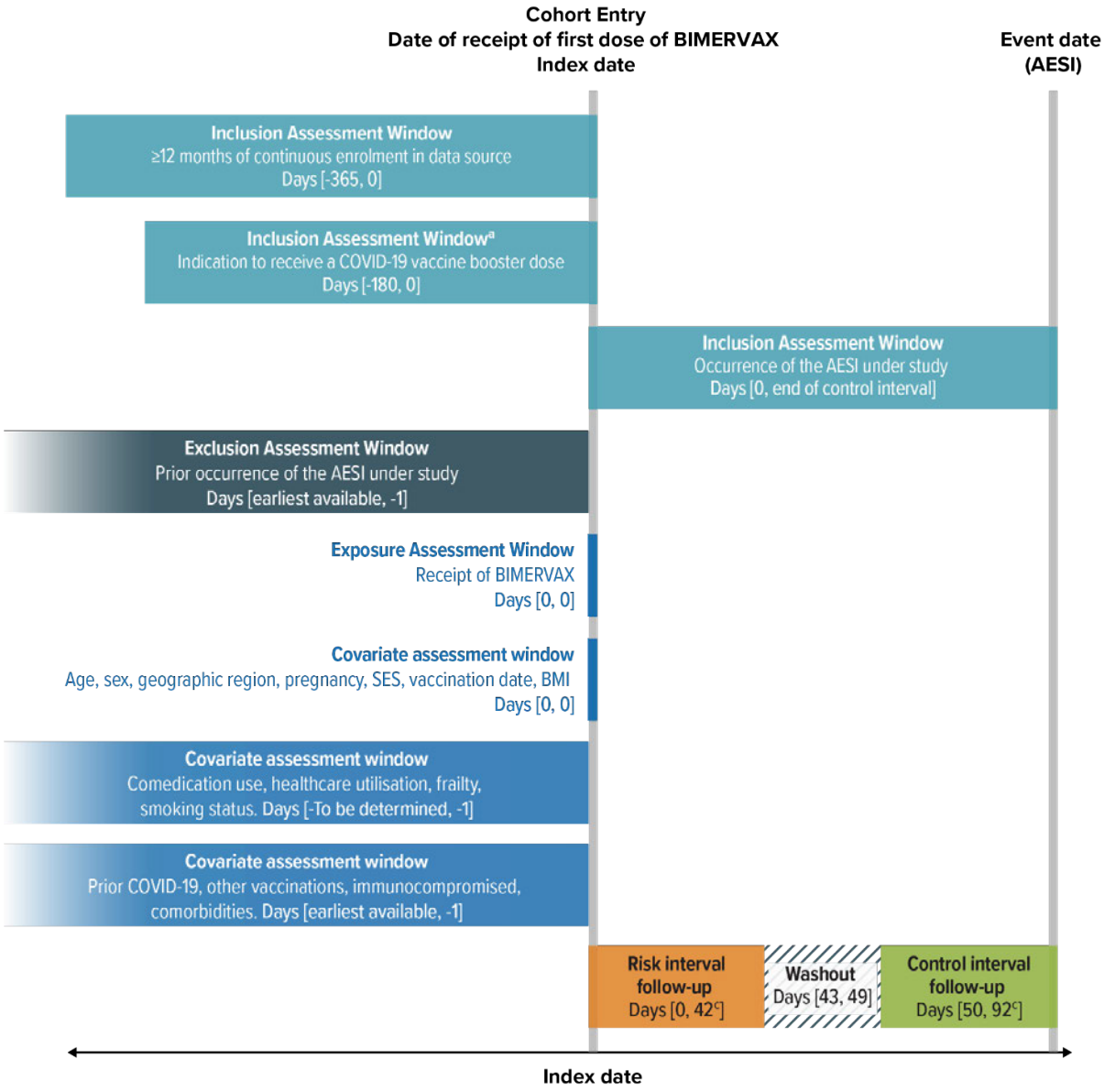
9.1.2.4. Follow-up

Individuals will be followed from time zero until the end of the study period (36 months after BIMERVAX® rollout), the occurrence of the AESI under analysis, death, or disenrolment from the data source, whichever occurs first (further details on censoring criteria specified in Section 9.7.2.6). For pregnancy outcomes, the end of the study period will be 48 months after BIMERVAX® rollout.

9.1.3. Self-controlled Risk Interval Design

The SCRI study will be a causal inference exercise [7]. The SCRI design (Figure 2) will be used to compare the occurrence of specific AESIs during a risk period following receipt of BIMERVAX® with the occurrence of the same specific AESI during a post-risk control interval; this will only be done for AESIs for which the SCRI is the recommended design [16,17].

Figure 2. Self-controlled Risk Interval Study Design



AESI = adverse event of special interest; BMI = body mass index; COVID-19 = coronavirus disease 2019; SES = socioeconomic status.

[a] Individuals are indicated to receive a booster vaccine if they are aged 16 years or older and have previously been vaccinated with an mRNA COVID-19 vaccine. Individuals will be included in the study if at least 6 months have elapsed after a prior COVID-19 vaccination.

[c] Example of an AESI with a risk and control interval of 42-day length and a 7-day washout period.

Figure template source: Schneeweiss et al. [8].

AESIs that are appropriate for this study design (see Section 9.3.2, Outcomes):

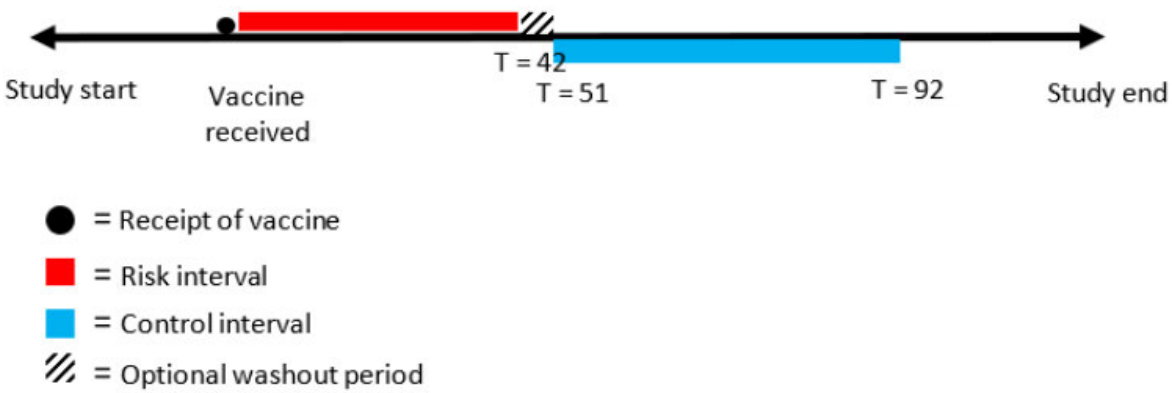
- Are rare, with a transient risk after exposure
- Have a constant event rate within the observation periods
- Their occurrence does not alter the duration of the observation window

The index date in the SCRI design will be the date of vaccination. The risk of each AESI during a prespecified period following BIMERVAX® vaccination ("risk interval") will be compared with the occurrence of the same AESI in a later interval ("control interval"), in the same individual (Figure 2). The risk and control intervals will be of the same length with a washout period between them. A sensitivity analysis will use a control interval of a different length, 127 days (Section 9.7.3.5).

The risk periods proposed for each AESI and the AESIs that will be analysed using the SCRI design are summarised in Section 9.3.2.

The use of a control period after the risk period (as opposed to use of a control period before the risk period) avoids bias from outcomes affecting the probability of exposure (e.g., the outcome is a contraindication for exposure or delays exposure) (Figure 3).

Figure 3. Self-controlled Risk Interval Design



T = time, in days.

Note: Example with a risk period of 42 days and a control period of 42 days, see specific risk periods in outcomes Table 1.

Source: Kawai et al. [16].

9.2. Setting

9.2.1. Source Population

The source population will comprise all individuals actively enrolled in each of the selected European health data sources who are recommended to receive a dose of BIMERVAX® vaccine within the study period. The study population will include all eligible individuals from the source population as per the eligibility criteria detailed below.

9.2.2. Inclusion Criteria

9.2.2.1. Vaccine Utilisation Study

Individuals must meet the following criteria for inclusion in the vaccine utilisation study:

- Have received a dose of BIMERVAX®
- Have a minimum of 12 months of continuous enrolment in the data source by the time they received the first dose of BIMERVAX®

While BIMERVAX® is indicated for individuals aged 16 years and older, this vaccine utilisation study will not have any age restriction in order to describe any off-label use and to gather additional information from a population not included in the clinical trials.

9.2.2.2. Matched Cohort Design

Individuals must meet all the following criteria at time zero (Section 9.1.2.2) to be eligible for inclusion in the cohort study:

- Have received 1 dose of BIMERVAX® vaccine or 1 dose of another COVID-19 vaccine authorised as a booster
- Be 16 years of age or older
- Have received a COVID-19 vaccine in the past
- Have received the last administration of a COVID-19 vaccine at least 6 months ago
- Have a minimum of 12 months of continuous enrolment in the data source
- Have complete information on the matching variables

9.2.2.3. Self-controlled Risk Interval Design

Individuals must meet all the following criteria at the index date for inclusion in the SCRI design:

- Have received a dose of BIMERVAX® (this will be the index date when the rest of the inclusion criteria will be evaluated)
- Be 16 years of age or older
- Have received a COVID-19 vaccine in the past
- Have received the last administration of a COVID-19 vaccine at least 6 months ago
- Have experienced the specific AESI during the risk or control interval
- Have full accrual of data used to define the event in both the risk and control interval
- Have a minimum of 12 months of continuous enrolment in the data source

9.2.3. Exclusion Criteria

9.2.3.1. Vaccine Utilisation Study

Individuals who have received a dose of BIMERVAX® in the past will be excluded.

9.2.3.2. Cohort and Self-controlled Risk Interval Design

Individuals who have had a diagnosis of the specific AESI being analysed within 1 year before time zero (cohort design) or before index date (SCRI design) will be excluded to distinguish the recording of previous events from true new events. For type 1 diabetes, individuals will be excluded if they receive a diagnosis at any time before time zero/index date.

9.2.4. Study Period

For all studies, the study period will start on the first date of launch of BIMERVAX® in each country where the participating data sources are located and will end 36 months later (48 months later for pregnancy outcomes) or on the date of the latest data availability.

9.3. Variables

9.3.1. Exposure

9.3.1.1. Vaccine Utilisation Study

All individuals who receive a first dose of BIMERVAX® will be considered exposed and will be characterised in the vaccine utilisation study.

9.3.1.2. Matched Cohort Design

The exposure strategies will be as follows (see Section 9.1.2.2 for the definition of time zero):

- **BIMERVAX® group**: Receive 1 dose of BIMERVAX® vaccine. Individuals subsequently can receive other COVID-19 vaccinations as per local policies
- **Non-BIMERVAX® vaccine group**: Receive 1 dose of a COVID-19 vaccine approved as a booster other than BIMERVAX®. Individuals subsequently can receive other COVID-19 vaccination as per local policies, using any brand except BIMERVAX®

9.3.1.3. Self-controlled Risk Interval Design

All participants in the SCRI will have received BIMERVAX®. They will be considered exposed during the risk period and unexposed during the control period (Section 9.1.3).

9.3.1.4. Exposure Assessment

For all study designs, exposure status will be assessed from recorded prescriptions, dispensing, or administration data for BIMERVAX® and other COVID-19 booster vaccines. The type of vaccine received and date of vaccination should be obtained from all possible sources that capture COVID-19 vaccination, such as pharmacy dispensing records, general practice records, immunisation registers, vaccination records, medical records, or other secondary data sources. Depending on the data source, vaccines may be identified via nationally used product codes where possible.

Each contributing dataset will identify vaccination as follows:

- **EpiChron – Aragon data sources (Spain):** The Aragon Health System (Aragon, Spain) has implemented a specific vaccination register embedded in the electronic health record system. COVID-19 vaccination is systematically registered in this register by healthcare professionals. This register will contain all the relevant information regarding the vaccination process, such as the patient's identifier; date of administration and due date for next dose, if applicable; centre of administration; part of the body where vaccine was administered; name of the vaccine; brand (laboratory); dose; and vaccination criterion (risk group to which the patient belongs). There is also a free-text section in which healthcare professionals can include their observations (e.g., presence or not of an allergic reaction).
- **Information System for Research in Primary Care, SIDIAP (Spain):** SIDIAP will have information available on COVID-19 vaccine administration to individuals linked to a unique and anonymous identifier for all 8 million individuals under the Catalan Institute of Health–Primary Care teams. The information will come from the electronic medical records. For each patient, SIDIAP will have date and centre of administration; dose, brand; reasons for vaccination (e.g., risk of group); and other information related to vaccination.
- **Valencia Health System Integrated Database, VID (Spain)**: Data on vaccine exposure may be obtained from the Vaccine Information System (VIS), which includes information on vaccine type, manufacturer, number of doses, batch numbers, location and administration date, and, if applicable, risk groups, all linked with the population information database. Information in the VIS is updated daily as all vaccinations in Valencia are delivered by the regional public health system, automatically recorded in the system, and transferred to the vaccination registry. Recording and availability of vaccination information in the region of Valencia is expected to be complete in the vaccination registry used for this study.
- **Clinical Practice Research Datalink, CPRD (United Kingdom [UK]):** CPRD contains information recorded by National Health Service primary care general practitioners. Information on the administration of COVID-19 vaccines will be available. This will include an encrypted unique patient identifier; the name of the vaccine; manufacturer; dose; administration route; date of administration; and medical observations, events, referrals, test results, and prescribed medications recorded by the general practitioner prior to, on, or after the vaccination date. In addition, patient demographic, practice-level, and staff-level information will also be available.
- **Système National Des Données de Santé, SNDS (France):** Exposure to COVID-19 vaccines will be obtained through a linkage of the SNDS to the SI Vaccin COVID, the information system implemented by the Caisse Nationale de l'Assurance Maladie (CNAM), to enable the preparation, management, and monitoring of the COVID-19 vaccination campaign. It captures, among other things, vaccine brand and date of injection [18].

9.3.2. Outcomes

The outcomes will be those AESIs agreed upon in the current BIMERVAX® EU RMP. Table 1 lists these AESIs, indicates which events are deemed suitable for analysis using the Cohort and/or SCRI analysis, and outlines the proposed risk intervals. The proposed risk intervals are based on the available evidence suggesting that any biological effect of a vaccine is expected to occur during the proposed risk intervals.

Table 1. Safety Outcomes: Adverse Events of Special Interest With Estimated Risk Intervals and Preferred Study Design

Body system/ classification	AESI	Preferred study design according to ACCESS protocol	Risk interval (days)[a]	Reference
Neurologic	Guillain-Barré syndrome	Cohort/SCRI	0-42	Based on Yih et al. [19] and FDA [20]
	Acute disseminated encephalomyelitis	Cohort/SCRI	0-42	Based on FDA [20]
	Transverse myelitis	Cohort/SCRI	0-90	Based on FDA [20]
	Encephalopathy	Cohort/SCRI[b]	0-21	Based on case reports of outcome following receipt of a COVID-19 vaccine [21]
	Aseptic meningitis, meningoencephalitis	Cohort/SCRI	0-42	Based on Yih et al. [19]
	Generalised convulsion (seizures)	Cohort/SCRI	0-2	Based on Yih et al. [19] and FDA [20]
	Facial nerve palsy, Bell's palsy	Cohort/SCRI[b]	0-42	Based on Yih et al. [19] and FDA [20]
	Narcolepsy	Cohort	0-42	Based on FDA [20]
	Anosmia, ageusia	Cohort/SCRI	0-42	Based on a previous VAC4EU COVID-19 vaccine PASS protocol [22]
Immunologic	Anaphylaxis	Cohort/SCRI	0-2	Based on Yih et al. [19] and FDA [20]
	Multisystem inflammatory syndrome	Cohort/SCRI	0-42	Based on FDA [20]
	Acute aseptic arthritis	Cohort/SCRI	0-42	Based on a previous VAC4EU COVID-19 vaccine PASS protocol [23]
	Subacute thyroiditis	Cohort[b]	0-365	Published risk intervals for autoimmune disorders were applied to similar autoimmune rheumatic conditions (i.e., thyroiditis) as done in a previous VAC4EU COVID-19 vaccine PASS protocol [22]
	Diabetes mellitus (type 1)[c]	Cohort	0-365	No consensus evidence for a risk period was identified, defaulted to 365 days as done in a previous VAC4EU COVID-19 vaccine PASS protocol [22]

Body system/ classification	AESI	Preferred study design according to ACCESS protocol	Risk interval (days)[a]	Reference
	Diabetes mellitus (any type)	Cohort	0-365	No consensus evidence for a risk period was identified, defaulted to 365 days as done in a previous VAC4EU COVID-19 vaccine PASS protocol [22]
Cardiologic	Acute cardiac injury (including microangiopathy, heart failure, stress cardiomyopathy, coronary artery disease, arrhythmia, myocarditis/pericarditis)	Cohort/SCRI	0-42	Based on the FDA [20]´s published risk intervals for myocarditis and pericarditis, the same risk intervals were applied to other acute cardiac injuries
Haematologic	Coagulation disorders (including DVT, pulmonary embolus, cerebrovascular stroke, limb ischaemia, cerebral venous sinus thrombosis, haemorrhagic disease)	Cohort/SCRI	0-28	Based on the FDA [20]´s published risk intervals for DVT and pulmonary embolism, the same risk intervals were applied to other cardiovascular and haematological disorders characterised by damage to the blood vessels and/or arteries and clotting
	Disseminated intravascular coagulation	Cohort/SCRI[b]	0-28	Based on FDA [20]
	Thrombocytopenia	Cohort/SCRI	0-42	Based on Liu et al. [24]
	Immune thrombocytopenia, thrombosis with thrombocytopenia syndrome	Cohort/SCRI[b]	0-42	Based on FDA [20]
	Single organ cutaneous vasculitis	Cohort/SCRI	0-28	Based on the FDA [20]´s published risk intervals for DVT and pulmonary embolism, the same risk intervals were applied to other cardiovascular and haematological disorders characterised by damage to the blood vessels and/or arteries and clotting

Body system/ classification	AESI	Preferred study design according to ACCESS protocol	Risk interval (days)[a]	Reference
Dermatologic	Erythema multiforme	Cohort/SCRI	0-28	Based on the FDA [20]´s published risk intervals for DVT and pulmonary embolism, the same risk intervals were applied to other haematological disorders characterised by damage to the blood vessels and/or arteries and clotting
	Chilblain-like lesions	Cohort/SCRI	0-28	Based on the FDA [20]´s published risk intervals for DVT and pulmonary embolism, the same risk intervals were applied to other haematological disorders characterised by damage to the blood vessels and/or arteries and clotting
Respiratory	Acute respiratory distress syndrome	Cohort/SCRI	0-28	Based on a previous VAC4EU COVID-19 vaccine PASS protocol [23]
Renal	Acute kidney injury	Cohort/SCRI	0-14	Based on a previous VAC4EU COVID-19 vaccine PASS protocol [23]
Hepato-gastrointestinal	Acute liver injury	Cohort/SCRI	0-14	Based on a previous VAC4EU COVID-19 vaccine PASS protocol [23]
	Acute pancreatitis	Cohort[b]	0-365	Based on a previous VAC4EU COVID-19 vaccine PASS protocol [23]
	Appendicitis	Cohort/SCRI[b]	0-42	Based on FDA [20]
Musculoskeletal	Rhabdomyolysis	Cohort/SCRI[b]	0-42	Based on a previous VAC4EU COVID-19 vaccine PASS protocol [23]
Death	Death (any causes)	Cohort	0-365	No consensus evidence for a risk period was identified, defaulted to 1 calendar year as done in a previous VAC4EU COVID-19 vaccine PASS protocol [22]
	Sudden death	Cohort	0-6	Based on a previous VAC4EU COVID-19 vaccine PASS protocol [23]
Pregnancy and neonatal outcomes	Spontaneous abortion, stillbirth	Cohort	At delivery	Based on a previous VAC4EU COVID-19 vaccine PASS protocol [22]

Body system/ classification	AESI	Preferred study design according to ACCESS protocol	Risk interval (days)[a]	Reference
	Foetal growth restriction	Cohort	Any time during pregnancy	Based on a previous VAC4EU COVID-19 vaccine PASS protocol [22]
	Preterm birth	Cohort	At delivery	Based on a previous VAC4EU COVID-19 vaccine PASS protocol [22]
	Major congenital anomalies	Cohort	1 year after birth	Based on a previous VAC4EU COVID-19 vaccine PASS protocol [22]
	Microcephaly	Cohort	At delivery	Based on a previous VAC4EU COVID-19 vaccine PASS protocol [22]
	Neonatal death	Cohort	At delivery	Based on a previous VAC4EU COVID-19 vaccine PASS protocol [22]
	Gestational diabetes	Cohort	Any time during pregnancy	Based on a previous VAC4EU COVID-19 vaccine PASS protocol [22]
	Preeclampsia	Cohort	After 20 weeks gestation	Based on a previous VAC4EU COVID-19 vaccine PASS protocol [22]
	Maternal death	Cohort	Any time during pregnancy	Based on a previous VAC4EU COVID-19 vaccine PASS protocol [22]
Reproductive system and breast disorders	Menstrual disorder	Cohort[b]	0-365	No consensus evidence for a risk period was identified, defaulted to 1 calendar year

ACCESS = vACCine covid-19 monitoring readinESS; AESI = adverse event of special interest; COVID-19 = coronavirus disease 2019; DVT = deep vein thrombosis; FDA = Food and Drug Administration; PASS = postauthorisation safety study; SCRI = self-controlled risk interval; VAC4EU = Vaccine Monitoring Collaboration for Europe (study network).

[a] Day 0 corresponds to day of receipt of booster dose or first day of control interval (for SCRI).

[b] Preferred study design is unspecified in the ACCESS protocol but was assumed as per the description of suitable outcomes for SCRI in Section 9.1.3.

[c] In the ACCESS report [25], this AESI is specified as “Diabetes (type 1 and broader),” which we will operationalise as 2 outcomes—”Diabetes type 1” and “Diabetes of any type”—for completeness.

9.3.2.1. Outcome Identification, by Data Source

Outcome definition relies on the accuracy of codes and algorithms to identify outcomes in the data available in each data source. To reduce the probability of outcome misclassification and reconcile differences across terminologies in the different data sources, standard algorithms for each outcome definition [26] will be applied to participant data sources, based on the results of the ACCESS project [27] and its updates. The ACCESS algorithms will be adapted to each data source according to the information components (e.g., primary care, secondary care, hospital registries) and the coding systems (e.g., Systemized Nomenclature of Medicine-Clinical Terms [SNOMED-CT], Read, International Classification of Diseases [ICD-9/ICD-10]) available in each data source, as specified in the ACCESS project [27]. Multiple algorithms for the same outcome may be included in the analysis for some AESIs to assess the potential impact of differential misclassification.

9.3.3. Covariates

The following variables will be assessed at time zero, and as available in each of the contributing data sources. They will be used to characterise populations (Sections 9.7.2.2 and 9.7.3.1*),* to define subgroups (Sections 9.7.2.4 and 9.7.3.3), and to control for confounding (Section 9.7.2.5). The corresponding lookback periods will be defined in the SAP. Conditions considered by the Centers for Disease Control and Prevention (CDC) posing the patient at "higher risk (conclusive)" for severe illness from COVID-19 [28] are marked with an asterisk (*).

- Demographics
  - Age (it will be grouped using the following categories [used to report background incidence rates from ACCESS: ≤ 17, 18-29, 30-39, 40-49, 50-59, 60-65, 66-69, 70-79, ≥ 80 years])
  - Sex
  - Pregnancy* status and pregnancy trimester
  - Geographic region as available in each contributing data source; granularity level to be defined in the SAP
  - Socioeconomic status as available in each contributing data source (e.g., housing, employment, income)
  - Date of vaccination
  - Months of continuous enrolment in the data source
- COVID-19 history
  - Previous diagnosis of or positive test for COVID-19
  - Previous visit to emergency department because of COVID-19
  - Previous admission because of COVID-19
- COVID-19 vaccination history
  - Time since last COVID-19 vaccination
  - Prior number of doses of mRNA-1273
  - Prior number of doses of ChAdOx1-S
  - Prior number of doses of Ad26.COV2.S
  - Prior number of doses of BNT162b2
  - Prior number of doses of BIMERVAX®

- Personal lifestyle characteristics
  - Smoking* status
  - Body mass index*
- Comorbidities
  - Asthma*
  - History of anaphylaxis
  - History of allergies
  - Diabetes mellitus (types 1 and 2)*
  - Hypertension
  - Cardiovascular disease*
  - Cerebrovascular disease*
  - Chronic respiratory disease (bronchiectasis, chronic obstructive pulmonary disease, interstitial lung disease, pulmonary embolism, pulmonary hypertension)*
  - Chronic kidney disease*
  - Chronic liver disease (cirrhosis, non-alcoholic fatty liver disease, alcoholic liver disease, autoimmune hepatitis)*
  - Cancer*
  - Cystic fibrosis*
  - Dementia*
  - Autoimmune disorders
  - Influenza infection or other respiratory infections
  - Charlson Comorbidity Index (component morbidities will be reported)
  - Mental health conditions (depression, schizophrenia)*
  - Obesity*
  - Tuberculosis*
- Immunocompromised conditions
  - Immunodeficiencies*
  - Immunosuppressant medication use*
  - Human immunodeficiency virus* and other immunosuppressing conditions
  - Solid organ or blood stem cell transplantation*
- Comedication use during the year before time zero
  - Analgesics
  - Antibiotics
  - Antiviral medications
  - Corticosteroids
  - Non-steroidal anti-inflammatory drugs
  - Psychotropics
  - Statins
  - Novel oral anticoagulants
  - Warfarin
- Healthcare utilisation in the year and in the 2 weeks before time zero
  - Number of hospitalisations
  - Number of emergency department visits
  - Primary care utilisation
  - Cancer screening

- Other vaccinations, against
  - Influenza
  - Pneumococcus
  - DPT (diphtheria, tetanus, pertussis)
  - Trivalent Oral Polio Vaccine (polio)
  - Trivalent MMR Vaccine (Measles, Mumps, and Rubella)
  - Haemophilus influenzae type B
  - Hepatitis B virus
  - Varicella zoster virus
  - Herpes-zoster virus
  - Human papilloma virus
  - Meningococcus
  - Rotavirus
- Surrogates of frailty (as available). The use of frailty scores [29,30] as a summary of these variables will be considered.
  - Paralysis
  - Parkinson's disease
  - Skin ulcer
  - Weakness
  - Fatigue
  - Undernutrition
  - Repeated falls
  - Stroke/brain injury
  - Ambulance transport
  - Dementia or cognitive impairment
  - Difficulty walking
  - Psychiatric illness
  - Sepsis
  - Heart failure
  - Podiatric care
  - Bladder incontinence
  - Diabetes complications
  - Osteoarthritis
  - Coagulation deficiencies
  - Vertigo
  - Lipid abnormalities
  - Functional decline
  - Use of devices associated with loss of autonomy (wheelchair, cane, oxygen, medical bed, deafness equipment, orthopaedic support and shoes, etc.)
  - Daily physiotherapy or nursing act
  - Living institution

9.3.4. Subgroups

Subgroups will be defined by the following baseline variables:

- Pregnancy status
- Immunocompromised status

- Frail subjects with comorbidities (e.g., chronic obstructive pulmonary disease, diabetes, chronic neurological disease, cardiovascular disorders)
- Presence of autoimmune and inflammatory disorders
- Prior use (concomitant or within the vaccination campaign/season) of influenza vaccine
- Calendar time. If adaptations of BIMERVAX® targeting new variants of SARS-CoV-2 occur, periods corresponding to the use of each adaptation will be analysed separately.

If the size of the subgroup is adequate, a formal comparison will be implemented; otherwise, a description of the estimated risk of AESIs in that subgroup will be provided.

9.4. Data Sources

Timing and countries/regions where BIMERVAX® will be available is, at this time, unknown. As of day/month/year, the marketing authorisation holder (MAH) confirmed that BIMERVAX® may be supplied to Spain, France, and the UK. At this time, this study aims at using the following data sources. Additional potential data sources will be monitored.

9.4.1. EpiChron (Spain)

The EpiChron Cohort Study links sociodemographic and clinical anonymised information for all the inhabitants of Aragon region, built from the BIGAN platform. The Aragon BIGAN platform integrates a technical infrastructure and a data lake gathering individual patient data from the regional health service information systems, including primary care, specialised care, hospitalisations, emergency department visits, drug prescriptions, image diagnosis, laboratory tests, diagnostics, vaccination, medical history, and demographics from the users of the public health system of Aragon, which comprises about 2 million individuals historic data and an active population of 1.3 million individuals.

9.4.2. SIDIAP (Spain)

The Information System for the Improvement of Research in Primary Care (SIDIAP) includes data from 328 primary care centres managed by the Catalan Health Institute in Catalonia, Spain. The data source contains pseudo-anonymised records for > 8 million people since 2006, with 5.8 million people active in June 2021 (75% of the Catalan population). SIDIAP is representative of the general population living in Catalonia in terms of age, sex, and geographic distribution [31]. SIDIAP includes data on the clinical and referral events registered by primary healthcare professionals and administrative staff in electronic health records (EHRs), demographic information, community pharmacy invoicing data, specialist referrals, and primary care laboratory test results. SIDIAP data can be linked to other data sources and registers at the local and national level.

9.4.3. VID (Spain)

VID is a set of population-wide electronic databases covering residents of the Valencia region in Spain, representing approximately 5 million individuals [32]. All the information in the VID databases can be linked at the individual level through a single personal identification. The different VID databases collate information on the health system coverage (e.g., health system entitlement, insurance modality), sociodemographic data (e.g., sex, age, geographical location), data from the mortality registry (e.g., date of death), as well as data on primary care and specialised outpatient care (e.g., outpatient consultations, hospitalisation, emergencies, diagnoses, surgeries, critical care, social work), outpatient pharmaceutical

prescriptions and dispensing, and clinical and administrative information (e.g., on all hospital admissions and ambulatory procedures, including public-private hospitals). The VID databases use either the ICD-9 or ICD-10 for coding diagnosis.

All databases included in the VID are updated frequently (every 1 to 3 months), except the Minimum Basic Hospital Data database (which includes a summary of hospital admissions), which is updated every 6 months.

9.4.4. CPRD (United Kingdom)

The CPRD includes data from EHRs of general practitioners in the UK who act as gatekeepers for healthcare and maintains individuals' life-long EHRs. Secondary care teams also provide information to general practitioners about their patients, including key diagnoses and procedures. The data recorded in the CPRD include demographic information, prescription details, clinical events, preventive care, specialist referrals, hospital admissions, and major outcomes, including death. Currently, CPRD Aurum contains data for approximately 13.3 million individuals [Current acceptable patients (i.e., registered at practices currently contributing data, excluding transferred out and deceased patients)].

9.4.5. SNDS (France)

The SNDS contains individual-level, pseudonymised information on all outpatient reimbursed claims from all main French healthcare insurance schemes linked to the national hospital discharge summaries database and the national death register. It currently covers the overall French population—about 67 million persons—from birth (or immigration) to death (or emigration), even if a subject changes occupation or retires and captures data from 2011 [33]. Medical history data goes back to 2006 for 86% of the population. For each individual, information exists for general demographic characteristics, chronic conditions and diagnoses, occupational accidents and diseases, medications dispensed in primary or secondary outpatient pharmacies as well as in hospitals, physician and paramedical visits, laboratory tests, hospital discharge summaries, medical history data, date of death [33], and data on pregnancies and deliveries [34,35].

If available, results of all antigenic and PCR COVID-19 tests carried out in France will be retrieved from the National Population Screening Information System (SI-DEP). Linkage of the SI-DEP to the SNDS is currently ongoing at the national level under the supervision of CNAM [36].

By law, it is not possible to go back to the patient to collect additional information. Most outcomes are identified with hospital diagnosis codes. For some studies, independent expert validation using reconstituted EHRs using all information in the database (i.e., assembling a chronological listing of diagnoses, procedures, and medications recorded for a patient, can be conducted) [37].

9.5. Study Size

The study size will be determined by the uptake of BIMERVAX® in the contributing countries and data sources during the study period. Width of the 95% confidence intervals (CIs) [38] for different potential values of the true risk ratio of the AESIs is presented in Table 2, under different risk scenarios in the unvaccinated population and of sample sizes, assuming complete follow-up, both for the cohort study design and the SCRI study design.

Table 2. Confidence Interval Limits for AESI Risks in the Comparator Group for Different Scenarios of True Risk Ratio and of Study Sizes

Number of individuals per group	AESI risk in comparator group	Risk ratio	Matched cohort design		SCRI design	
			Lower bound of 95% CI	Upper bound of 95% CI	Lower bound of 95% CI	Upper bound of 95% CI
10,000	1 per 100,000	2	0.00	> 1,000	0.00	> 1,000
10,000	1 per 100,000	5	0.01	> 1,000	0.00	> 1,000
10,000	1 per 100,000	10	0.02	> 1,000	0.00	> 1,000
10,000	10 per 100,000	2	0.18	22.05	0.03	127.85
10,000	10 per 100,000	5	0.58	42.79	0.03	961.58
10,000	10 per 100,000	10	1.28	78.11	0.01	> 1,000
10,000	100 per 100,000	2	0.94	4.27	0.54	7.45
10,000	100 per 100,000	5	2.54	9.85	0.95	26.38
10,000	100 per 100,000	10	5.22	19.15	1.16	86.36
50,000	1 per 100,000	2	0.07	59.62	0.01	715.54
50,000	1 per 100,000	5	0.24	104.15	0.00	> 1,000
50,000	1 per 100,000	10	0.55	183.04	0.00	> 1,000
50,000	10 per 100,000	2	0.68	5.85	0.31	12.84
50,000	10 per 100,000	5	1.91	13.06	0.48	52.53
50,000	10 per 100,000	10	3.99	25.07	0.47	210.94
50,000	100 per 100,000	2	1.42	2.81	1.11	3.60
50,000	100 per 100,000	5	3.69	6.77	2.38	10.52
50,000	100 per 100,000	10	7.48	13.37	3.81	26.23
100,000	1 per 100,000	2	0.18	22.06	0.03	127.85
100,000	1 per 100,000	5	0.58	42.80	0.03	961.58
100,000	1 per 100,000	10	1.28	78.12	0.01	9,139.22
100,000	10 per 100,000	2	0.94	4.27	0.54	7.45
100,000	10 per 100,000	5	2.54	9.86	0.95	26.38
100,000	10 per 100,000	10	5.22	19.16	1.16	86.36
100,000	100 per 100,000	2	1.57	2.54	1.32	3.03
100,000	100 per 100,000	5	4.03	6.20	2.96	8.46
100,000	100 per 100,000	10	8.14	12.28	5.06	19.77

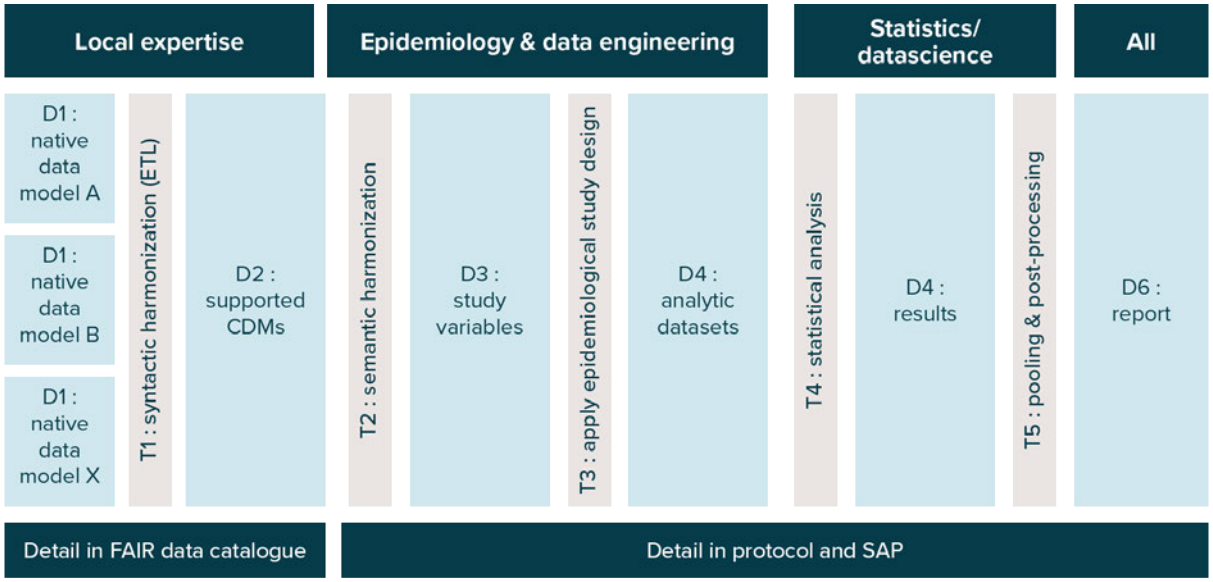
AESI = adverse event of special interest; CI = confidence interval; SCRI = self-controlled risk interval.

9.6. Data Management

This study will be conducted in a distributed manner using a common protocol, the ConcePTION common data model (CDM), and common analytics programmes using existing healthcare data. The following transformation steps (T) will be implemented:

- T1: Extraction, transformation, and loading (ETL) of data to a CDM. To harmonise the structure of the data sets stored and maintained by each research partner providing data access, a shared syntactic foundation will be used and each research partner will create script to perform the transformation into the CDM. The CDM that will be used was developed during the IMI-ConcePTION project [39,40]. In this CDM, data are represented in a common structure, but the content of the data remain in their original format. The ETL design for each study will be shared in a searchable catalogue that meets the FAIR principles: findable, accessible, interoperable, and re-usable. The VAC4EU FAIR data catalogue is a meta-data management tool designed to contain searchable meta-data describing organisations that can provide access to specific data sources. Data quality checks will be conducted to measure the integrity of the ETL as well as internal consistency within the context of the CDM (see Section 9.8).
- T2: To reconcile differences between terminologies, a shared semantic foundation will be built for the definition of the events to be analysed by collecting relevant concepts in a structured fashion using a standardised event definition template. The CodeMapper tool was used to create diagnosis code lists based on completed event definition templates for each AESI and comorbid risk condition in the ACCESS project [41]. Based on the relevant diagnostic medical codes and keywords, as well as other relevant concepts (e.g., medications), 1 or more algorithms will be constructed (typically 1 sensitive, or broad, algorithm and 1 specific, or narrow, algorithm) to operationalise the identification and measurement of each event. These algorithms may differ between data sources, as the components involved in the study variables may differ. Manual review of electronic records will be conducted for a sample of the events. Specifications for both ETL and semantic harmonisation will be shared in the catalogue.
- T3: Following conversion to harmonised study variable sets, R programmes for the application of the specific design will be created.
- T4: Programmes for the calculation of incidence and prevalence and comparative analysis estimates, if needed, will be distributed to research partners for local deployment. The aggregated results produced by these scripts will then be uploaded to the Digital Research Environment (DRE). The DRE is a cloud-based, globally available research environment where data are stored and organised securely and where researchers can collaborate (myDRE – Trusted Research Environment).
- T5: Pooled analysis and visualisation of results (Figure 4) will occur at DRE. The DRE will be made available through University Medical Center Utrecht (UMCU)/VAC4EU (https://www.andrea-cloud.eu/).

Figure 4. Data Management Plan



CDMs = common data models; D*n* = data type; ETL = extraction, transformation, and loading; FAIR = findable, accessible, interoperable, re-usable; SAP = statistical analysis plan; T*n* = transformation step; VAC4EU = Vaccine Monitoring Collaboration for Europe (study network).

Source: Figure from Sturkenboom, M. Overview of the VAC4EU pipeline. 13 June 2022 (unpublished material).

9.6.1. Record Retention

The final study aggregated results sets and statistical programmes will be archived and stored on the DRE and the VAC4EU SharePoint site. Validation of the quality control (QC) of the statistical analyses will be documented. The final study protocol and any amendments, the final SAP, statistical programmes, and output files will be archived on a specific and secured central drive. Study records or documents may also include the analyses files, syntaxes (usually stored at the data source site), ETL specifications, and output from data quality checks.

To enable evaluation or inspections/audits from regulatory authorities or HIPRA, research partners providing data access agree to keep all study-related records, including the identity of all participating subjects (sufficient information to link records, for example, case report forms, hospital records), copies of all case report forms, safety reporting forms, source documents, detailed records of treatment disposition, and adequate documentation of relevant correspondence (e.g., letters, meeting minutes, telephone call reports). The records should be retained by research partners according to local regulations or as specified in the vendor contract, whichever is the longest. Research partners must ensure that the records continue to be stored securely for as long as they are retained.

If, for any reason, VAC4EU becomes unable to continue to retain study records for the required period, HIPRA should be prospectively notified. In this case, the study records must be transferred to a designee acceptable to HIPRA.

Study records must be kept for up to 15 years after completion or discontinuation of the study, unless VAC4EU, RTI-HS, and HIPRA have expressly agreed to a different retention via a separate written agreement. Records must be retained for longer than 15 years if required by applicable local regulations.

9.6.2. Data Extraction

Each research partner providing data access will create ETL specifications using the standard ConcePTION ETL design template (accessible via this link: https://docs.google.com/document/d/1ITGlaw9dQV1axn8iIIEyqHVbDybx8s7S/edit). Following completion of this template and review by study statisticians or epidemiologists, each research partner will extract the relevant study data locally using its software (e.g., Stata, SAS, R, Oracle). These data will be loaded into the CDM structure in csv format. These data remain local (Figure 4).

9.6.3. Data Processing and Transformation

The central scripts will first transform the data from the syntactically harmonised CDM to semantically harmonised study variables (Figure 4). Subsequently, scripts to conduct analysis against semantically harmonised study variables will be distributed and run locally to produce aggregated results. The scripts for these processing and analysis steps will be developed and tested centrally and sent to the research partners.

The scripts will be structured in a modular format to ensure transparency. Functions to be used in the modules will be either standard packages or packages specifically designed, developed, and tested for multi-database studies. Scripts will be double coded in SAS or R and quality checks will be thoroughly documented.

The research partners will run the scripts locally and send aggregated analysis results to the DRE using a secure file transfer protocol. In the DRE, results will be further plotted, inspected (for quality assessment), and pooled (if needed) for final reporting.

All final statistical computations will be performed using R or SAS. Research partners will have access to the workspace for script verification.

Aggregated results, ETL specifications, and a repository of study scripts will be stored in the DRE.

9.6.4. Data Access

Within the DRE, each project-specific area will consist of a separate secure folder called a workspace. Each workspace will be completely secure, and researchers will be in full control of their data. Each workspace will have their own list of users, which will be managed by its administrators.

The DRE architecture will allow researchers to use a solution within the boundaries of data management rules and regulations. Although General Data Protection Regulation and Good (Clinical) Research Practice still apply to researchers, the DRE offers tools to better control and monitor which activities take place within projects.

All researchers who need access to the DRE will be granted access to study-specific secure workspaces. Access to this workspace is only possible with double authentication, which uses an identification code and password together with the user's mobile phone for authentication.

All researchers with access to the workspace within the DRE will be able to upload of files. The download of files will be possible only after requesting and receiving permission from a workspace member with an "owner" role.

9.7. Data Analysis

Detailed methodology for summary and statistical analyses of data collected in this study will be documented in the SAP, which will be dated, filed, and maintained by the sponsor. The SAP may modify or update the plans outlined in the protocol; any major modifications of primary endpoint definitions or their analyses will be detailed in a protocol amendment. No specific hypotheses will be tested during the study described in this protocol.

The progress report (to be submitted 3 months after protocol endorsement by the EMA) will contain confirmation of participating data sources, a description of project start-up and subsequent activities, as well as identified challenges and proposals to address them.

The interim report 1 will provide a description of the cohorts and crude risks of AESIs in the BIMERVAX® and the comparator cohorts. The interim report 2 will also include, study size allowing, the main cohort comparative analysis of AESIs, and the final report will include all the analyses described below based on the available information at the time of the corresponding data extraction.

The final report will be submitted 36 months after rollout of BIMERVAX® in the first participating country, containing all the analyses described in this protocol. An update on pregnancy outcomes will be submitted 48 months after rollout of BIMERVAX® in the first participating country. The study periods to be included in each interim report will depend on the data source, linkages, lag times, and the time required to obtain the data by the research institutions. See Table 3 for an estimation of the available information for each deliverable. In addition, for the first interim report, the study period can be affected by the time needed to allow for protocol endorsement by the EMA, contracting between research institutions, writing of the SAP, data extraction, analysis, and reporting.

Table 3. Maximum Follow-up for Each Study Report According to Data Source

Data sources	Time lag for data updates	Interim report 1 (Q4 2025)[a]	Interim report 2 (Q4 2026)[a]	Final report (Q4 2027)[a]
EpiChron (ES)	≈ 6 months	≈ 6 months	≈ 18 months (6 + 12)	≈ 30 months (6 + 24)
SIDIAP (ES)	≈ 6 months	≈ 6 months	≈ 18 months (6 + 12)	≈ 30 months (6 + 24)
VID (ES)	≈ 6 months	≈ 6 months	≈ 18 months (6 + 12)	≈ 30 months (6 + 24)
CPRD (UK)	Variable	—	—	—
SNDS (FR)	Data updated in Q3 of the following year in each period	≈ 9 months	≈ 21 months	≈ 33 months

CPRD = Clinical Practice Research Datalink; ES = Spain; FR = France; SIDIAP = Information System for Research in Primary Care (Spain); SNDS = French Administrative Healthcare Database; UK = United Kingdom; VID = Valencia Health System Integrated Database (Spain).

[a] Based on BIMERVAX® rollout of the vaccine adaptation expected in Q1 2024. First use of the original vaccine in Spain occurred during 2023.

9.7.1. Vaccine Utilisation Study

This study will describe all covariates in Section 9.3.3 at the time of reception of the first BIMERVAX® dose. An additional category for age, corresponding to age of childbearing potential, will be created for women. For continuous variables, means, standard deviations, medians, and other quartiles will be estimated. For categorical variables, counts and proportions will be estimated. The missingness of variables will also be described. Further details will be described in the SAP.

Additionally, to describe the subsequent vaccination trajectories, the following will be computed:

- Counts and percentages of individuals receiving a subsequent COVID-19 vaccine
- Brand of subsequent COVID-19 vaccine
- Time to administration of subsequent COVID-19 vaccine

Graphical representation via a Sankey plot will be considered.

9.7.2. Matched Cohort Design

Comparative analyses will be performed if at least 3 events per exposure group in each data source are observed.

9.7.2.1. Exposure Assignment and Follow-up

The exposures under study are outlined in Section 9.3.1. Individuals will be assigned to each vaccination category according to their data at time zero, as outlined below:

- BIMERVAX® group: eligible individuals will be assigned to this group when they receive a dose of BIMERVAX®.
- Non-BIMERVAX® vaccine group: eligible individuals will be assigned to this group when they receive a dose of any COVID-19 vaccine that is not BIMERVAX®. Individuals will be censored if and when they receive a dose BIMERVAX® during follow-up.

Individuals will be followed for incident AESIs from time zero (see Section 9.1.2.2) until the censoring described above, SARS-CoV-2 infection (Section 9.7.2.6), death, administrative end of follow-up, or end of study period (36 months after BIMERVAX® rollout in the first data source), whichever occurs first.

The same individual could therefore be eligible for inclusion in both groups, the BIMERVAX® and non-BIMERVAX® vaccine group, at different points in time, as long as they fulfil the eligibility criteria at baseline.

9.7.2.2. Descriptive Statistics

The distributions of baseline characteristics at time zero 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 other quartiles will be estimated. For categorical variables, counts and proportions will be estimated. The missingness of variables

will also be described. Additionally, to describe the subsequent vaccination trajectories, the following will be computed:

- Counts and percentages of individuals receiving a subsequent COVID-19 vaccine
- Brand of subsequent COVID-19 vaccine
- Time to administration of subsequent COVID-19 vaccine

Further details will be described in the SAP.

To describe the relative imbalance of characteristics between exposed and comparator groups, absolute standardised differences will be calculated for each baseline characteristic [42,43]. An overall standardised difference across all levels will be calculated for multilevel categorical variables [43].

9.7.2.3. Crude Outcome Measures

The risk of the study outcomes will be estimated at the end of the risk interval and at 90 days intervals up to 365 days of follow-up (Table 1, Section 9.3.2) using the 1– Kaplan-Meier estimator. Effect estimates will be calculated both as risk differences and as risk ratios, for those exposed to BIMERVAX® compared with those exposed to a comparator vaccine. All estimates will be bounded with a percentile-based 95% CI.

Time to outcome will be defined as the time from the baseline date (time zero) until the occurrence of the outcome or censoring (Section 9.1.2.2 and Section 9.1.2.4). The variance will be computed using approaches that account for autocorrelation (e.g., the robust estimator or via bootstrapping) [44].

9.7.2.4. Subgroup Analyses

If the sample size allows for informative comparative analyses, subgroups defined in Section 9.3.4 will be analysed.

9.7.2.5. Adjustment for Baseline Imbalances

To account for potential residual baseline confounding after matching, propensity score methods will be used to estimate the adjusted risks, effect estimates and their corresponding 95% CIs. Specifically, the propensity score (i.e., the probability of receiving BIMERVAX® conditional on baseline covariates listed in Section 9.3.2.1) will be used to construct inverse probability weights [45]. More details, including the variable selection and construction of weights, will be provided in the SAP. Given the 7- to 14-day time lag for immunity to build following receipt of a COVID-19 vaccine dose, the incidence of COVID-19 hospitalisations in the first 7 days after baseline will be evaluated as a negative control outcome for baseline exchangeability [14]. Baseline covariate balance after matching and weighting will be assessed by evaluating the standardised mean difference for continuous [42] and categorical [43] variables.

9.7.2.6. Censoring to Estimate the Direct Effect on AESIs Under Complete Follow-up and Under Complete Adherence to the Vaccination Strategies

Many of the observed or hypothetical post-vaccination AESIs may also be associated with COVID-19 infection. Previous studies that evaluated the association between various aspects of COVID-19 infection (e.g., COVID-19 hospitalisation, diagnosis, or positive test) and select AESIs showed increased risks of acute kidney injury and arrhythmia [46], deep vein thrombosis/pulmonary embolism [46,47], intracranial haemorrhage [46], myocardial infarction [46-49], ischaemic stroke [47-49], and myocarditis/pericarditis [46] in various populations.

The primary objective of this study specifies the effect to be estimated as vaccination with BIMERVAX® versus vaccination with a COVID-19 vaccine other than BIMERVAX® (i.e., the *direct* effect) (Section 8). The study focuses on the direct effect because of its safety nature. Thus, its aim is to evaluate the effects on the incidence of AESIs which are not mediated by the vaccines' preventive effect on infection. If we assessed the *total* effect (i.e., both the effect that is mediated by the vaccines' preventive effect on infection plus the direct effect on the AESIs), we might observe that, compared with other vaccines, BIMERVAX® protects against medical complications of SARS-CoV-2 infections (e.g., respiratory distress) because BIMERVAX® protects against infection with SARS-CoV-2, which in turn causes the corresponding medical complications. For example, if respiratory distress were an AESI, the effect of BIMERVAX® on this AESI could potentially be masked by the protective effect of BIMERVAX® against COVID-19 [13].

In addition, if the study estimated the total effect (as opposed to the direct effect), the incidence of the events mediated by COVID-19 infection would depend on the background rate of COVID-19 infection in the study population, which would make the effect estimates highly dependent on the level of pandemic activity during the follow-up period. A limitation of this approach is that some infections may not be documented, which will mean that some of the estimated direct effects may be mediated through COVID-19 infection prevention. The total effect will be assessed by a sensitivity analysis (Section 9.7.2.9).

The following censoring will be applied to estimate the direct effect under complete follow-up and complete adherence to the vaccination strategies. The corresponding assumptions for validity are outlined:

- *Censoring of the matched pair when either member has a documented COVID-19 infection.* This censoring will be implemented to estimate the effect of BIMERVAX® compared with other booster vaccines on the incidence of AESIs that is not mediated by the preventive effect on infection (i.e., the controlled direct effect). This approach assumes that uncensored individuals will have a similar risk for the AESI as that of the censored individuals if they had not been infected, conditional on the baseline covariates that were adjusted for (via matching and weighting).
- *Censoring of the matched pair when either member is lost to follow-up (i.e., disenrols from the data source).* This censoring will be implemented to estimate the effect under complete follow-up. This approach assumes that uncensored individuals will have a similar risk for the AESI as the individuals who were disenrolled from the data source if they had remained in follow-up, conditional on the baseline covariates that were adjusted for (via matching and weighting).
- *Censoring of the matched pair when the individual in the comparator group receives a dose of BIMERVAX®.* This censoring will be implemented to estimate the effect under

complete adherence to the vaccination strategies. This approach assumes that the risk of the AESI for individuals that did not deviate from the vaccination strategy would be similar to that of the individuals who deviated from the vaccination strategy, had they not deviated, conditional on the baseline covariates that were adjusted for (via matching and weighting).

9.7.2.7. Missing Data Handling

Several approaches for handling missing data will be considered (e.g., inverse probability weighting of the complete case population, complete case analysis), based on the amount of missing data and the most reasonable assumption on the pattern of how the data are missing. Additional details on when and which method will be used will be described in the SAP.

9.7.2.8. Meta-Analysis

The vaccine effect on specific AESIs will be meta-analysed using appropriate random-effects meta-analytic methods in the absence of relevant heterogeneity. The heterogeneity of effects will be assessed using the I^2 statistic [50]. If the percentage of heterogeneity estimated by I^2 is high (e.g., > 50%; specific threshold to be specified in the SAP), a combined effect will not be estimated. In the case of few or no events for some of the outcomes in some of the study data sources, specific methods to deal with this (e.g., continuity correction methods [51], generalised mixed models [52]) will be considered.

9.7.2.9. Sensitivity Analyses

The following sensitivity analyses will be implemented:

- Analysis to estimate the total effect of BIMERVAX® vaccination on the AESIs (as opposed to the main analysis, which estimates the controlled direct effect) by not censoring the pair if a component is diagnosed with a COVID-19 infection. This analysis will estimate the total effect of the vaccines on potential adverse events through all causal pathways between the vaccines and outcomes, including those potentially mediated by infection (i.e., these risks capture complications arising both from the vaccine themselves and from the incident infections that they are intended to prevent). Differences with the main analysis should be minimal if the SARS-CoV-2 virus circulation is low [13].
- Analysis to estimate the direct effect of BIMERVAX® vaccination on the incidence of pneumonia. This analysis will gauge the amount of unreported SARS-CoV-2 infections because pneumonia is not expected to be a complication of any vaccination [13].
- Analysis to avoid discarding information by matching. In the main analysis, individuals vaccinated with BIMERVAX® who do not find a match by the proposed matching variables will be discarded from the analysis. If the number of exposed individuals or outcomes are scarce, matching can contribute to imprecise effect estimates. In this situation, a sensitivity analysis where all eligible vaccinees are included and baseline characteristics are adjusted for via inverse probability weighting will be considered. Other than the absence of matching and the construction of baseline weights using models that include the matching variables in addition to the variables of the weights used in the main analysis, the rest of the analytical procedures will be the same as in the main analysis.

9.7.3. Self-controlled Risk Interval Design Study

9.7.3.1. Descriptive Statistics

The distributions of subjects' characteristics at the time of vaccination with BIMERVAX® will be calculated to characterise the study sample. Means, standard deviations, and quartiles will be estimated for continuous variables. Counts and proportions will be estimated for categorical variables. The missingness of variables will also be described.

9.7.3.2. Measures of Association

Conditional Poisson regression will be used to estimate incidence rate ratios and their corresponding 95% CIs. AESIs for which the SCRI design will be used and their risk windows are specified in Table 1. The control intervals will be the same length as the risk intervals for each AESI and will begin after a 7-day washout period that will separate the risk and control intervals; more details will be provided in the SAP.

The SCRI inherently adjusts for both measured and unmeasured time constant factors, such as sex and chronic health conditions with onset before the start of follow-up. Time-varying confounders may be included as covariates in regression models.

9.7.3.3. Subgroup Analysis

If the sample size allows for informative analyses, subgroups as defined in Section 9.3.4 (except for the pregnancy status subgroup) will be analysed.

9.7.3.4. Meta-Analysis

As in the cohort study, the vaccine effect on specific AESIs will be meta-analysed using appropriate random-effects meta-analytic methods in the absence of relevant heterogeneity. The heterogeneity of effects will be assessed using the I^2 statistic [50]. If the percentage of heterogeneity estimated by I^2 is high (e.g., > 50%, specific threshold to be specified in the SAP), a combined effect will not be estimated.

9.7.3.5. Sensitivity Analysis

A sensitivity analysis of the SCRI study will be implemented by extending the proposed control intervals to 127 days. This analysis can increase the precision of the effect estimates.

9.7.4. Handling of Small Cell Counts

Some of the analyses may be limited due to a small number of events and/or data privacy–driven cell count restrictions at a research partner (see Table 4).

The possibility of unintentional (deductive) disclosure arises when cells with small numbers of subjects are quoted. When reporting the data, the policy is that no cell should contain fewer than 5 events in CPRD and SIDIAP. When distributed outside the research team and the client, the exact number of events will be replaced by < 5 or ≤ 10, as appropriate, and other cells (such as person-years) will be masked to avoid back calculation, if needed.

Table 4. Small Cell Count Rules in Each Data Source

	EpiChron	SIDIAP, Catalonia	VID, Valencia	CPRD Aurum	SNDS
Numbers to be masked	1-4	1-4	NA	1-4	1-10
Text used	< 5	< 5	NA	< 5	≤ 10
Possible to share with research partners	Yes	Yes	Yes	Yes	No
Possible to share with HIPRA, who submits report to regulatory authorities	No	No	Yes	Yes	No
Comments			There must be no identifiable information to be shared	A waiver may be needed to share with regulatory authorities; however, this requires providing an additional report to be shared outside the regulatory bodies and indications for each affected cell	

CPRD = Clinical Practice Research Datalink; NA = not applicable; SIDIAP = Information System for Research in Primary Care (Spain); SNDS = French Administrative Healthcare Database; VID = Valencia Health System Integrated Database (Spain).

9.8. Quality Control

9.8.1. RTI as Coordinating and Research Centre (CPRD, United Kingdom)

Standard operating procedures or guidance documents at the participating institutions will be used to guide the conduct of the study.

At RTI-HS, these procedures 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. All key study documents, such as the analysis plan, abstraction forms, and study reports, will undergo quality-control review, senior scientific review, and editorial review.

Experienced RTI-HS programmers will perform the ETL for the CPRD data. To ensure the integrity and quality of the study results, RTI-HS will follow the programming validation life cycle process for all analyses. This includes quality-checking programmes, logs, and output for accuracy according to relevant standard operating procedures. All programmes will be independently reviewed by a second programmer/analyst.

For RTI-HS, an independent Office of Quality (OQ) will perform audits and assessments that involve various aspects of the project, including, but not limited to, education and training documentation, data entry and data transfer procedures and documentation, and institutional review board (IRB) documentation. Such audits will be conducted by the OQ according to established criteria in standard operating procedures and other applicable procedures. Standard procedures will be in place to restore files in the event of a hardware or software failure.

A quality-assurance audit of this study may be conducted by the sponsor or the sponsor's designees.

Appropriate data storage and archiving procedures will be followed (i.e., storage on CD-ROM and DVD), with periodic back-up of files to tape. Standard procedures will be in place to restore files in the event of a hardware or software failure at each research centre.

Two members from the independent VAC4EU scientific advisory board will provide independent external review of key study documents, such as the protocol, statistical analysis plans, and reports. This review will focus on scientific soundness and interpretation of the results from reports and publications. The peer-review process with the external experts, appointed and contracted by VAC4EU, will support scientific quality, independence, and transparency. Their comments will be made available to all parties involved in the study.

9.8.2. EpiChron (Spain)

The EpiChron cohort will be built from the BIGAN platform, which integrates a technical infrastructure and a data lake, collecting individual patient data from the regional health service information systems. The BIGAN platform includes several mechanisms to control and improve the quality of data, mainly in the ETL processes for capture and persistence in the data lake. These mechanisms include validation rules (e.g., for dates and time intervals) and cross-checks with master tables, requiring that certain coded data exist in a standardised dictionary. Analyses of the distribution of variables will also be carried out periodically to detect "outliers" that identify errors in the data capture or transformation processes. Generally, records that do not pass the quality-assurance procedures are kept in a "holding" area for review and decision to discard or reprocess. The resulting databases will be pseudonymised to encrypt individual-level identification codes, protecting individuals' privacy, and complying with data protection laws. They will be stored on a central computer server, with access restricted to the members of the research group, via a 2-step authentication process. The research group will comprise a multidisciplinary qualified team, including public health specialists, epidemiologists, clinicians, pharmacists, statisticians, and data managers, who are all trained in data management and patient data protection.

9.8.3. SIDIAP (Spain)

Quality-control processes will be implemented at each phase of the data flow cycle. The QC checks will be performed at the extraction and uploading steps. To assess data completeness, the presence of elements will be described by geographical area, registering physician, time, and the distribution of values. The accuracy of the data will be assessed by validity checks on outliers, out of range values, formatting errors, and logical date incompatibilities. Completeness and accuracy measures will be used to inform decisions on the required transformations to improve data quality (e.g., harmonisation, normalisation, and clean-up) and the fitness for purpose of the data for use in this study.

9.8.4. VID (Spain)

Once the final version of the protocol is available, The Foundation for the Promotion of Health and Biomedical Research of Valencia Region (FISABIO) needs to develop its own version of the protocol outlining the tasks to be performed by the research team. This protocol, along with the original version, must receive approval from the Research Ethics Committee. Once the approval from the Ethics Committee is obtained, it is necessary to

submit all the documentation to the PROSIGA Committee of the Conselleria de Sanitat. Through meetings with the research team, this Committee grants authorisation for data usage and sets the data extraction process.

After that, raw data will be extracted in text file format and will undergo a data quality check. Data will be stored on secure servers at FISABIO in accordance with Spanish and data protection requirements and ensuring that no identifiable data will be stored longer than required.

All the procedures that will be implemented for data collection, storage, protection, retention, and destruction will comply with national and EU legislation. The research team will stay up to date with the detailed provisions of the EU General Data Protection Regulation (GDPR), which came into effect in May 2018 and which will supersede national legislation within the EU Member States.

9.8.5. SNDS (France)

The Bordeaux PharmacoEpi (BPE) platform is certified ISO 9001:v2015 for its activities in pharmaco-epidemiology research. All key study documents will undergo a quality-control review, a scientific review, and an editorial review. Reviewers with expertise in the appropriate subject matter area will provide advice on the design of research study approaches, the conduct and management of the study, and will review results, reports, and other key study documents.

Analysis of SNDS data are supported by a robust quality management system. CNAM data extraction will be validated using the expected population size estimated using the SNDS. All statistical logs are kept and can be provided. In case of interim analyses, the database for the interim analysis is locked and kept for ulterior validation, if needed. All data management and statistical analysis steps will be executed on the BPE secured server according to internal/local SOPs, following guidance from the International Society for Pharmacoepidemiology (ISPE) and ENCePP. Associated programmes, logs, and reports are reviewed and validated by senior data managers, epidemiologists, and statisticians throughout the duration of the project.

9.9. Limitations of the Research Methods

This study is subject to limitations related to both the study design and to the use of secondary healthcare data.

A data-related limitation of this study is the reliance on the accuracy of codes and algorithms to identify outcomes. Exposure identification may be based on immunisation registers, pharmacy dispensing records, general practice records, medical records, or other secondary data sources. The ability to identify specific COVID-19 vaccine products and dates of vaccination in these data sources is described in Section 9.3.1. Errors in the recording of the brand of the vaccine administered could lead to exposure misclassification, although such errors are unlikely and not necessarily differential by vaccine brand. It is possible that vaccination of individuals outside the healthcare system will not be recorded in secondary data sources, although this should not affect neither the matched cohort design (where both exposure groups are vaccinated) nor the SCRI design (where the control risk period is adjacent to the exposure period of the same individual). This study requires 12 months of enrolment in the data source before study start to be eligible, to properly characterise

individuals based on at least 12 months of data history. Because the data will arise from European public health systems where individuals are enrolled for a lifetime, with the exception of moving away from the covered geography, we expect that data history will be available well beyond 12 months before study start for the majority of individuals.

A limitation of the cohort design is the potential for residual or unmeasured baseline confounding. Such confounding can occur if the reasons for receiving a specific brand (i.e., BIMERVAX® vs. non-BIMERVAX®) are associated with the probability or AESI occurrence, and those reasons (or their surrogates) are not accurately measured and/or adjusted for. A prior study evaluating the comparative safety of different COVID-19 vaccines achieved a good confounding control with a design akin to our matched cohort [13]. Of note, much less confounding is expected when recipients of different vaccines are compared than when vaccinated and unvaccinated persons are compared. The SCRI, which compares a time period following vaccination with BIMERVAX® versus a subsequent time period, automatically adjusts for time-invariant confounders. However, the SCRI is not well suited to study outcomes with gradual onset, long latency, or risk periods that are not well known. It also may be subject to bias for outcomes that affect the probability of exposure.

The matching procedure in the cohort design produces a study population (i.e., a set of matched pairs) with a distribution of matching variables representative of those who received BIMERVAX® by matching comparator individuals to exposed individuals based on a prespecified set of baseline variables. Therefore, it will estimate the average causal effect in BIMERVAX® recipients (i.e., in a population that has the distribution of matching variables of the BIMERVAX® recipients). The application of further adjustment via inverse probability weighting will not change the estimand (the causal effect in a population that has the distribution of matching variables of the BIMERVAX® recipients). The average causal effect in the BIMERVAX® recipients and the average causal effect in the whole vaccinated population (with and without BIMERVAX®) should differ only (apart from random variation) if effect modification by any baseline variable exists. This will have to be considered when comparing effect estimates with those from other studies

In the main analysis, we propose to estimate a controlled direct effect of the vaccines on potential adverse events not mediated by infection, by censoring individuals if and when they are diagnosed with a SARS-CoV-2 infection. That is, these risks reflect potential complications arising only from the vaccines themselves. This analysis assumes a complete capture of SARS-CoV-2 infection. If that is not the case (e.g., because infections are underdiagnosed or because infections are diagnosed but not recorded), identified effects can be a mix of true harmful effects plus lower efficacy. We propose to study “pneumonia” because it is not expected to be an adverse event of vaccination but can capture vaccine effectiveness and will serve as an indirect marker of undocumented SARS-CoV-2 infections. Additionally, we propose a sensitivity analysis where individuals are not censored in the event of SARS-CoV-2 infection. This analysis will estimate the total effect of the vaccines on potential AESIs through all causal pathways between the vaccines and outcomes, including those potentially mediated by infection [13]. In times of low circulation of the SARS-CoV-2 virus, the difference between the controlled direct effect and the total effect should be negligible.

A study design–related limitation of both the cohort and SCRI designs is that any uncertainty regarding risk periods will lead to misclassification and attenuation of risk estimates. Adverse events remote from the vaccination date are less likely to be a vaccine effect, but if remote person-time is not assessed, then there is a risk of misclassifying the outcome. The estimation

of cumulative incidence curves with a time zero aligned with the exposure assignment and eligibility assessment lessens the impact of unknown risk periods because they evaluate the whole available follow-up [9].

This PASS study evaluates AESIs that tend to be rare, and COVID-19 booster vaccination may end up being recommended for the elderly and/or sick, which may decrease the study size. Additionally, the proposed cohort design, which is based on matching, may discard exposed individuals who did not find a match. All this can lead to imprecise and poorly informative effect estimates. To mitigate this potential limitation, our matched cohort design will allow for multiple eligibility. Additionally, a proposed sensitivity analysis would analyse all eligible individuals, regardless of whether they found a match.

The outcomes “enhanced COVID-19 disease” (meaning a maladaptive immune response to SARS-CoV-2 infection) and “vaccine-associated enhanced disease” (meaning a maladaptive immune response to SARS-CoV-2 infection promoted by vaccination) will not be evaluated in this study because immune maladaptation cannot be measured nor surrogated within the study data sources. COVID-19 disease and its severity will be studied in the companion postauthorisation effectiveness study sponsored by the MAH. Likewise, the subgroup analysis during breastfeeding and lactation cannot be studied due to lack of data on this status. This will be covered in a companion PASS in C-VIPER.

There is uncertainty about the uptake of a new COVID-19 vaccination booster, in the context of the COVID-19 pandemic emergency ending and multiple other options for vaccination boosters becoming available. This could result into decreased precision of estimates, especially for subgroups (e.g., pregnant women) and certain sensitivity analysis.

10. PROTECTION OF HUMAN SUBJECTS

This is a non-interventional study using secondary data collection and does not pose any risks for individuals. All data collected in the study will be de-identified with no breach of confidentiality with regard to personal identifiers or health information. Each data source research partner will apply for an independent ethics committee review according to local regulations; in addition, RTI Health Solutions as the coordinating centre will obtain approval or exemption from the RTI International IRB.

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

10.1. CPRD

RTI-HS will submit the final study protocol for approval via CPRD’s Research Data Governance Process (https://cprd.com/research-applications). The CPRD has obtained ethical approval from a Multicentre Research Ethics Committee for all observational research using CPRD data without patient involvement; however, the Independent Scientific Advisory Committee may recommend that the Multicentre Research Ethics Committee review the study documentation if any ethical issues arise (Section 9.7.4).

10.2. EpiChron

EpiChron will submit the final study protocol (and the potential updates and/or amendments) to the Research Ethics Committee of the Autonomous Community of Aragon (CEICA; https://www.iacs.es/investigacion/comite-de-etica-de-la-investigacion-de-aragon-ceica/) for approval. EpiChron will also submit the protocol and a data management plan to the IACS Biocomputing Unit to assess and verify the availability of the requested data in the BIGAN platform; its adequacy to the project; and compliance with all security, privacy, and data minimisation requirements required by current regulations. Access to pseudonymised data will then be regularly granted only for the specific purposes of this study.

10.3. SIDIAP

A 5-step procedure takes place before the approval of the study is granted: (1) the researcher(s) must send an application (standardised form available at www.sidiap.org and study protocol) to the SIDIAP team; (2) the application is approved by SIDIAP's Scientific Committee, which evaluates the scientific quality and feasibility of the proposal; (3) the study protocol is approved by the Clinical Research Ethics Committee of IDIAP-Jordi Gol; (4) the principal investigator or coordinator of the study must sign a Good Practice form and, in some cases, an agreement between parties is needed; and (5) a meeting between the research team and the SIDIAP team is arranged to discuss the procedures and set the data extraction. Further information is available online (https://www.sidiap.org/index.php/menu-solicitudesen/application-proccedure).

10.4. VID

Once the final version of the protocol is available, FISABIO needs to develop its own version of the protocol, outlining the tasks to be performed by the research team. This protocol, along with the original version, must receive approval from the Research Ethics Committee. Once the approval from the Ethics Committee is obtained, it is necessary to submit all the documentation to the PROSIGA Committee of the Conselleria de Sanitat. Through meetings with the research team, this Committee grants authorisation for data usage and sets the data extraction process.

10.5. SNDS

Access to the SNDS and its purposes of use are strictly regulated by French law [53]. It is totally forbidden to re-identify individual patients. Access to SNDS data requires approval from the Committee in Health Data Research (Comité éthique et scientifique pour les recherches, les études et les évaluations dans le domaine de la santé [CESREES]) and from the French Data Protection Commission (Commission Nationale de l'Informatique et des Libertés [CNIL]). Usually, 4 to 6 months are required to obtain CESREES and CNIL approvals. Then, an agreement between the CNAM (SNDS data access provider) and the requester needs to be signed to access data extraction. The BPE will oversee requesting access to SNDS data, which have already been used for vaccine studies, including COVID-19 vaccines [54-56].

11. MANAGEMENT AND REPORTING OF ADVERSE EVENTS/ADVERSE REACTIONS

For non-interventional study designs that are based on secondary use of data, such as studies based on medical chart reviews or electronic healthcare records, systematic reviews or meta-analyses, reporting of adverse events/adverse drug reactions is not required. Reports of adverse events/adverse drug reactions should be summarised only in the study report, where applicable [57].

According to the EMA *Guideline on Good Pharmacovigilance Practices (GVP), Module VI – Collection, Management and Submission of Reports of Suspected Adverse Reactions to Medicinal Products (Rev 2)* [57]:

> *"For non-interventional study designs, which are based on secondary use of data, adverse reactions reporting is not required. All adverse events/reactions should be summarized in the final study report."*

Module VIII – Post-Authorisation Safety Studies (Rev 3) echoes this approach. Legislation in the EU further states that for certain study designs, such as cohort studies, particularly those involving EHRs, it may not be feasible to make a causality assessment at the individual case level.

11.1. Other Good Research Practice

This study adheres to the *Guidelines for Good Pharmacoepidemiology Practices (GPP)* [58] and has been designed in line with the ENCePP *Guide on Methodological Standards in Pharmacoepidemiology* [59] and the UK Medicines and Healthcare products Regulatory Agency guidance on the use of real-world data in clinical studies to support regulatory decisions [60]. The *ENCePP Checklist for Study Protocols* [61] has been completed (see Annex 2).

The study is a PASS and will comply with the definition of the non-interventional (observational) study referred to in the International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use tripartite guideline *Pharmacovigilance Planning E2E* and provided in the EMA *Guideline on Good Pharmacovigilance Practices (GVP) Module VIII: Post-Authorisation Safety Studies*, as well as with the 2012 EU pharmacovigilance legislation, adopted on 19 June 2012 [62]. 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 on Good Pharmacovigilance Practices.*

In alignment with GVP Module VIII [2], Section VIII.B.2, Study registration, the study and its protocol will be registered in the EU PAS Register prior to the start of data collection [63]. At completion, the final report, or its summary, will be posted.

The research team and study sponsor will adhere to the principles of transparency and independence in the ENCePP Code of Conduct [5].

The research team will apply for the ENCePP Study Seal [64].

12. PLANS FOR DISSEMINATING AND COMMUNICATING STUDY RESULTS

The study protocol, study progress reports, interim and final study reports will be included in regulatory communications in line with the RMP, Periodic Safety Update Reports, and other regulatory reporting requirements. Study reports will be prepared using a template following the GVP Module VIII Section B.6.3 [2]. See content of reports in Section 9.7.

In its *Guidelines for Good Pharmacoepidemiology Practices (GPP) [58]*, the International Society for Pharmacoepidemiology (ISPE) contends that *"…there is an ethical obligation to disseminate findings of potential scientific or public health importance"*; 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 submitted for publication following guidelines, including those for authorship, established by the International Committee of Medical Journal Editors [65]. When reporting results of this study, the appropriate Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) checklist will be followed [66]. The Consolidated Standards of Reporting Trials (CONSORT) statement [67] refers to randomised studies, but provides useful guidance applicable to non-randomised studies as well.

Communication via appropriate scientific venues (e.g., International Society for Pharmacoepidemiology) will be considered.

In alignment with the EMA GVP *Module VIII: Post-Authorisation Safety Studies* [2], Section VIII.B.5, and the *ENCePP Code of Conduct* [5], the MAH and the investigator will agree upon a publication policy allowing the principal investigator to independently prepare publications based on the study results, irrespective of data ownership. The MAH will be entitled to view the results and interpretations included in the manuscript and provide comments prior to submission of the manuscript for publication. The MAH and the research team are aware that the MAH should communicate to the Agency and the competent authorities of the Member States in which the product is authorised the final manuscript of the article within 2 weeks after first acceptance for publication [2].

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ANNEX 1 LIST OF STAND-ALONE DOCUMENTS

None.

ANNEX 2 ENCePP CHECKLIST FOR STUDY PROTOCOLS

Doc.Ref. EMA/540136/2009

ENCePP Checklist for Study Protocols (Revision 4)

Adopted by the ENCePP Steering Group on 15/10/2018

The European Network of Centres for Pharmacoepidemiology and Pharmacovigilance (ENCePP) welcomes innovative designs and new methods of research. This Checklist has been developed by ENCePP to stimulate consideration of important principles when designing and writing a pharmacoepidemiological or pharmacovigilance study protocol. The Checklist is intended to promote the quality of such studies, not their uniformity. The user is also referred to the ENCePP Guide on Methodological Standards in Pharmacoepidemiology, which reviews and gives direct electronic access to guidance for research in pharmacoepidemiology and pharmacovigilance.

For each question of the Checklist, the investigator should indicate whether or not it has been addressed in the study protocol. If the answer is "Yes," the section number of the protocol where this issue has been discussed should be specified. It is possible that some questions do not apply to a particular study (for example, in the case of an innovative study design). In this case, the answer 'N/A' (Not Applicable) can be checked and the "Comments" field included for each section should be used to explain why. The "Comments" field can also be used to elaborate on a "No" answer.

This Checklist should be included as an Annex by marketing authorisation holders when submitting the protocol of a non-interventional postauthorisation safety study (PASS) to a regulatory authority (see the Guidance on the format and content of the protocol of non-interventional post-authorisation safety studies). The Checklist is a supporting document and does not replace the format of the protocol for PASS presented in the Guidance and Module VIII of the Good pharmacovigilance practices (GVP).

Study title: VAC4EU Postauthorisation Safety Study of BIMERVAX® Vaccine in Europe

EU PAS Register® number:
Study reference number (if applicable):

Section 1: Milestones	**Yes**	**No**	**N/A**	**Section number**
1.1 Does the protocol specify timelines for				
1.1.1 Start of data collection[1]	☒	☐	☐	6
1.1.2 End of data collection[2]	☒	☐	☐	6
1.1.3 Progress report(s)	☒	☐	☐	6
1.1.4 Interim report(s)	☒	☐	☐	6
1.1.5 Registration in the EU PAS Register®	☒	☐	☐	6

[1] Date from which information on the first study is first recorded in the study dataset or, in the case of secondary use of data, the date from which data extraction starts.

[2] Date from which the analytical dataset is completely available.

Section 1: Milestones	**Yes**	**No**	**N/A**	**Section number**
1.1.6 Final report of study results	☒	☐	☐	6

Comments:

Section 2: Research question	**Yes**	**No**	**N/A**	**Section number**
2.1 Does the formulation of the research question and objectives clearly explain:	☒	☐	☐	
2.1.1 Why the study is conducted? (e.g., to address an important public health concern, a risk identified in the risk management plan, an emerging safety issue)	☒	☐	☐	
2.1.2 The objective(s) of the study?	☒	☐	☐	
2.1.3 The target population? (i.e., population or subgroup to whom the study results are intended to be generalised)	☒	☐	☐	
2.1.4 Which hypothesis(-es) is (are) to be tested?	☐	☐	☒	8
2.1.5 If applicable, that there is no *a priori* hypothesis?	☐	☐	☒	

Comments:

Section 3: Study design	**Yes**	**No**	**N/A**	**Section number**
3.1 Is the study design described? (e.g., cohort, case-control, cross-sectional, other design)	☒	☐	☐	9.1
3.2 Does the protocol specify whether the study is based on primary, secondary or combined data collection?	☒	☐	☐	9.1
3.3 Does the protocol specify measures of occurrence? (e.g., rate, risk, prevalence)	☒	☐	☐	9.1.1, 9.7.1
3.4 Does the protocol specify measure(s) of association? (e.g., relative risk, odds ratio, excess risk, incidence rate ratio, hazard ratio, number needed to harm [NNH])	☒	☐	☐	9.1.2, 9.7.2.3
3.5 Does the protocol describe the approach for the collection and reporting of adverse events/adverse reactions? (e.g., adverse events that will not be collected in case of primary data collection)	☒	☐	☐	11

Comments:

Section 4: Source and study populations	**Yes**	**No**	**N/A**	**Section number**
4.1 Is the source population described?	☒	☐	☐	9.2.1
4.2 Is the planned study population defined in terms of:				9.2.2
4.2.1 Study time period	☒	☐	☐	
4.2.2 Age and sex	☒	☐	☐	
4.2.3 Country of origin	☒	☐	☐	
4.2.4 Disease/indication	☒	☐	☐	
4.2.5 Duration of follow-up	☒	☐	☐	

Section 4: Source and study populations		**Yes**	**No**	**N/A**	**Section number**
4.3	Does the protocol define how the study population will be sampled from the source population? (e.g., event or inclusion/exclusion criteria)	☒	☐	☐	9.2.2 9.2.3

Comments:

The planned study population is defined by the detailed inclusion and exclusion criteria.

Section 5: Exposure definition and measurement		**Yes**	**No**	**N/A**	**Section number**
5.1	Does the protocol describe how the study exposure is defined and measured? (e.g., operational details for defining and categorising exposure, measurement of dose and duration of drug exposure)	☒	☐	☐	9.3.1
5.2	Does the protocol address the validity of the exposure measurement? (e.g., precision, accuracy, use of validation sub-study)	☒	☐	☐	9.3.1.4
5.3	Is exposure categorised according to time windows?	☒	☐	☐	9.3.1.4
5.4	Is intensity of exposure addressed? (e.g., dose, duration)	☒	☐	☐	9.3.1.4
5.5	Is exposure categorised based on biological mechanism of action and taking into account the pharmacokinetics and pharmacodynamics of the drug?	☒	☐	☐	9.3.1.4
5.6	Is (are) an appropriate comparator(s) identified?	☒	☐	☐	9.3.1.2

Comments:

Exposure assessments are data source dependant.

Section 6: Outcome definition and measurement		**Yes**	**No**	**N/A**	**Section number**
6.1	Does the protocol specify the primary and secondary (if applicable) outcome(s) to be investigated?	☒	☐	☐	9.3.2
6.2	Does the protocol describe how the outcomes are defined and measured?	☒	☐	☐	9.3.2.1
6.3	Does the protocol address the validity of outcome measurement? (e.g., precision, accuracy, sensitivity, specificity, positive predictive value, use of validation sub-study)	☒	☐	☐	9.3.2
6.4	Does the protocol describe specific outcomes relevant for Health Technology Assessment? (e.g., HRQOL, QALYs, DALYS, healthcare services utilisation, burden of disease or treatment, compliance, disease management)	☒	☐	☐	9.3.2

Comments:

Given the long list of outcomes, further details on the definition, measurement, and validity of outcomes will be provided in the SAP for each contributing data source.

Section 7: Bias		**Yes**	**No**	**N/A**	**Section number**
7.1	Does the protocol address ways to measure confounding? (e.g., confounding by indication)	☒	☐	☐	9.7.2.5
7.2	Does the protocol address selection bias? (e.g., healthy user/adherer bias)	☒	☐	☐	9.1.2.2
7.3	Does the protocol address information bias? (e.g., misclassification of exposure and outcomes, time-related bias)	☒	☐	☐	9.1.2.2

Comments:

The explicit definition of time zero in Section 9.1.2.2 and the alignment of exposure assignment and start of follow-up prevents selection bias and time-related bias.

Section 8: Effect measure modification		**Yes**	**No**	**N/A**	**Section number**
8.1	Does the protocol address effect modifiers? (e.g., collection of data on known effect modifiers, subgroup analyses, anticipated direction of effect)	☒	☐	☐	9.7.2.4

Comments:

Section 9: Data sources		**Yes**	**No**	**N/A**	**Section number**
9.1	Does the protocol describe the data source(s) used in the study for the ascertainment of:				
	9.1.1 Exposure? (e.g., pharmacy dispensing, general practice prescribing, claims data, self-report, face-to-face interview)	☒	☐	☐	9.3.1.4
	9.1.2 Outcomes? (e.g., clinical records, laboratory markers or values, claims data, self-report, patient interview including scales and questionnaires, vital statistics)	☒	☐	☐	9.3.2.1
	9.1.3 Covariates and other characteristics?	☒	☐	☐	9.4
9.2	Does the protocol describe the information available from the data source(s) on:				
	9.2.1 Exposure? (e.g., date of dispensing, drug quantity, dose, number of days of supply prescription, daily dosage, prescriber)	☒	☐	☐	9.4
	9.2.2 Outcomes? (e.g., date of occurrence, multiple event, severity measures related to event)	☒	☐	☐	9.4
	9.2.3 Covariates and other characteristics? (e.g., age, sex, clinical and drug use history, comorbidity, comedications, lifestyle)	☒	☐	☐	9.4
9.3	Is a coding system described for:				
	9.3.1 Exposure? (e.g., WHO Drug Dictionary, Anatomical Therapeutic Chemical (ATC) Classification System)	☒	☐	☐	9.4
	9.3.2 Outcomes? (e.g., International Classification of Diseases (ICD), Medical Dictionary for Regulatory Activities (MedDRA))	☒	☐	☐	9.4
	9.3.3 Covariates and other characteristics?	☒	☐	☐	9.4
9.4	Is a linkage method between data sources described? (e.g., based on a unique identifier or other)	☐	☐	☒	

Comments:

Research partners confirmed the availability of the required information in their data sources prior to engaging in the study. Details regarding the coding systems or linkages available for each data source have been provided in Section 9.4 when relevant.

Section 10: Analysis plan		**Yes**	**No**	**N/A**	**Section number**
10.1	Are the statistical methods and the reason for their choice described?	☒	☐	☐	9.7
10.2	Is study size and/or statistical precision estimated?	☒	☐	☐	9.5
10.3	Are descriptive analyses included?	☒	☐	☐	9.7.1
10.4	Are stratified analyses included?	☒	☐	☐	9.7.2.4

Section 10: Analysis plan	**Yes**	**No**	**N/A**	**Section number**
10.5 Does the plan describe methods for analytic control of confounding?	☒	☐	☐	9.7.2.5
10.6 Does the plan describe methods for analytic control of outcome misclassification?	☐	☐	☒	9.9
10.7 Does the plan describe methods for handling missing data?	☒	☐	☐	9.7.2.7
10.8 Are relevant sensitivity analyses described?	☒	☐	☐	9.7.2.9

Comments:

Outcome misclassification is a data-related limitation acknowledged in Section 9.9.

Section 11: Data management and quality control	**Yes**	**No**	**N/A**	**Section number**
11.1 Does the protocol provide information on data storage? (e.g., software and IT environment, database maintenance and anti-fraud protection, archiving)	☒	☐	☐	9.8
11.2 Are methods of quality assurance described?	☒	☐	☐	9.8
11.3 Is there a system in place for independent review of study results?	☒	☐	☐	9.8

Comments:

Section 12: Limitations	**Yes**	**No**	**N/A**	**Section number**
12.1 Does the protocol discuss the impact on the study results of:				
12.1.1 Selection bias?	☒	☐	☐	
12.1.2 Information bias?	☒	☐	☐	9.9
12.1.3 Residual/unmeasured confounding? (e.g., anticipated direction and magnitude of such biases, validation sub-study, use of validation and external data, analytical methods)	☒	☐	☐	
12.2 Does the protocol discuss study feasibility? (e.g., study size, anticipated exposure uptake, duration of follow-up in a cohort study, patient recruitment, precision of the estimates)	☒	☐	☐	9.9

Comments:

Section 13: Ethical issues	**Yes**	**No**	**N/A**	**Section number**
13.1 Have requirements of Ethics Committee/ Institutional Review Board been described?	☒	☐	☐	10
13.2 Has any outcome of an ethical review procedure been addressed?	☐	☐	☒	
13.3 Have data protection requirements been described?	☒	☐	☐	10

Comments:

Section 14: Amendments and deviations	**Yes**	**No**	**N/A**	**Section number**
14.1 Does the protocol include a section to document amendments and deviations?	☐	☐	☒	

Comments:

Section 15: Plans for communication of study results	**Yes**	**No**	**N/A**	**Section number**
15.1 Are plans described for communicating study results (e.g., to regulatory authorities)?	☒	☐	☐	12
15.2 Are plans described for disseminating study results externally, including publication?	☒	☐	☐	12

Comments:

Name of the main author of the protocol: [redacted]

Date: 12/January/2024

Signature: [redacted]