## POSTAUTHORISATION EFFECTIVENESS STUDY INFORMATION

| | |
|---|---|
| **Title** | VAC4EU Postauthorisation Effectiveness Study of BIMERVAX® Vaccine in Europe |
| **Protocol version identifier** | Final Protocol Version 3.0 |
| **Date** | 31 October 2025 |
| **HMA-EMA Catalogue of RWD Studies number** | EUPAS1000000337 |
| **Active substance** | SARS-CoV-2 virus recombinant spike (S) protein receptor binding domain (RBD) fusion dimer: the original formulation is a heterodimer (covering B.1.351 – B.1.1.7 strains), the adapted formulations are homodimers (Omicron XBB.1.16 – XBB.1.16 strain; Omicron LP.8.1 – LP.8.1 strain).<br>(Anatomical Therapeutic Chemical (ATC) code J07BN) |
| **Medicinal product** | BIMERVAX® emulsion for injection<br>COVID-19 vaccine, recombinant, adjuvanted<br>The term BIMERVAX® includes all variations of the vaccine that may be distributed during the conduct of this study |
| **Product reference** | EU number: EU/1/22/1709 |
| **Procedure number** | EMA number: EMEA/H/C/006058/0000 |
| **Marketing authorisation holder(s)** | HIPRA Human Health, S.L.U.<br>Avda. la Selva, 135, 17170 Amer (Girona)<br>Spain |
| **Joint PASS** | No |
| **Research question and objectives** | To evaluate the effectiveness of BIMERVAX® vaccine compared with use of other COVID-19 vaccines, this study will address the following research question: What is the risk of COVID-19 outcomes after vaccination with BIMERVAX® compared with the risk after vaccination with other COVID-19 vaccines?<br>The primary study objective is to estimate the effect of BIMERVAX® on COVID-19–related outcomes—i.e., COVID-19 requiring hospitalisation or emergency department visits and COVID-19 diagnosis in any setting—compared with other COVID-19 vaccines authorised for the same indication. |

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| **Country(-ies) of study** | The country currently planned for is Spain (ES). Other European countries are under evaluation. |
| **Authors** | [redacted] |

**MARKETING AUTHORISATION HOLDER**

| | |
|---|---|
| **Marketing authorisation holder** | HIPRA Human Health, S.L.U.<br>Avda. la Selva 135<br>17170 Amer (Girona)<br>Spain |
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**APPROVAL PAGE: RTI HEALTH SOLUTIONS ON BEHALF OF THE RESEARCH TEAM**

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

Protocol ID Number: HIPRA-HH-13

Authors [redacted]

Version and Date: 3.0, 31 October 2025 (Final)

This protocol was reviewed by [redacted]

The following person has reviewed the protocol and gives approval on behalf of the BIMERVAX® Postauthorisation Effectiveness Study Research Team:

[redacted]

_____ _____

Date

**APPROVAL PAGE: HIPRA HUMAN HEALTH, S.L.U.**

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

Protocol ID Number: HIPRA-HH-13

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| Authors | [redacted] |
| Version and Date: | 3.0, 31 October 2025 (Final) |

The following people have reviewed the protocol and give their approval:

[redacted]

Date

[redacted]

Date

## 1. TABLE OF CONTENTS

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## 2. LIST OF ABBREVIATIONS

| Abbreviation | Definition |
|---|---|
| ACCESS | vACCine covid-19 monitoring readinESS |
| BMI | body mass index |
| CDM | common data model |
| CHMP | Committee for Medicinal Products for Human Use (of the EMA) |
| CI | confidence interval |
| CONSORT | Consolidated Standards of Reporting Trials |
| COVID-19 | coronavirus disease 2019 |
| CRF | case report form |
| DPT | diphtheria, tetanus, pertussis |
| DRE | Digital Research Environment |
| ED | emergency department |
| EHR | electronic health record |
| EMA | European Medicines Agency |
| ENCePP | European Network of Centres for Pharmacoepidemiology and Pharmacovigilance |
| ES | Spain |
| ETL | extraction, transformation, and loading |
| EU | European Union |
| FAIR principles | findable, accessible, interoperable, re-usable |
| FISABIO | Foundation for the Promotion of Health and Biomedical Research of Valencia Region |
| GDPR | General Data Protection Regulation |
| GPP | Good Pharmacoepidemiology Practices |
| GVP | Guidelines on Good Pharmacovigilance Practices |
| HMA-EMA Catalogue | Heads of Medicines Agencies-European Medicines Agency Catalogue of Real-World Data Studies |
| ICD-10 | *International Classification of Diseases, Tenth Revision* |
| ICD-9 | *International Classification of Diseases, Ninth Revision* |
| 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 |
| OQ | Office of Quality |
| PASS | postauthorisation safety study |
| PRAC | Pharmacovigilance Risk Assessment Committee |
| PSUR | Periodic Safety Update Report |
| QC | quality control |
| Q*n* yyyy | quarter of the calendar year |

| Abbreviation | Definition |
|---|---|
| RR | risk ratio |
| RTI | RTI International |
| RTI-HS | RTI Health Solutions |
| RT-PCR | reverse transcription polymerase chain reaction |
| RWD | real-world data |
| SAP | statistical analysis plan |
| SARS-CoV-2 | severe acute respiratory syndrome coronavirus 2 |
| SES | socioeconomic status |
| SIDIAP | Information System for Research in Primary Care (Sistema d'Informació per al Desenvolupament de la Investigació en Atenció Primària) (Spain) |
| SOP | standard operating procedure |
| STROBE | Strengthening the Reporting of Observational Studies in Epidemiology |
| TVP | polio vaccine |
| UMCU | University Medical Center Utrecht |
| VAC4EU | Vaccine Monitoring Collaboration for Europe study network |
| VID | Valencia Health System Integrated Database |
| VIS | Vaccine Information System (VID) |

## 3. RESPONSIBLE PARTIES

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| **Marketing Authorisation Holder and Funding Institution**<br>**HIPRA Human Health, S.L.U**<br>**Avinguda la Selva 135, 17170 Amer (Girona), Spain** |
|---|
| [redacted] |
| [redacted] |

## 4. ABSTRACT

**Title**: VAC4EU Postauthorisation Effectiveness 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 in individuals 12 years of age and older. The term BIMERVAX® includes all variations of the vaccine that may be distributed during the conduct of this study. In March 2023, the European Commission granted marketing authorisation of BIMERVAX® vaccine for use in the European Union [1]. This study will evaluate the effectiveness of BIMERVAX® vaccine compared with non-BIMERVAX® vaccines using real-world data from European data sources.

**Research question and objectives**:

Overall research question: What is the relative effectiveness of receiving BIMERVAX® vaccine on COVID-19–related outcomes compared with receipt of another authorised COVID-19 vaccine for the same indication?

Objectives:

- The primary objective is to estimate the effect of BIMERVAX® on the following COVID-19–related outcome compared with other COVID-19 vaccines authorised for the same indication:
  - Primary outcome: COVID-19–requiring a hospitalisation or emergency department (ED) visit
- The secondary objective is to estimate the effect of BIMERVAX® on the following COVID-19–related outcome compared with other COVID-19 vaccines authorised for the same indication:
  - Secondary outcome: COVID-19 diagnosis in any setting

**Study design**: A cohort design will be used to estimate the effectiveness of BIMERVAX® on COVID-19–related outcomes compared with other COVID-19 vaccines.

**Population**: The eligible population will be all individuals who have received a dose of BIMERVAX® or a comparator COVID-19 vaccine and are actively enroled in one of the selected European health data sources for at least 12 months before receipt of the vaccination. The study period will begin from the date of first availability of the BIMERVAX® original vaccine in each participating data source and will end 36 months after the start of data collection. The start of data collection will be anchored on the threshold of a total of 4,000 BIMERVAX® doses administered across the participating data sources.

**Variables**:

- Exposures will be based on recorded prescription, dispensing, or administration of COVID-19 vaccines during the study period.

- The outcomes will be based on recorded diagnoses of COVID-19, which will be identified as COVID-19 requiring a hospitalisation or ED visit or COVID-19 diagnosis in any medical care setting.

- 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 comorbidities, immunocompromised status, vaccinations, and others.

**Data sources**: The planned data sources for this study, pending vaccine rollout confirmation, are EpiChron (Spain), Information System for Research in Primary Care (SIDIAP) (Spain), and Valencia Health System Integrated Database (VID) (Spain). Rollout in other European countries will be monitored to evaluate other potential data sources

**Study size**: The study size for the effectiveness study will be determined by the uptake of BIMERVAX® in the participating data sources.

**Data analysis**: The cohort study will estimate the risk of COVID-19–related outcomes among individuals receiving BIMERVAX® compared with that among individuals receiving a contemporary COVID-19 vaccine. The data analysis will be characterised by the following:

- Baseline will be defined as the date on which eligible individuals receive the vaccine (BIMERVAX® or a comparator vaccine). Follow-up starts and eligibility criteria are applied at baseline.

Eligible vaccinated individuals will be followed from baseline until the occurrence of a COVID-19–related outcome, death, disenrolment from the data source, or end of the study period, whichever occurs first.

- The study will estimate the effect of receiving 1 dose of BIMERVAX® versus the effect of receiving 1 dose of other COVID-19 vaccines. Standard epidemiological methods will be used to achieve baseline exchangeability conditional on the measured confounders.

- Outcomes will be treated as time-to-event variables and will be analysed accordingly. Effect estimates will be provided in both relative (e.g., risk ratio) and absolute (e.g., risk differences) scales. Relative vaccine effectiveness will be estimated as 1 minus the risk ratio.

**Milestones**: Key milestones are as follows:

- Protocol submission: 19 September 2023

- Protocol regulatory endorsement (v1.1): 30 May 2024

- Protocol regulatory endorsement (v2.0): 5 June 2025

- Protocol regulatory endorsement (v3.0): estimated Q4 2025-Q1 2026
- Progress report: 29 July 2024
- Final study report: 36 months after administration of at least 4,000 BIMERVAX® doses.

## 5. AMENDMENTS AND UPDATES

None.

## 6. MILESTONES AND TIMELINE

### Table 1. Study Milestones

| Milestone | Date |
|---|---|
| Protocol submission to EMA PRAC (v1.0) | 19 September 2023 |
| Protocol regulatory endorsement (v1.1) | 30 May 2024 |
| Protocol regulatory endorsement (v2.0) | 5 June 2025 |
| Protocol regulatory endorsement (v3.0) | Estimated Q4 2025-Q1 2026 |
| Registration in the HMA-EMA Catalogue | 21 October 2024 |
| Start of data collection[a] | Estimated Q3 2026 (will be anchored on the administration of a least 4,000 doses of BIMERVAX®)[b] |
| Study progress report | 29 July 2024 |
| Interim report | Estimated Q3 2027 (12 months after the start of data collection) |
| End of data collection[c] | Estimated Q4 2028 |
| Final report of study results | Estimated Q3 2029 (36 months after the start of data collection) |

HMA-EMA Catalogue = Heads of Medicines Agencies–European Medicines Agency Catalogue of RWD Studies; PRAC = Pharmacovigilance Risk Assessment Committee; Q*n* yyyy = quarter of the calendar year; RWD = real-world data.

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 "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. The rollout of the BIMERVAX adapted vaccine to be used for the 2025-2026 autumn-winter vaccination campaign in Spain is expected by Q4 2025. 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), led to a global pandemic. The World Health Organization views COVID-19 as a major threat and considers crucial, among other measures, the administration of vaccine to high-risk groups [3]. BIMERVAX® is a recombinant protein-based bivalent variant vaccine developed by HIPRA and is intended for use for active immunisation against COVID-19.

In March 2023, the European Commission granted marketing authorisation of BIMERVAX® (targeting SARS-CoV-2 B.1.351 and B.1.1.7 strains) 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]. In October 2024, the Committee for Medicinal Products for Human Use (CHMP) of the European Medicines Agency (EMA) recommended the marketing authorisation of BIMERVAX® XBB.1.16 (targeting Omicron XBB.1.16 strain) with an indication for active immunisation (i.e., as primary vaccination and as a booster) in individuals aged 16 years or older [4]. In September 2025, the European Commission approved the updated composition of BIMERVAX targeting the new SARS-CoV-2 LP.8.1 variant and extended the indication to include individuals aged 12 years or older. In this protocol, the term BIMERVAX® includes all variations of the vaccine that may be distributed during the conduct of this study

The results of laboratory-based and clinical studies [5,6] 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 was also comparable to that of other COVID-19 vaccines. Based on these results, the CHMP 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, monitoring of the effectiveness of the BIMERVAX® vaccine is needed in European data sources.

As part of Risk Management Plan (RMP) version 2.0 reviewed by the EMA Pharmacovigilance Risk Assessment Committee (PRAC) [7], HIPRA presents the current postauthorisation effectiveness study to be conducted within the Vaccine Monitoring Collaboration for Europe (VAC4EU) study network. This cohort study will evaluate the risk of COVID-19–related outcomes among individuals receiving the BIMERVAX® vaccine compared with that among individuals receiving other COVID-19 vaccines with the same indication.

This postauthorisation effectiveness study is a commitment to the EMA and complies with the European Network of Centres for Pharmacoepidemiology and Pharmacovigilance (ENCePP) code of conduct [8]. 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 effectiveness of BIMERVAX® compared with use of other COVID-19 vaccines with the same indication, this study will address the following research question:

What is the risk of COVID-19–related outcomes after vaccination with BIMERVAX® compared with vaccination with other COVID-19 vaccines for the same indication?

The primary study objective is as follows:

- To estimate the effect of BIMERVAX® on the following COVID-19–related outcome compared with that of other COVID-19 vaccines authorised for the same indication:
  - Primary outcome: COVID-19 requiring a hospitalisation or emergency department (ED) visit

The secondary study objective is as follows:

- To estimate the effect of BIMERVAX® on the following COVID-19–related outcome compared with that of other COVID-19 vaccines authorised for the same indication:
  - Secondary outcome: COVID-19 diagnosis in any setting

Given the evolving nature of the SARS-CoV-2 virus, the vaccine's composition may periodically be updated. Therefore, the effect of BIMERVAX® vaccination on the study outcomes may be evaluated separately by using calendar time periods reflecting periods of different vaccine composition.

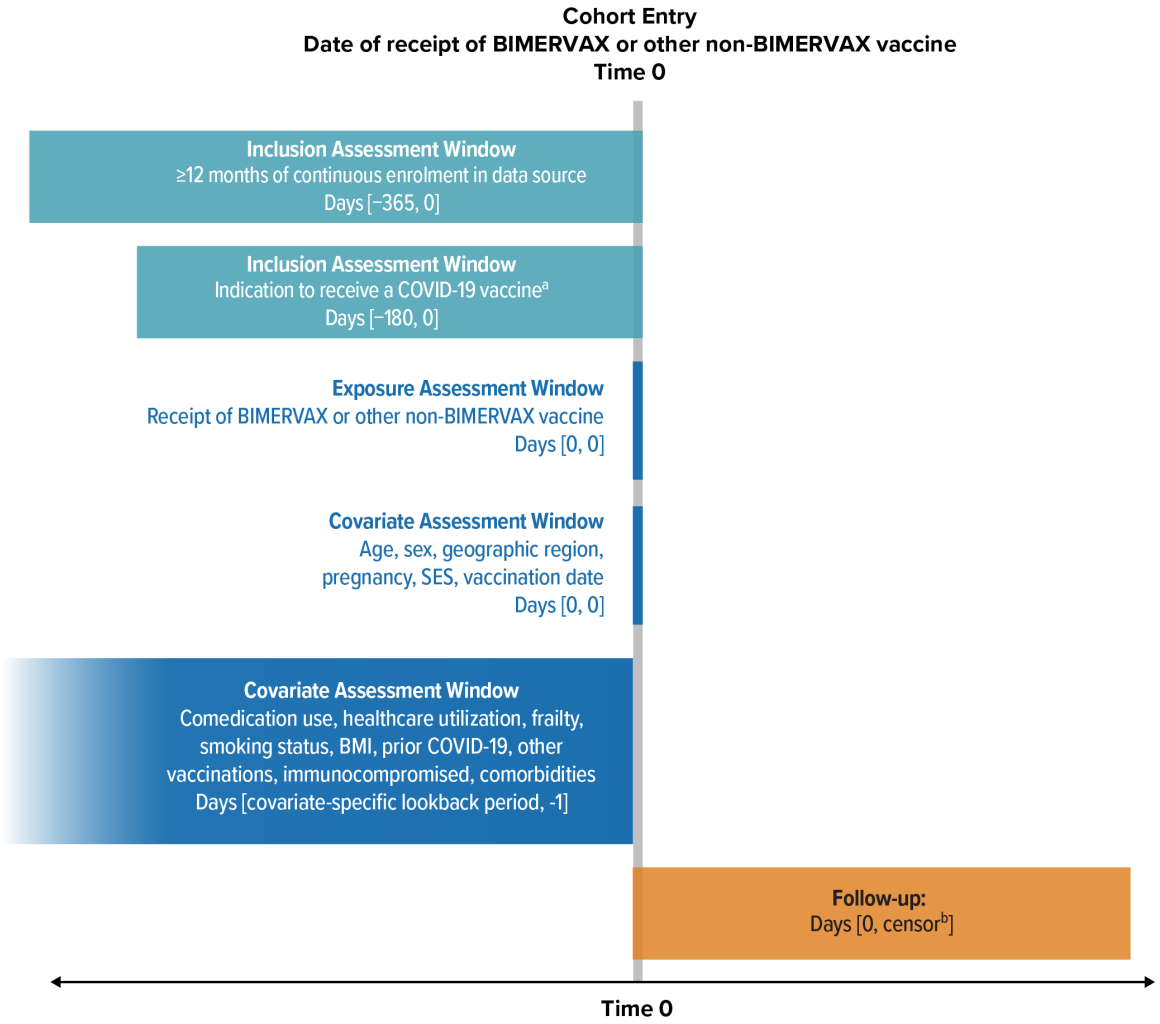
## 9. RESEARCH METHODS

### 9.1. Study Design

This will be a non-interventional, multi-database study based on the secondary use of healthcare data from different European data sources within the VAC4EU network. This study will use a matched cohort design following vACCine covid-19 monitoring readinESS (ACCESS) specifications for vaccine effectiveness studies [9]. No specific hypotheses will be tested during the study described in this protocol.

The matched cohort design (Figure 1) will be a causal inference exercise [10]. The matched cohort design will estimate the incidence of COVID-19–related outcomes after receipt of BIMERVAX® (exposed group) and will compare it with the incidence of the same COVID-19–related outcomes in individuals who received non-BIMERVAX® vaccines (comparator group). Propensity score methods will be used to account for any residual confounding after matching. Additionally, subgroup analyses will be conducted by key variables of interest. In addition, the risk difference and risk ratio will be calculated at specific timepoints during follow-up depending on local guidelines for COVID-19 vaccinations. The time period–specific relative vaccine effectiveness will be estimated as 1 minus the time period–specific risk ratio.

**Figure 1. Matched Cohort Study Design**




BMI = body mass index; COVID-19 = coronavirus disease 2019; SAP = statistical analysis plan; SES = socioeconomic status.

[a] Individuals are eligible to receive a COVID-19 vaccine if they (1) are aged 12 years and older, and (2) have received their most recent COVID-19 vaccine at least 6 months before time zero.

[b] The lookback periods for each covariate will be defined in the SAP with input from data access partners and pending data availability.

[c] Censoring will happen at the occurrence of a study outcome, end of the study period, death, or disenrolment from the data source, whichever occurs first (Section 9.1.4). Additionally, individuals will be censored as per the strategies described in Section 9.7.1.

Source: Figure template from Schneeweiss et al. [11].

### 9.1.1. Causal Contrast or Estimand

The causal contrast of interest will be the observational analogue of a per-protocol effect, i.e., the effect under complete adherence to the following vaccination strategies:

- Receive 1 dose of BIMERVAX® vaccine. Individuals subsequently can receive other COVID-19 vaccinations as per local policies.

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

### 9.1.2. 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 the follow-up for study outcomes will start [12-15], and will be operationalised as follows:

- BIMERVAX® group: date of BIMERVAX® administration
- Non-BIMERVAX® COVID-19 vaccine group: date of administration of the non-BIMERVAX® vaccine, matched to date of BIMERVAX® vaccine in the corresponding match

### 9.1.3. Matching Process

The matching process will aim at being similar to those for prior applications of observational studies comparing head-to-head vaccines for COVID-19 [16-18]. The matching process will ensure that the distribution of calendar time is balanced between exposure groups, thus accounting for calendar periods of different circulating strains of COVID-19 and differing severity. The cohort study will match individuals vaccinated with BIMERVAX® to individuals vaccinated with non-BIMERVAX® vaccines in a 1:1 ratio, using the following variables:

- Calendar date of BIMERVAX® dose (time zero); granularity (e.g., week, month, trimester) to be defined in the statistical analysis plan (SAP)
- Age, in 3-year age groups
- Sex, exact matching
- Geographic location, as appropriate for each data source, exact matching, level of granularity to be defined
- Having received a COVID-19 vaccine in the past (received any COVID-19 vaccine vs. did not receive any COVID-19 vaccine), exact matching

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

### 9.1.4. Follow-up

Individuals will be followed from time zero until the end of the study period, the occurrence of the COVID-19–related outcome under analysis, death, disenrolment from the data source, or a censoring event, whichever occurs first (further details on censoring events are specified in Section 9.7.6).

## 9.2. Setting

### 9.2.1. Source Population

The source population will comprise all individuals actively enroled in each of the selected European health data sources who 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

Individuals must meet the following criteria at time zero (Section 9.1.2) 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 for the same indication
- Be 12 years of age or older
- Have received the most recent 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

### 9.2.3. Exclusion Criteria

None.

### 9.2.4. Study Period

The study period will begin from the date of first availability of the BIMERVAX® original vaccine in each participating data source and will end 36 months after the start of data collection. The start of data collection will be anchored on the threshold of a total of 4,000 BIMERVAX® doses administered across the participating data sources.

## 9.3. Variables

### 9.3.1. Exposure

The exposure strategies will be as follows (see Section 9.1.2 for the definition of time zero):

- BIMERVAX® group: Receive one dose of BIMERVAX® vaccine. Individuals can subsequently receive other COVID-19 vaccinations as per local policies.
- Non-BIMERVAX® vaccine group: Receive one dose of a COVID-19 vaccine approved for the same indication as BIMERVAX®. Individuals can subsequently receive other COVID-19 vaccinations as per local policies, using any brand except BIMERVAX®.

For all study designs, exposure status will be assessed from recorded prescriptions, dispensing, or administration data for BIMERVAX® and other COVID-19 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 data source 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 (EHR) system. COVID-19 vaccination is systematically registered in this register by healthcare professionals. This register will contain all 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 the 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 vaccines administered 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 EHRs. For each patient, SIDIAP will have data on centre and date of administration; dose; brand; reasons for vaccination (e.g., risk 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, 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 are expected to be complete in the vaccination registry used for this study.

### 9.3.2. Outcomes

Preventing COVID-19 severe enough to require hospitalisation or an ED visit is the primary objective of most public health vaccination campaigns. Thus, the primary COVID-19–related outcome evaluated by this study will be as follows:

- COVID-19 requiring hospitalisation or an ED visit, defined as a diagnosis of COVID-19 leading to a hospital admission or ED visit

Outcome algorithms will be tailored to the data source and will consider the nature of the records that have identified the outcome—e.g., primary care, access to hospital care, access to emergency care—to differentiate COVID-19 requiring hospitalisation or emergency care from incidental or minor COVID-19 diagnoses recorded while seeking care for other conditions.

Procedures for COVID-19 testing, reporting, and diagnosis have changed over time, and many COVID-19 infections go unrecognised, untreated, and unrecorded in population databases. Thus, this study will evaluate only medically attended COVID-19 diagnoses to evaluate more meaningful, severe infections rather than all COVID-19 infections.

In addition to the primary hospital/ED–based definition, the following broader secondary outcome will also be evaluated:

- COVID-19 diagnosis, defined as a medical diagnosis of COVID-19 occurring in any healthcare encounter: in a hospital, an ED, or an outpatient setting

### 9.3.3. Covariates

Depending on data availability, the following variables will be assessed relative to time zero. They will be used to characterise populations (Section 9.7.2*),* to define subgroups (Section 9.7.4), and to control for confounding (Section 9.7.5). The corresponding lookback periods are defined in the SAP. Conditions considered by the US Centers for Disease Control and Prevention (CDC) to place the patient at "higher risk (conclusive)" for severe illness from COVID-19 [19] are marked with an asterisk (*).

- Demographics
- Age (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 ED because of COVID-19
  - Previous hospital admission because of COVID-19

- COVID-19 vaccination history
  - Time since last COVID-19 vaccination
  - Prior number of doses of each of the COVID-19 vaccines approved during the study period, e.g., mRNA-1273, ChAdOx1-S, Ad26.COV2.S, Nuvaxovid, BNT162b2, 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*
- Immunocompromising 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 ED visits
  - Primary care utilisation
  - Cancer screening
- Other vaccinations, against:
  - Influenza
  - Pneumococcus
  - DPT (diphtheria, tetanus, pertussis)
  - Trivalent Oral Polio (polio)
  - Trivalent MMR (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); use of frailty scores [20,21] 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 (e.g., wheelchair, cane, oxygen, medical bed, deafness equipment, orthopaedic support and shoes)
  - Daily physiotherapy or nursing act
  - Living institution

### 9.3.4. Subgroups

Subgroups will be defined by the following baseline variables:

- Age group, to be determined based on use patterns and vaccination policies
- Pregnancy status
- Immunocompromised status
- Frail subjects with comorbidities (e.g., chronic obstructive pulmonary disease [COPD], diabetes, chronic neurological disease, cardiovascular disorders)
- Calendar time period, corresponding to the use of original BIMERVAX® and adaptations of BIMERVAX® targeting new variants of SARS-CoV-2

If the size of the subgroup is adequate, a formal comparison will be implemented; otherwise, a description of the estimated risk of COVID-19–related outcomes in that subgroup will be provided.

## 9.4. Data Sources

The timing and countries/regions where BIMERVAX® will be available are, at this time, unknown. The marketing authorisation holder (MAH) anticipates that BIMERVAX® may be supplied to Spain. This study currently aims to use the data sources described in the subsequent sections. 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 the Aragon region of Spain and was 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, ED visits, drug prescriptions, image diagnoses, laboratory tests, diagnostics, vaccinations, medical history, and demographics from the users of the public health system of Aragon, which comprises approximately 2 million individuals with 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 [22]. SIDIAP includes data on clinical and referral events registered by primary healthcare professionals and administrative staff in 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 levels.

### 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 [23]. All information in the VID databases can be linked at the individual level through a single personal identification number. The different VID databases collect information on health system coverage (e.g., health system entitlement, insurance modality), sociodemographic data (e.g., sex, age, geographic location), and 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, hospitalisations, emergency care, 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 *International Classification of Diseases, Ninth Revision* (ICD-9) or the *International Classification of Diseases, Tenth Revision* (ICD-10) for coding diagnosis.

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

## 9.5. Study Size

Study size will be determined by the uptake of BIMERVAX® in the contributing data sources during the study period. Bounds of the 95% confidence intervals (CIs) [24] for different potential values of the true relative vaccine effectiveness estimate are presented in Table 2, under different risk scenarios in the comparator population (informed by European estimates of COVID-19 hospitalisation rates; e.g., hospitalisation rates in Spain have ranged from over 20 cases per 100,000 persons to approximately 1 case per 100,000 persons over the course of 2022 and 2023 [25]) and different sample sizes, assuming complete follow-up.

**Table 2. Confidence Interval Limits for Relative Vaccine Effectiveness Estimates in the Control Group for Different Scenarios of True Risk Ratio and of Study Sizes**

| Number of individuals per group | Risk of COVID-19 in the comparator group | Relative vaccine effectiveness[a] | Lower bound of the CI | Upper bound of the CI |
|---|---|---|---|---|
| 10,000 | 1 per 100,000 | 15% (RR = 0.85) | −795,244% | 100% |
| 10,000 | 1 per 100,000 | 0% (RR = 1.00) | −640,726% | 100% |
| 10,000 | 1 per 100,000 | −15% (RR = 1.15) | −550,975% | 100% |
| 10,000 | 10 per 100,000 | 15% (RR = 0.85) | −1,432% | 95% |
| 10,000 | 10 per 100,000 | 0% (RR = 1.00) | −1,499% | 94% |
| 10,000 | 10 per 100,000 | −15% (RR = 1.15) | −1,577% | 92% |
| 10,000 | 100 per 100,000 | 15% (RR = 0.85) | −112% | 66% |
| 10,000 | 100 per 100,000 | 0% (RR = 1.00) | −140% | 58% |
| 10,000 | 100 per 100,000 | −15% (RR = 1.15) | −168% | 51% |
| 50,000 | 1 per 100,000 | 15% (RR = 0.85) | −4,974% | 99% |
| 50,000 | 1 per 100,000 | 0% (RR = 1.00) | −4,940% | 98% |
| 50,000 | 1 per 100,000 | −15% (RR = 1.15) | −4,989% | 97% |
| 50,000 | 10 per 100,000 | 15% (RR = 0.85) | −210% | 77% |
| 50,000 | 10 per 100,000 | 0% (RR = 1.00) | −245% | 71% |
| 50,000 | 10 per 100,000 | −15% (RR = 1.15) | −281% | 65% |
| 50,000 | 100 per 100,000 | 15% (RR = 0.85) | −28% | 44% |
| 50,000 | 100 per 100,000 | 0% (RR = 1.00) | −48% | 32% |
| 50,000 | 100 per 100,000 | −15% (RR = 1.15) | −68% | 21% |
| 100,000 | 1 per 100,000 | 15% (RR = 0.85) | −1,432% | 95% |
| 100,000 | 1 per 100,000 | 0% (RR = 1.00) | −1,499% | 94% |
| 100,000 | 1 per 100,000 | −15% (RR = 1.15) | −1,577% | 92% |
| 100,000 | 10 per 100,000 | 15% (RR = 0.85) | −112% | 66% |
| 100,000 | 10 per 100,000 | 0% (RR = 1.00) | −140% | 58% |
| 100,000 | 10 per 100,000 | −15% (RR = 1.15) | −168% | 51% |
| 100,000 | 100 per 100,000 | 15% (RR = 0.85) | −13% | 36% |
| 100,000 | 100 per 100,000 | 0% (RR = 1.00) | −32% | 24% |
| 100,000 | 100 per 100,000 | −15% (RR = 1.15) | −50% | 12% |

CI = confidence interval; COVID-19 = coronavirus disease 2019; RR = risk ratio.

[a] Relative vaccine effectiveness was estimated as 1 minus the RR. A relative vaccine effectiveness of 0% indicates equivalent effectiveness between the vaccination groups.

### 9.6. Data Management

This study will be conducted in a distributed manner using a common protocol, the ConcePTION common data model (CDM) [26,27], 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 [28]. 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 ConcePTION project [29]. In this CDM, data are represented in a common structure, but the content of the data remains in its original format. The ETL design for each study will be shared in a searchable catalogue that follows 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 [30]. 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).

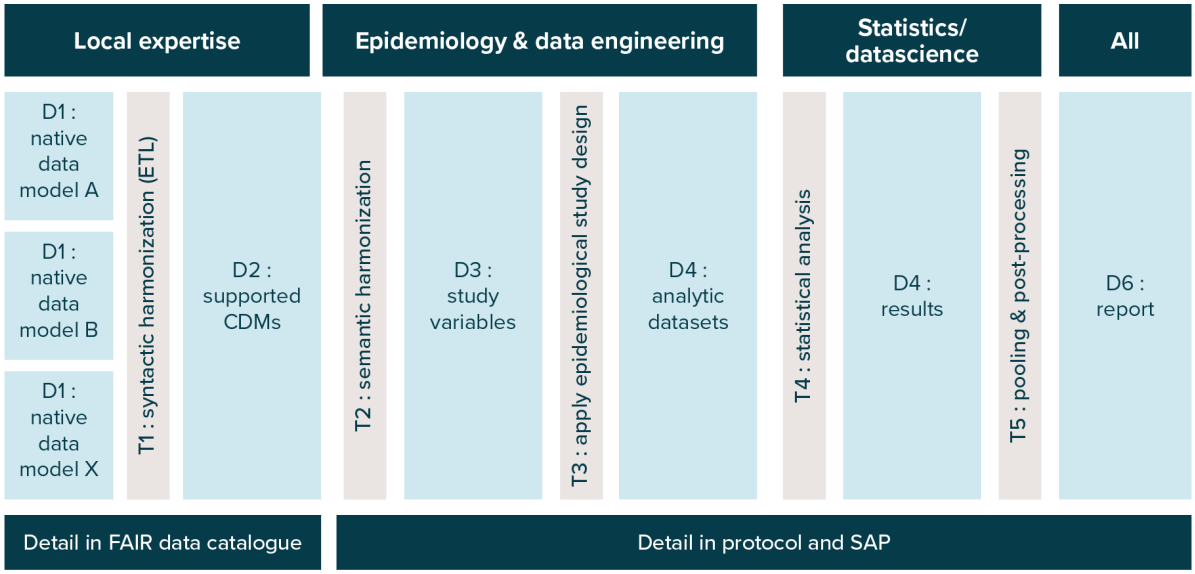
- T2: To reconcile differences between terminologies, a shared semantic foundation will be built for the definition of the events to be analysed by collecting relevant concepts in a structured fashion using a standardised event definition template. The CodeMapper tool [31] was used to create diagnosis code lists based on completed event definition templates for each adverse event of special interest and comorbid risk condition in the ACCESS project. 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; myDRE – Trusted Research Environment). The DRE is a cloud-based, globally available research environment where data are stored and organised securely and where researchers can collaborate. The DRE will be made available through University Medical Center Utrecht (UMCU)/ (https://www.andrea-cloud.eu/).

- T5: Pooled analysis will occur in the DRE and creation of tabulated results (post-processing) will occur locally using SAS (Figure 2).

**Figure 2. Data Management Plan**




CDM = common data model; ETL = extraction, transformation, and loading; FAIR = findable, accessible, interoperable, re-usable; SAP = statistical analysis plan; Tn = transformation step.

Source: Figure from Cid Royo et al. [32].

### 9.6.1. Record Retention

The final study aggregated results sets will be archived and stored on the DRE. Validation of the quality control (QC) of the statistical analyses will be documented. RTI-HS will archive on a specific and secured central drive, the final study protocol and any amendments, the final SAP, statistical programmes, and output files. Study records or documents may also include the analysis 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 patients (sufficient information to link records, e.g., case report forms [CRFs], hospital records), copies of all CRFs, 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, RTI-HS 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 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. After 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 2).

### 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 2). 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 pooled (if needed) for final reporting.

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

### 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 its 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 the General Data Protection Regulation (GDPR) and Good (Clinical) Research Practice still apply to researchers, the DRE offers tools to more easily 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 a workspace is only possible with double authentication using an identification code and password together with the user's mobile phone for authentication.

Selected researchers with access to the workspace within the DRE will be able to upload files. File downloads will only be possible 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 a 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 (submitted on 29 July2024, 3 months after protocol V1.1 endorsement by the EMA) provided confirmation of participating data sources and described the status of project start-up and subsequent activities. The report also identified challenges and proposals for addressing them.

The interim report will provide a description of the cohorts and crude risks of COVID-19–related outcomes in the BIMERVAX® and comparator cohorts. The final report will include all the analyses described below based on available information at the time of the corresponding data extraction.

The final report will be submitted 36 months after the start of data collection and will contain all the analyses described in this protocol. The study periods to be included in the interim report will depend on the data source, linkages, lag times, and time required to obtain the data by the research institutions. Table 3 shows estimations of the available information for each deliverable. In addition, for the interim report, the study period may 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. Estimated Maximum Follow-up for Each Study Report According to Data Source**

| Data sources | Time lag for data updates | Interim report (Q3 2027)[a] | Final report (Q3 2029)[a] |
|---|---|---|---|
| EpiChron (ES) | ≈ 6 months | ≈ 6 months | ≈ 18 months (6 + 12) or 30 months (6 + 24) |
| SIDIAP (ES) | ≈ 6 months | ≈ 6 months | ≈ 18 months (6 + 12) or 30 months (6 + 24) |
| VID (ES) | ≈ 6 months | ≈ 6 months | ≈ 18 months (6 + 12) or 30 months (6 + 24) |

ES = Spain; SIDIAP = Information System for Research in Primary Care (Spain); VID = Valencia Health System Integrated Database (Spain).

[a] Based on administration of a least 4,000 doses of BIMERVAX® expected in Q3 2026. First use of the original vaccine in Spain occurred during 2023.

### 9.7.1. 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, outlined as follows:

- BIMERVAX® group: Eligible individuals will be assigned to this group when they receive a dose of BIMERVAX®.
- Non-BIMERVAX® 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 of BIMERVAX® during follow-up.

Individuals will be followed from time zero (Section 9.1.2) until the censoring described above, death, administrative end of follow-up, or end of the study period, whichever occurs first.

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

### 9.7.2. Descriptive Statistics

The distributions of baseline characteristics by exposure group will be calculated to describe the study cohort and illustrate differences between the groups. For continuous variables, means, standard deviations (SDs), 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.

To describe the relative imbalance of baseline characteristics between exposed and unexposed groups, absolute standardised differences will be calculated for each baseline characteristic [33,34]. An overall standardised difference across all levels will be calculated for multilevel categorical variables [34].

### 9.7.3. Crude Outcome Measures

The risk of the study outcomes will be estimated at days 7 (negative control outcome), 30, 60, 90, 120, 180, and 365 using 1 minus the Kaplan-Meier estimator. Effect estimates will be calculated at specified timepoints 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. The relative vaccine effectiveness at the specific timepoints will be estimated as 1 minus the time period–specific risk ratio [35]. The specific timepoints for outcome evaluation may be updated in each data source based on local guidelines for COVID-19 vaccine administration or campaigns.

Time to outcome will be defined as the time from the baseline date (time zero) until the occurrence of the outcome or censoring (Section 9.3.2 and Section 9.1.4). The variance will be computed using approaches that account for autocorrelation (e.g., the robust estimator or via bootstrapping) [36,37].

### 9.7.4. Subgroup Analyses

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

### 9.7.5. 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 9.3.3) will be used to construct inverse probability weights [38]. 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–related

outcomes in the first 7 days after baseline will be evaluated as a negative control outcome for baseline exchangeability [17]. Additional negative control outcomes may be considered, as appropriate.

Baseline covariate balance after matching and weighting will be assessed by evaluating their standardised mean difference for continuous [33] and categorical [34] variables.

### 9.7.6. Censoring to Estimate the Effect on COVID-19 Outcomes Under Complete Follow-up and Under Complete Adherence to the Vaccination Strategies

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

- *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 COVID-19 as individuals who were disenroled from the database if they had remained in follow-up, conditional on the baseline covariates that were adjusted for (via matching and weighting). This approach ensures that calendar time is equally represented in both exposure groups.

- *Censoring of the matched pair when the individual in the control 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 COVID-19 for individuals who did not deviate from the vaccination strategy would be similar to that for individuals who deviated from the vaccination strategy, had they not deviated, conditional on the baseline covariates that were adjusted for (via matching and weighting).

### 9.7.7. 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.

### 9.7.8. Meta-analysis

A combined time period–specific vaccine effectiveness estimate (measured from the time period–specific RRs estimated from the risk measured at each timepoint) and its 95% CI will be estimated at 30, 60, 90, 120, 180, and 365 days using the DerSimonian-Laird random effects approach [39]. The standard error for each RR will be estimated by the sample SD of the bootstrap replications [40].

Heterogeneity of vaccine effectiveness estimates across data sources will be assessed using the $I^2$ statistic [41]. Regardless of the $I^2$ statistic value, effect estimates (with the highest level of adjustment implemented) will be meta-analysed across databases; however, the $I^2$ statistic and consistency of the direction of the effects will be taken into consideration to interpret the meta-analysis results.

The meta-analysis will be performed for the matched population analyses, for sensitivity analyses of the non-matched population, and for the subgroup of the matched and non-matched population analyses, when conducted.

### 9.7.9. Sensitivity Analyses

The following sensitivity analyses will be implemented:

- *Analysis to evaluate the effect of prior COVID-19 diagnosis on subsequent COVID-19 diagnosis and COVID19 hospitalisations/ED visits*: A sensitivity analysis will be performed excluding patients who had a COVID-19 diagnosis or a COVID-19 hospitalisation/ED visit in 30 days, 60 days, 90 days (recent diagnosis), or 365 days (longer baseline) before time zero.

- *Analysis to evaluate the robustness of the definition of COVID-19 requiring hospitalisation or ED visit*: A sensitivity analysis will be performed identifying all COVID-19 diagnoses occurring in hospital or ED settings.

- *Analysis to avoid discarding information by matching:* In the main analysis, individuals vaccinated with BIMERVAX® for whom a match is not found by the proposed matching variables will be discarded from the analysis. If the number of exposed individuals is scarce, this can contribute to imprecise effect estimates. 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 on top of the variables of the weights used in the main analysis, the remaining the analytical procedures will be the same as those in the main analysis.

### 9.7.10. 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 (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 EpiChron and SIDIAP, though values of 0 can be reported. When distributed outside the research team and the client, the exact number of events will be replaced by $< 5$ or $\leq 10$, 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**

| Rule | EpiChron | SIDIAP, Catalonia | VID, Valencia |
|---|---|---|---|
| Numbers to be masked | 1-4 | 1-4 | NA |
| Text used | < 5 | < 5 | NA |
| Possible to share with research partners | Yes | Yes | Yes |
| Possible to share with HIPRA, which submits report to regulatory authorities | No | No | Yes |
| Comments | | | There must be no identifiable information to be shared |

NA = not applicable; SIDIAP = Information System for Research in Primary Care (Spain); VID = Valencia Health System Integrated Database (Spain).

## 9.8. Quality Control

### 9.8.1. RTI-HS as Coordinating Centre

Standard operating procedures (SOPs) or internal process guidance at each research centre will be used to guide the conduct of the study.

At RTI Health Solutions (RTI-HS), these procedures include internal quality audits, rules for secure and confidential data storage, methods to maintain and archive project documents, QC 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 QC review, senior scientific review, and editorial review.

Experienced RTI-HS programmers will perform the ETL. 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 SOPs. 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 documentation. Such audits will be conducted by the OQ according to established criteria in SOPs 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 with periodic back-up of files. 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, SAP, 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 (for example, 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, and 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) will 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 approval from the Research 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.

Next, 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 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 GDPR, which came into effect in May 2018, and which will supersede national legislation within the EU Member States.

### 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, though 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 the matched cohort design (in which both exposure groups are vaccinated). This study requires 12 months of enrolment in the database 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 in which individuals are enroled 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.

Additionally, this study is reliant on recorded diagnoses of COVID-19 and COVID-19 hospitalisations/ED visits rather than on other measures of COVID-19 (e.g., laboratory-confirmed infection, symptomatic infection). COVID-19 testing and care-seeking behaviour have changed substantially since the beginning of the pandemic; currently, most infections may not result in medical evaluation, testing, or treatment. Thus, this study uses as the primary outcome medical diagnoses from and cases managed in the hospital or ED to identify severe cases in the forms most likely to be meaningful to public health authorities. Milder cases of COVID-19 that are managed only in an outpatient setting will be identified and captured as a part of the broader secondary outcome, i.e., COVID-19 in any care setting.

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 vaccine brand (i.e., BIMERVAX® vs. non-BIMERVAX®) are associated with the probability of acquiring COVID-19, 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 good confounding control with a design akin to our matched cohort [16]. Of note, much less confounding is expected when recipients of different vaccines are compared than when vaccinated and unvaccinated individuals are compared.

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 control 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® vaccination) should differ only (apart from random variation) if effect modification by any baseline variable exists. This possibility will have to be considered when comparing effect estimates with those from other studies.

Additionally, the proposed cohort design, which is based on matching, may discard exposed individuals for whom a match was not found. This can lead to imprecise, poorly informative effect estimates. To mitigate this potential limitation, our matched cohort design will allow for multiple eligibility. Additionally, an alternative analysis, currently described as a sensitivity analysis, could be conducted analysing all eligible individuals, regardless of whether they are matched.

In the context of the ending of the COVID-19 pandemic emergency and multiple options for COVID-19 vaccination already available, there is uncertainty about the uptake of a new COVID-19 vaccination. If the study size is not sufficiently large, this could result in decreased precision of estimates given the relatively small expected effect sizes when comparing vaccines, especially for subgroup analyses and certain sensitivity analyses.

Given the evolving nature of SARS-CoV-2 virus and potential adaptations of BIMERVAX® targeting new variants of SARS-CoV-2, additional subgroup analysis by calendar time reflecting the use of different BIMERVAX® vaccine compositions within each data source will be conducted.

## 10. PROTECTION OF HUMAN SUBJECTS

This is a non-interventional study using secondary data collection and does not pose any risks for patients. All data collected in the study will be 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-HS as the coordinating centre will obtain approval or exemption from the RTI International institutional review board.

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

### 10.1. 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 for 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.

### 10.2. SIDIAP

A 5-step procedure will take place before approval of the study is granted: (i) the researcher(s) must send an application (standardised form available at www.sidiap.org and in the study protocol) to the SIDIAP team; (ii) the application is approved by SIDIAP's Scientific Committee, which will evaluate the scientific quality and feasibility of the proposal; (iii) the study protocol is approved by the Clinical Research Ethics Committee of IDIAP-Jordi Gol; (iv) 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 (v) a meeting between the research team and the SIDIAP team will be arranged to discuss the procedures and set the data extraction process. Further information is available online (https://www.sidiap.org/index.php/en/solicituds-en).

### 10.3. VID

Once the final version of the protocol is available, FISABIO will 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 approval from the Research 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.

## 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 EHRs, systematic reviews or meta-analyses, reporting of adverse events/adverse drug reactions is not required. Reports of adverse events/adverse drug reactions should only be summarised in the study report, where applicable [42].

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) [42]: *"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 summarised in the final study report."*

GVP Module VIII: Post-Authorisation Safety Studies (Rev 3) [2] echoes this approach. Legislation in the EU further states that for certain study designs such as retrospective 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)* [43] and has been designed in line with the ENCePP *Guide on Methodological Standards in Pharmacoepidemiology* [44] and the UK Medicines and Healthcare products Regulatory Agency guidance on the use of real-world data in clinical studies to support regulatory decisions [45]. The *ENCePP Checklist for Study Protocols* [46] has been completed (see Annex 2).

The study is a postauthorisation effectiveness study and will comply with the definition of the non-interventional (observational) study referred to in the International Council for Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use tripartite guideline *Pharmacovigilance Planning E2E* [47] and provided in the EMA *Guideline on Good Pharmacovigilance Practices (GVP) Module VIII: Post-Authorisation Safety Studies* [2], as well as with the 2012 EU pharmacovigilance legislation, adopted 19 June 2012 [48]. The study will comply with the study reporting requirements specified in Module VIII, Section VIII.B.6.3.1. "Progress reports" and VIII.B.6.3.2. "Final study report" of the *Guideline of Good Pharmacovigilance Practices* [2].

In alignment with GVP Module VIII [2], Section VIII.B.2, study registration, the study and its protocol will be registered in the HMA-EMA Catalogue [49] (currently registered with EU PAS number EUPAS000000337) before the start of data collection. 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* [8].

The research team will apply for the ENCePP Study Seal [50].

## 12. PLANS FOR DISSEMINATING AND COMMUNICATING STUDY RESULTS

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

In its *Guidelines for Good Pharmacoepidemiology Practices (GPP)*, the ISPE contends that *"there is an ethical obligation to disseminate findings of potential scientific or public health importance"* [43]; 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 2 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 [51]. When reporting results of this study, the appropriate Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) checklist [52] will be followed. The Consolidated Standards of Reporting Trials (CONSORT) statement [53] refers to randomised studies, but provides useful guidance applicable to non-randomised studies as well.

Communication via appropriate scientific venues, e.g., ISPE, 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* [8], 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 before 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

EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

Doc.Ref. EMA/540136/2009

European Network of Centres for Pharmacoepidemiology and Pharmacovigilance

# ENCePP Checklist for Study Protocols (Revision 4)

Adopted by the ENCePP Steering Group on 15 October 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 Effectiveness Study of BIMERVAX® Vaccine in Europe |

| |
|---|
| **HMA-EMA Catalogue of RWD Studies number:** EUPAS1000000337. |
| **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] | ☒ | ☐ | ☐ | |
| | 1.1.2 End of data collection[2] | ☒ | ☐ | ☐ | |
| | 1.1.3 Progress report(s) | ☒ | ☐ | ☐ | 6 |
| | 1.1.4 Interim report(s) | ☒ | ☐ | ☐ | |
| | 1.1.5 Registration in the EU PAS Register | ☒ | ☐ | ☐ | |
| | 1.1.6 Final report of study results | ☒ | ☐ | ☐ | |

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? | ☒ | ☐ | ☐ | 8 |
| | 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? | ☐ | ☐ | ☒ | |
| | 2.1.5 If applicable, that there is no *a priori* hypothesis? | ☐ | ☐ | ☒ | |

Comments:

| |
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| **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) | ☒ | ☐ | ☐ | 9.7.3 |
| 3.4 | Does the protocol specify measure(s) of association? (e.g. risk, odds ratio, excess risk, rate ratio, hazard ratio, risk/rate difference, number needed to harm (NNH)) | ☒ | ☐ | ☐ | 9.7.3 |
| 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:

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[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 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: | | | | |
| | 4.2.1 Study time period | ☒ | ☐ | ☐ | |
| | 4.2.2 Age and sex | ☒ | ☐ | ☐ | |
| | 4.2.3 Country of origin | ☒ | ☐ | ☐ | 9.2.2 |
| | 4.2.4 Disease/indication | ☒ | ☐ | ☐ | |
| | 4.2.5 Duration of follow-up | ☒ | ☐ | ☐ | |
| 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 |

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 |
| 5.3 | Is exposure categorised according to time windows? | ☒ | ☐ | ☐ | 9.3.1 |
| 5.4 | Is intensity of exposure addressed? (e.g., dose, duration) | ☒ | ☐ | ☐ | 9.3.1 |
| 5.5 | Is exposure categorised based on biological mechanism of action and taking into account the pharmacokinetics and pharmacodynamics of the drug? | ☐ | ☐ | ☒ | - |
| 5.6 | Is (are) (an) appropriate comparator(s) identified? | ☒ | ☐ | ☐ | 9.3.1 |

Comments:

Exposure assessments are data source dependent

| **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 |
| 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) | ☐ | ☒ | ☐ | - |
| 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) | ☐ | ☒ | ☐ | - |

Comments:

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) | ☒ | ☐ | ☐ | 9.7.5 |
| 7.2 | Does the protocol address selection bias? (e.g., healthy user/adherer bias) | ☒ | ☐ | ☐ | 9.1.2 |
| 7.3 | Does the protocol address information bias? (e.g. misclassification of exposure and outcomes, time-related bias) | ☒ | ☐ | ☐ | 9.1.2 |

Comments:

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| The explicit definition of time zero in Section 9.1.2 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) | ☒ | ☐ | ☐ | 9.3.4 |

Comments:

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| **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 |
| | 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 |
| | 9.1.3 Covariates and other characteristics? | ☒ | ☐ | ☐ | 9.3.3 |
| 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:

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| 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? | ☒ | ☐ | ☐ | 9.7.2 |
| 10.4 Are stratified analyses included? | ☒ | ☐ | ☐ | 9.7.4 |
| 10.5 Does the plan describe methods for analytic control of confounding? | ☒ | ☐ | ☐ | 9.7.5 |
| 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? | ☒ | ☐ | ☐ | 9.7.7 |
| 10.8 Are relevant sensitivity analyses described? | ☒ | ☐ | ☐ | 9.7.9 |

Comments:

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| 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:

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| **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:

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| **Section 13: Ethical/data protection 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:

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| **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:

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| **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:

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

Date: 31 October 2025

Signature: [redacted]