# NON-INTERVENTIONAL (NI) STUDY PROTOCOL

## PASS Information

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| **Title** | A Post-Authorisation Safety Study (PASS) of ABRYSVO (Respiratory Syncytial Virus Stabilised Prefusion F Subunit Vaccine) in Pregnant Women and their Offspring in a Real World Setting in Europe and UK |
| **Protocol number** | C3671026 |
| **Protocol version identifier** | Version 5.0 |
| **Date** | 30 Apr 2026 |
| **EU Post Authorisation Study (PAS) register number** | EUPAS1000000399 |
| **Active substance** | Respiratory syncytial virus vaccine (bivalent, recombinant) J07BX05 |
| **Medicinal product** | ABRYSVO |
| **Product reference** | EU/1/23/1752/001-009PLGB 00057/1722 |
| **Procedure number** | EMEA/H/C/006027 |
| **Marketing Authorisation Holder(s)** | Pfizer Europe MA EEIG<br>Boulevard de la Plaine 17<br>1050 Bruxelles<br>Belgium<br><br>Pfizer Limited<br>Ramsgate Road<br>Sandwich<br>Kent<br>CT13 9NJ<br>United Kingdom |
| **Joint PASS** | No |
| **Research question and objectives** | The main research question is: What is the occurrence of safety events of interest, in particular, preterm birth, preterm delivery or any reduction in time between vaccination and live and non-live births, among all pregnant women who |

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| | receive ABRYSVO (and their offspring) compared to a matched group of pregnant women who do not receive ABRYSVO during pregnancy (and their offspring)?<br><br>*Primary objective*<br>The primary study objective is to estimate the incidence, birth prevalence, prevalence ratios and risk ratios (depending on the specific outcome) and time between vaccination and birth (live or non-live) of the following adverse pregnancy, maternal and birth outcomes in women who receive ABRYSVO during pregnancy (and their offspring), compared with a matched group of pregnant women who do not receive ABRYSVO during pregnancy (and their offspring):<br>• *Pregnancy outcomes*<br>o Preterm delivery or birth (less than 37 weeks) among livebirths:<br>▪ Extremely preterm delivery or birth (less than 28 weeks)<br>▪ Very preterm delivery or birth (28 to less than 32 weeks)<br>▪ Moderate to late preterm delivery or birth (32 to less than 37 weeks)<br>o Time between vaccination and birth among live and non-live births (vaccination date for unvaccinated pregnant woman is the vaccination date of their matched vaccinated pregnant woman)<br>o Stillbirth among live and non-live births<br><br>• *Maternal outcomes during pregnancy*<br>o Hypertensive disorders of pregnancy<br>o Guillain-Barré Syndrome (GBS)<br>o Placental abruption<br><br>• *Birth outcomes (at birth)*<br>o Low birth weight among live births<br>o Small for gestational age among live births<br><br>*Secondary objectives*<br>The secondary objectives are:<br>1. To estimate the incidence, birth prevalence, prevalence ratios and risk ratios (depending on the specific outcome) of the above mentioned pregnancy, maternal and birth outcomes and time between |

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| | vaccination and birth (live or non-live) in immunocompromised pregnant women or women with high-risk pregnancies who receive ABRYSVO during pregnancy (and their offspring), compared with a matched group of immunocompromised pregnant women or women with high-risk pregnancies who do not receive ABRYSVO during pregnancy (and their offspring).<br><br>2. To estimate the prevalence ratio of preterm delivery or birth and time between vaccination and birth (live or non-live) between pregnant women who receive ABRYSVO (and their offspring) compared with a matched group of pregnant women who do not receive ABRYSVO during pregnancy (and their offspring), by week of gestation of vaccination. |
| **Country(ies) of study** | Spain (ES), United Kingdom (UK), France (FR), Norway (NO), Denmark (DK), the Netherlands (NL) |
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## 1. TABLE OF CONTENTS

## 2. LIST OF ABBREVIATIONS

| Abbreviation | Definition |
|---|---|
| ACOG | American College of Obstetricians and Gynaecologists |
| ATC | Anatomical Therapeutic Chemical |
| ART | Assisted Reproductive Technology |
| CDC | Centers for Disease Control and Prevention |
| CDM | common data model |
| CHMP | Committee for Medicinal Products for Human Use |
| CPRD | Clinical Practice Research Datalink |
| CRS | Civil Registration System |
| DAP | data access provider |
| DEAP | data expert and access partner |
| DHR | Danish Health Registers |
| DNPR | Danish National Patient Registry |
| DRE | Digital Research Environment |
| DSRU | Drug Safety Research Unit |
| ECDC | European Centre for Disease Prevention and Control |
| EC | Ethics Committee |
| EMA | European Medicine Agency |
| ENCePP | European Network of Centres for Pharmacoepidemiology and Pharmacovigilance |
| EpiChron | EpiChron Research Group |
| ETL | extract, transform, load |
| EU | European Union |
| FDA | Food and Drug Administration |
| FISABIO | Foundation for the Promotion of Health and Biomedical Research of Valencia Region |
| GBS | Guillain-Barré Syndrome |
| GPP | Good Pharmacoepidemiology Practices |
| GVP | Guideline on Good Pharmacovigilance Practices |
| HELLP | Haemolysis Elevated Liver Enzyme Low Platelet |
| HES | Hospital Episode Statistics |
| IBD | Inflammatory Bowel Disease |
| ICD-9 | International Classification of Diseases, ninth revision |
| ICD-10 | International Classification of Diseases, tenth revision |
| ICMJE | International Committee of Medical Journal Editors |
| ICPC | International Classification of Primary Care |
| IPW | inverse probability weighting |
| ISPE | International Society for Pharmacoepidemiology |
| LRTI | lower respiratory tract illness |

| Abbreviation | Definition |
|---|---|
| LRTD | lower respiratory tract disease |
| LMP | first day of last menstrual period |
| MBRN | The Medical Birth Registry |
| N/A | Not applicable |
| NHR | Norwegian Health Registers |
| NIP | National Immunisation Programme |
| NITAG | National Immunisation Technical Advisory Groups |
| NPR | The National Patient Register |
| PASS | post-authorisation safety study |
| PCR | polymerase chain reaction |
| PHARMO | PHARMO Data Network |
| PPRN | PHARMO Perinatal Research Network |
| PrA | pregnancy algorithm |
| PSUR | periodic safety update report |
| PVP | pharmacovigilance plan |
| RMP | risk management plan |
| RR | relative risk |
| RSV | respiratory syncytial virus |
| RSVpreF | respiratory syncytial virus prefusion F vaccine |
| SAP | statistical analysis plan |
| SGA | small for gestational age |
| SIDIAP | Sistema d'Informació per al desenvolupament de la Investigació en Atenció Primària |
| SLE | Systemic Lupus Erythematosus |
| SNDS | Système National des Données de Santé |
| STIZON | Stichting Informatievoorziening voor Zorg en Onderzoek |
| Tdap | Tetanus, diphtheria, pertussis vaccine |
| TTP | trusted third party |
| T0 | Time zero |
| UiO | Universitetet i Oslo |
| UK | United Kingdom |
| UMCU | University Medical Center Utrecht |
| VAC4EU | Vaccine Monitoring Collaboration for Europe |
| VID | Valencia Integrated Database |
| WHO | World Health Organization |

# 3. RESPONSIBLE PARTIES

## Principal Investigator(s) of the Protocol

| Name, Degree(s) | Job Title | Affiliation | Address |
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| Cynthia de Luise, PhD, MPH | Senior Director, Safety Surveillance Research | Pfizer, Inc. | 66 Hudson Blvd E, NY 10001 USA |
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| Emmy Manders | Scientific programmer | | |
| Mattia Cinelli | Scientific programmer | | |

*At the time of this protocol amendment, this individual is no longer affiliated with the study but originally contributed to the development of the protocol.

## 4. ABSTRACT

**Title:** A Post-Authorisation Safety Study of ABRYSVO (Respiratory Syncytial Virus Stabilised Prefusion F Subunit Vaccine) in Pregnant Women and their Offspring in a Real World Setting in Europe and the UK

**Version**: 5.0

**Date**: 29 Apr 2026

**Main authors:** Vjola Hoxhaj[1], Odette de Bruin[1,2] & Miriam Sturkenboom[1] on behalf of the VAC4EU Network ABRYSVO Maternal Immunisation PASS Research team & Cynthia de Luise[3].

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**Rationale and background**

On 23 August 2023, Pfizer's candidate respiratory syncytial virus vaccine (hereafter RSVpreF) was approved by the European Commission under the trade name ABRYSVO for passive protection against lower respiratory tract disease caused by respiratory syncytial virus (RSV) in infants from birth through 6 months of age following maternal immunisation during pregnancy (between Weeks 24 and 36 of gestation). This marketing authorisation is valid in all 27 European Union (EU) member states plus Iceland, Liechtenstein, and Norway. On 21 August 2023, the Food and Drug Administration approved ABRYSVO for active immunisation of pregnant individuals at 32 through 36 Weeks gestational age for the prevention of lower respiratory tract disease (LRTD) and severe LRTD caused by RSV in infants from birth through 6 months of age. In November 2023, ABRYSVO was also approved in the UK by the Medicines and Healthcare Products Regulatory Agency (MHRA) between Weeks 28 and 36 of gestation.

The US, EU, and UK marketing authorisations for ABRYSVO in pregnant women are based on evidence from the MATISSE trial (NCT04424316, C3671008), a global, randomised, double-blinded, placebo-controlled study designed to evaluate the efficacy, safety, and immunogenicity of ABRYSVO against medically attended lower respiratory tract illness (MA-LRTI) and severe MA-LRTI due to RSV in infants born to healthy individuals vaccinated during pregnancy (between week 24 and 36 of gestation).

Immunocompromised pregnant women and women with high-risk pregnancies were excluded from the clinical trials that supported regulatory approvals, and the safety profile of ABRYSVO in these populations is unknown.

This protocol describes a post-authorisation safety study (PASS) to assess the safety of ABRYSVO in pregnant women in select European countries and the UK, with data sources

that can capture exposure and where the target populations, outcomes, and key covariates can be ascertained. This study is an additional pharmacovigilance activity (Category 3 study) in the approved EU risk management plan (RMP) for ABRYSVO (and is also included in the GB/UK-specific Annex to the EU RMP) and is a post-marketing requirement to the FDA.

**Research question and objectives**

The main research question is: What is the occurrence of safety events of interest, in particular, preterm birth, preterm delivery or any reduction in time between vaccination and live and non-live births, among all pregnant women who receive ABRYSVO (and their offspring) compared to a matched group of pregnant women who do not receive ABRYSVO during pregnancy (and their offspring)?

*Primary objective*
The primary study objective is to estimate the incidence, birth prevalence, prevalence ratios and risk ratios (depending on the specific outcome) and time between vaccination and birth (live or non-live) of the following adverse pregnancy, maternal and birth outcomes in women who receive ABRYSVO during pregnancy (and their offspring), compared with a matched group of pregnant women who do not receive ABRYSVO during pregnancy (and their offspring):

- *Pregnancy outcomes*
  - Preterm delivery or birth (less than 37 weeks) among livebirths:
    - Extremely preterm delivery or birth (less than 28 weeks)
    - Very preterm delivery or birth (28 to less than 32 weeks)
    - Moderate to late preterm delivery or birth (32 to less than 37 weeks)
  - Time between vaccination and birth among live and non-live births (vaccination date for the unvaccinated pregnant woman is the vaccination date of their matched vaccinated pregnant woman)
  - Stillbirth among live and non-live births

- *Maternal outcomes during pregnancy*
  - Hypertensive disorders of pregnancy
  - Guillain-Barré Syndrome (GBS)
  - Placental abruption

- *Birth outcomes (at birth)*
  - Low birth weight among live births
  - Small for gestational age among live births

*Secondary objectives*
The secondary objectives are:

1. To estimate the incidence, birth prevalence, prevalence ratios and risk ratios (depending on the specific outcome) of the above-mentioned pregnancy, maternal and birth outcomes and time between vaccination and birth (live or non-live) in immunocompromised pregnant women or women with high-risk pregnancies who

receive ABRYSVO during pregnancy (and their offspring), compared with a matched group of immunocompromised pregnant women or women with high-risk pregnancies who do not receive ABRYSVO during pregnancy (and their offspring).

2. To estimate the prevalence ratio of preterm delivery or birth and time between vaccination and birth (live or non-live) between pregnant women who receive ABRYSVO (and their offspring) compared with a matched group of pregnant women who do not receive ABRYSVO during pregnancy (and their offspring), by week of gestation of vaccination.

**Study design**

This study is a retrospective comparative cohort study using data access providers of the Vaccine Monitoring Collaboration for Europe (VAC4EU) that meet fit-for-purpose criteria. The data collection period will start, retrospectively, on 24 August 2023 (the day after the date of European Commission approval).

**Population**

The target study population is all pregnant women who receive ABRYSVO during pregnancy from 24 weeks' gestation compared to a matched comparator group of pregnant women who do not receive ABRYSVO during pregnancy. To be eligible, women need to be at least 24 weeks' pregnant at the time of vaccination with a maximum of 36 weeks of gestation, and have a look-back period of at least 12 months. There are no age restrictions, and women may have more than one pregnancy.

Time zero will be the day when participants meet all eligibility criteria and exposed women will be vaccinated with ABRYSVO. At Time zero, the exposed women will be matched 1:1 with unexposed women based on gestational age (same week of gestation), calendar time (same calendar week), age (year of birth), immunocompromised status, and high-risk pregnancy status.

**Follow-up**

Follow-up of pregnant exposed and unexposed women will start at Day 1, and end at the earliest of one month after childbirth, maternal death, disenrollment or migration, treatment crossover (unexposed becoming exposed), or end of data availability in the data source. In addition, follow-up for each outcome in women will end at the occurrence of a given outcome.

Follow-up of offspring to assess birth outcomes will last until the earliest of one month of age (to ensure assessment of low birth weight), infant death, disenrollment or migration, or end of data availability in the data source. In addition, follow-up for each outcome in offspring will end at the occurrence of the given outcome.

**Variables**

The exposure of interest is ABRYSVO vaccination which will be obtained from pharmacy dispensing records, general practice records, immunisation registers, vaccination records, medical records, or other secondary data sources. A woman is considered exposed from the date of vaccination until the end of pregnancy for all pregnancy and birth outcomes. The risk windows for Guillain-Barré Syndrome (GBS) are 21 days and 42 days following the date of vaccination.

Outcomes will be identified from each of the data sources based on diagnosis codes or algorithms of diagnosis codes, medication use, procedure codes and information recorded in birth registries. Outcomes of interest for this study are:

- *Pregnancy outcomes*
  - Preterm delivery or birth (less than 37 weeks):
    - Extremely preterm delivery or birth (less than 28 weeks)
    - Very preterm delivery or birth (28 to less than 32 weeks)
    - Moderate to late preterm delivery or birth (32 to less than 37 weeks)
  - Time between vaccination and delivery (in days)
  - Stillbirth
- *Maternal outcomes during pregnancy*
  - Hypertensive disorders of pregnancy
  - Guillain-Barré Syndrome (GBS)
  - Placental abruption
- *Birth outcomes (at birth)*
  - Low birth weight
  - Small for gestational age

Baseline characteristics at Time zero will include demographic and clinical characteristics, comorbidities and composite measures of maternal risk factors for high-risk pregnancies (prior maternal history of gestational diabetes or pre-eclampsia/HELLP and prior history of stillbirth or late miscarriage, small gestational age (SGA) infant or foetal growth restriction (FGR), and child with congenital anomaly), concurrent and past therapies at Time zero including maternal vaccinations, pregnancy characteristics (including prenatal care) and healthcare utilisation. The ConcePTION pregnancy algorithm will be used to identify pregnancies, unless otherwise specified by the data access provider (DAP) and the American College of Obstetricians and Gynaecologists (ACOG) definition will be used for the classification of pregnancy trimester.

Immunocompromised status of participants will encompass primary immunodeficiencies (e.g., combined immunodeficiency and common variable immune deficiency; assessed across the entire look-back period) and secondary immunodeficiencies (e.g., haematological malignancies, transplantation, HIV, immunosuppressive medication use; assessed within 365 days prior to baseline).

**Data sources**

As of 19 January 2024, the United Kingdom (UK) and European Union (EU) countries have approved ABRYSVO for maternal immunisation, but the National Immunisation Technical Advisory Groups (NITAGs) are still deciding on inclusion of ABRYSVO in the routine immunisation schedule. The proposed data sources for this study are Valencia Integrated Database (VID) (Spain), Sistema d'Informació per al desenvolupament de la Investigació en Atenció Primària (SIDIAP) (Spain), EpiChron (Spain), the Norwegian health registries (NHR) (Norway), the Danish health registries (DHR) (Denmark), PHARMO (the Netherlands), the French Administrative Healthcare Database (SNDS) (France), and the Clinical Practice Research Database (CPRD) (UK). The final selection will be based on NITAG decisions regarding maternal immunisation with ABRYSVO and capturing of ABRYSVO and relevant variables in the data sources.

The MAH (market authorisation holder) and members of VAC4EU will follow-up with relevant public health organisations to understand whether and how ABRYSVO will be included in the routine immunisation programs for maternal immunisation.

**Study size**

All individuals meeting eligibility criteria during the study observation period will be included in the study. The size will depend on NITAG decisions about inclusion of ABRYSVO in routine maternal immunisation programs. Therefore, every 6 months after the start of data collection in the first year and yearly thereafter, progress reports will be conducted to monitor uptake of ABRYSVO among pregnant women.

**Data analysis**

Study data will be analysed as a cohort, emulating a clinical trial with one dose of ABRYSVO during pregnancy. Comparative analyses will be based on the estimation of risk/rate ratios of events occurring and measurable during pregnancy, and prevalence ratios for birth outcomes (per total number of live births or live+non-live births, depending on the specific outcome), measurable at birth. Comparison of outcomes by exposure status will be conducted using multivariable generalised linear models. Comparative analyses will control for confounding through matching on calendar time, maternal age, gestational age, immunocompromised status, and high-risk pregnancy. Adjustment for other measurable confounders will be through Inverse Probability Weighting (IPW) for unbalanced covariates. Time from vaccination until birth will be analysed using regression or time-to-event, with gestational age at time of vaccination as a covariate. Analyses will be stratified by immunocompromised status, high-risk pregnancy and gestational week at the time of vaccination. Aggregated results and estimands from each DAP will be combined using two-stage random effects meta-analytic techniques.

**Milestones**

- Protocol submission: on or before 31 March 2024
- Start of data collection: 15 January 2025 (depending on the date of protocol endorsement). Progress reports: to be submitted every 6 months beginning in June 2025 through June 2026, and then annually through June 2028*
- Interim report: 31 December 2026
- End of data collection: 30 March 2029**
- Final report: 28 September 2029**

* Progress Reports #3, #4 and #5 are for submission to FDA only. For EMA and other regulatory agencies, the progress of the study will be described in the PSURs.

** The study will continue until sufficient power to detect a relative risk (RR) of 2.0 for the specified pregnancy and neonatal outcomes have been achieved.

## 5. AMENDMENTS AND UPDATES

| Amendment number | Date | Amendment Type (substantial or administrative ) | Section of protocol changed | Summary of amendment/update | Reason |
|---|---|---|---|---|---|
| 3 | 30 Apr 2026 | Administrative | 2. List of abbreviations | Updated abbreviation table | Inclusion of additional terms |
| 3 | 30 Apr 2026 | Administrative | 3. Responsible parties | Added new personnel involved in the study | To list current team members |
| 3 | 30 Apr 2026 | Administrative | 4. Abstract, and 6. Milestones | Progress Reports #3, #4 and #5 are for submission to FDA only. For EMA and other regulatory agencies, the progress of the study will be described in the PSURs. | To address the request from EMA to describe the progress of the study in the PSURs, beginning with Progress Report #3. |
| 3 | 30 Apr 2026 | Administrative | 6. Milestones | Revised table reallocated footnotes where necessary | To create a new heading and remove footnote 4 for Progress Report #2, 3, 4 and 5 |
| 3 | 30 Apr 2026 | Administrative | 9.5. Study Size. Figure 2 | Minor formatting update to include reference 34 in the bibliography. | To harmonize reference formatting |
| 3 | 30 Apr 2026 | Administrative | Table 5 | Included additional information in the Table 5 body and footnote section for the GBS outcome | To ensure internal consistency |
| 2 | 09 Jan 2026 | Substantial | 7. Rationale and Background | Added the statement that the FDA's vaccine adverse events reporting system, has identified an increase in the number of placental abruptions | To provide most up to date information |
| 2 | 09 Jan 2026 | | Title page, 4: Abstract, and 8. Research questions and objectives | Add placental abruption as a maternal outcome | Placental abruption has been added as a maternal outcome as per FDA request |
| 2 | 09 Jan 2026 | | 4: Abstract; 9.3.3: Outcomes | Added placental abruption in Table 4 and 5. | Placental abruption has been added as a maternal outcomes per FDA request |
| 2 | 09 Jan 2026 | | Table 4 | Added outcome type column | To improve clarity of table |
| 2. | 09 Jan 2026 | | Table 5 | Additional header rows added and addition of risk window for placental abruption. | To improve clarity of table |
| 2 | 09 Jan 2026 | | 9.3.4 Covariates | Added placental abruption to risk factors Table 6; | Placental abruption has been added as a |

| Amendment number | Date | Amendment Type (substantial or administrative ) | Section of protocol changed | Summary of amendment/update | Reason |
|---|---|---|---|---|---|
| | | | | added HEELP to covariate list | maternal outcome per FDA request |
| 2 | 09 Jan 2026 | | 9.5 Study size | Added placental abruption to prevalence Table 10 | Placental abruption has been added as a maternal outcome per FDA request |
| 2 | 09 Jan 2026 | | 9.9 Limitations of the Research Methods | Added limitations related to the determination of placental abruption | Placental abruption has been added as a maternal outcome per FDA request |
| 1 | 13 Nov 2025 | Substantial | Cover page | Added EU Post Authorisation Study (PAS) register number | To update protocol |
| 1 | 13 Nov 2025 | | 2. List of Abbreviations | Updated abbreviation table | Inclusion of additional terms |
| 1 | 13 Nov 2025 | | 3. Responsible parties | Added new personnel involved in the study | To list current team members |
| 1 | 13 Nov 2025 | | 4. Abstract | Added a new author | To list current team members |
| 1 | 13 Nov 2025 | | 6. Milestones | Updated date of registration on the HMA/ EMA Catalogue of RW Studies | To update date of registration |
| 1 | 13 Nov 2025 | | 6. Milestones | Updated date of Progress Report 2 | Incorrect date in initial protocol |
| 1 | 13 Nov 2025 | | 6. Milestones | Revised information on date of interim study report in footnote #5. | To clarify the soonest date when the interim report can be prepared |
| 1 | 13 Nov 2025 | | 7. Rationale and Background | Added the statement that the agency subsequently upgraded the event of GBS to an important identified risk. | To provide most up to date information |
| 1 | 13 Nov 2025 | | 9.2. Settings | Minor formatting changes have been made | Updated to provide clarity consistency with remainder of protocol |
| 1 | 13 Nov 2025 | | 9.2. Settings | Updated Figure 1 footnote | Updated to provide additional context |
| 1 | 13 Nov 2025 | | 9.2.1. Inclusion Criteria, 9.2. Setting. Table 1 and Abstract | Added clarification to the inclusion criterion: *"Vaccinated with ABRYSVO, during mid/late pregnancy (24 weeks of gestation or beyond with a maximum of 36 weeks of gestation),* | Inclusion criteria was updated to provide clarity and consistency with remainder of protocol |

| Amendment number | Date | Amendment Type (substantial or administrative ) | Section of protocol changed | Summary of amendment/update | Reason |
|---|---|---|---|---|---|
| | | | | *or not vaccinated during pregnancy at matched Time zero (comparator)"* | |
| 1 | 13 Nov 2025 | | 9.2.4 Study period | Clarified study period end date and validation timeline. | To provide clarity on the distinction between the end of the study period and the validation phase, without affecting the end of data collection. |
| 1 | 13 Nov 2025 | | 9.3.1. Pregnancy | Minor formatting of Table 3 | Updated to provide clarity and consistency with remainder of protocol |
| 1 | 13 Nov 2025 | | 9.3.1. Pregnancy | Updated data elements and algorithms used to identify pregnancies for this study in NHR and SNDS | To clarify data elements and algorithms in NHR and SNDS |
| 1 | 13 Nov 2025 | | 9.3.3 Outcomes | Added eclampsia in Table 4. | Missing information in initial protocol. |
| 1 | 13 Nov 2025 | | 9.3.4 Covariates | Minor formatting changes have been made | Updated to provide clarity and consistency with remainder of protocol |
| 1 | 13 Nov 2025 | | 9.3.4 Covariates | Revisions made to immunosuppressive treatments and definitions added to acronyms appearing for some medical conditions | To clarify treatments and medical conditions |
| 1 | 13 Nov 2025 | | 9.3.4 Covariates | Minor formatting changes have been made in Table 6.<br>Eclampsia and HELLP have been added as a risk factor for all outcomes and the assessment window for ART has been specified | Updated to provide clarity and consistency with remainder of protocol |
| 1 | 13 Nov 2025 | | 9.5 Study size | Added more detail for clarity and minor formatting changes | Updated to provide clarity and consistency with |

| Amendment number | Date | Amendment Type (substantial or administrative ) | Section of protocol changed | Summary of amendment/update | Reason |
|---|---|---|---|---|---|
| | | | | | remainder of protocol |
| 1 | 13 Nov 2025 | | 9.5 Study size Table 8 | Modified including up-to-date references | Updated to reflect the latest available information |
| 1 | 13 Nov 2025 | | 9.5 Study size Figure 2 | Replaced Figure 2 with a revised table that contains information based on Properzi et al. | Updated to reflect the latest available information |
| 1 | 13 Nov 2025 | | 9.7.6. Small cells count policy | Minor formatting changes have been made in Table 13 | Updated to provide clarity and consistency with remainder of protocol |
| 1 | 13 Nov 2025 | | 13. References | Added reference | To update reference table |
| 1 | 13 Nov 2025 | | 14. List of Tables And 15. List of Figures | Minor formatting changes have been made | Updated to provide clarity and consistency with remainder of protocol |

## 6. MILESTONES

| Milestone | Applicable Regulatory Agency | Planned/Actual Date of Deliverable[1] |
|---|---|---|
| Registration in the HMA-EMA Catalogue of RWD studies | N/A | 13 January 2025 |
| Start of data collection[2,3] | N/A | 15 January 2025 |
| Progress Report 1[4] | All | 30 June 2025 |
| Progress Report 2 | All | 31 December 2025 |
| Progress Report 3 | FDA only. For EMA and other regulatory agencies, the progress of the study will be described in the PSUR | 30 June 2026 |
| Progress Report 4 | FDA only. For EMA and other regulatory agencies, the progress of the study will be described in the PSUR | 30 June 2027 |
| Progress Report 5 | FDA only. For EMA and other regulatory agencies, the progress of the study will be described in the PSUR | 30 June 2028 |
| Interim report[5] | All | 31 December 2026 |
| End of data collection[6,7] | N/A | 30 March 2029 |
| Final study report[7] | All | 28 September 2029 |

1. The schedule is dependent on the protocol endorsement date, uptake of ABRYSVO, approvals for data extraction and contracts with data access providers (DEAPs). Some data extraction approvals may require a final or endorsed protocol.
2. The start of data collection is “the date from which information on the first study subject is first recorded in the study data set or, in the case of secondary use of data, the date from which data extraction into the CDM starts. Simple counts are not part of this definition.
3. Protocol endorsement is anticipated in Quarter 3 of 2024. Deliverable dates will be updated once the protocol endorsement date is known.
4. The first Progress Report is anticipated 9 months after protocol endorsement.
5. The timing of the interim report is dependent on having achieved adequate sample size. The number of exposures triggering the first interim report analysis is 600 vaccinated women based on 80% power, a 2% prevalence rate and targeting a minimal detectable risk

ratio of 2.5. If the combined number of vaccinated participants across all sites is below 600, the interim analysis will be deferred until this threshold is met. However, reaching this threshold earlier than expected will not accelerate the timing of the report; the analysis will proceed according to the predefined schedule.
6. End of data collection is “the date from which the analytical data set is completely available.”
7. The study will continue until sufficient power to detect a RR of 2.0 for the specified pregnancy and neonatal outcomes have been achieved.

## 7. RATIONALE AND BACKGROUND

Respiratory syncytial virus (RSV) is a major cause of lower respiratory tract illness (LRTI) in infants. RSV is the leading cause of bronchiolitis and viral pneumonia in infants, potentially resulting in fatal respiratory distress for infants with underlying cardiopulmonary disease, or in the absence of effective healthcare systems. Globally in 2019, RSV caused 33 million lower respiratory tract infections, resulting in 3.6 million hospitalisations and approximately 100,000 deaths overall(1). About 50% of the worldwide RSV burden is observed in infants under the age of 6 months, with a significant number occurring during the neonatal period. RSV infection is essentially universal by 2 years of age. A systematic review stated that the incidence of RSV infection in Europe is strongly associated with the winter season, with a general pattern of the RSV seasonal peak preceding the corresponding influenza seasonal peak by 6-8 weeks. For Europe, Broberg et al. used European Centre for Disease Prevention and Control (ECDC) data to estimate peak RSV seasonality for 15 European countries for the seasons spanning 2010-16. Across countries, the length of the RSV season in weeks was similar based on sentinel (median 16, range 9-24) and non-sentinel (median 18, range 8-24) surveillance. The peak weeks for RSV detections were likewise similar by both sentinel (median Week 4, range week number 48-11) and non-sentinel (Week 4.5, range 49-17) approaches. RSV detections peaked later, and seasons lasted longer with increasing latitude.(2)In the post-pandemic period, RSV seasonality has shifted, with delayed and intensified outbreaks observed following changes in public health measures, necessitating increased vigilance and preventive measures.

The US, EU and UK marketing authorisations for ABRYSVO in pregnant women are based on evidence from the MATISSE trial (NCT04424316, C3671008)(3), a global, randomised, double-blinded, placebo-controlled study designed to evaluate the efficacy, safety, and immunogenicity of ABRYSVO against medically attended lower respiratory tract illness (MA-LRTI) and severe MA-LRTI due to RSV in infants born to healthy individuals vaccinated during pregnancy (between Week 24 and 36 of gestation).

ABRYSVO contains two recombinant stabilised RSV prefusion F antigens representing subgroups RSV A and RSV B. Prefusion F is the primary target of neutralising antibodies that block RSV infection. Following intramuscular administration, the prefusion F antigens elicit an immune response, which protects against RSV-associated LRTI. In infants born to mothers who were vaccinated with ABRYSVO between Weeks 24 and 36 of gestation, protection against RSV-associated LRTI is due to transplacental transfer of RSV neutralising antibodies.

As immunocompromised pregnant women and women with high-risk pregnancies were excluded from the MATISSE trial, the safety profile of ABRYSVO in these populations is unknown. These populations are listed as missing information in the EU risk management plan (RMP).

Guillain-Barré syndrome (GBS) has been reported in the clinical trial in older adults ≥60 years of age (C3671013). Although GBS has not been reported in clinical trials in pregnant women, it has been voluntarily added by the MAH as an important potential risk in the EU

RMP for both the older adult and maternal populations intended to be vaccinated with ABRYSVO. The agency subsequently upgraded the event to an important identified risk. GBS is included as a prespecified safety event of interest in this study.

The EMA, MHRA and FDA have each approved the vaccine for maternal immunisation at different gestational ages. The EMA concluded that there are no major safety concerns based on the MATISSE trial and therefore decided that the benefits of vaccination are greater than its risks, and that the vaccine can be administered relatively early during pregnancy (e.g., beginning at 24 weeks). The FDA, on the other hand, has noted a small increase in preterm birth rates in the vaccine-receiving cohort in this trial.(4). The FDA's vaccine adverse events reporting system, has identified an increase in the number of placental abruption following vaccination, therefore this event was added as a safety event of interest in this study (5). To avoid the potential risk of preterm birth with use of ABRYSVO, the FDA has approved vaccination of pregnant women at 32 through 36 weeks gestational age. The MHRA has recommended that the vaccine may be given in the third trimester of pregnancy (Weeks 28 to 36 of gestation).

This protocol describes a post-authorisation safety study (PASS) to assess the safety of ABRYSVO in pregnant women in select European countries and in the UK, with data sources that can capture exposure and where the target populations, outcomes, and key covariates can be ascertained.

This study is an additional pharmacovigilance activity (Category 3 study) in the approved EU RMP for ABRYSVO (and is also included in the GB/UK specific Annex to the EU RMP) and is a post-marketing requirement to the FDA.

## 8. RESEARCH QUESTION AND OBJECTIVES

The main research question is: What is the occurrence of safety events of interest, in particular, preterm birth, preterm delivery or any reduction in time between vaccination and live and non-live births, among all pregnant women who receive ABRYSVO (and their offspring) compared to a matched group of pregnant women who do not receive ABRYSVO during pregnancy (and their offspring)?

*Primary objective*
The primary study objective is to estimate the incidence, birth prevalence, prevalence ratios and risk ratios (depending on the specific outcome) and time between vaccination and birth (live or non-live) of the following adverse pregnancy, maternal and birth outcomes in women who receive ABRYSVO during pregnancy (and their offspring), compared with a matched group of pregnant women who do not receive ABRYSVO during pregnancy (and their offspring):

- *Pregnancy outcomes*
    - Preterm delivery or birth (less than 37 weeks) among livebirths:
        - Extremely preterm delivery or birth (less than 28 weeks)

        - Very preterm delivery or birth (28 to less than 32 weeks)
        - Moderate to late preterm delivery or birth (32 to less than 37 weeks)
    - Time between vaccination and birth among live and non-live births (vaccination date for unvaccinated pregnant woman is the vaccination date of their matched vaccinated pregnant woman)
    - Stillbirth among live and non-live births

- *Maternal outcomes during pregnancy*
    - Hypertensive disorders of pregnancy
    - Guillain-Barré Syndrome (GBS)
    - Placental abruption

- *Birth outcomes (at birth)*
    - Low birth weight among live births
    - Small for gestational age among live births

*Secondary objectives*
The secondary objectives are:

1. To estimate the incidence, birth prevalence, prevalence ratios and risk ratios (depending on the specific outcome) of the abovementioned pregnancy, maternal and birth outcomes and time between vaccination and birth (live or non-live) in immunocompromised pregnant women or women with high-risk pregnancies who receive ABRYSVO during pregnancy (and their offspring), compared with a matched group of immunocompromised pregnant women or women with high-risk pregnancies who do not receive ABRYSVO during pregnancy (and their offspring).

2. To estimate the prevalence ratio of preterm delivery or birth and time between vaccination and birth (live or non-live) between pregnant women who receive ABRYSVO (and their offspring) compared with a matched group of pregnant women who do not receive ABRYSVO during pregnancy (and their offspring), by week of gestation of vaccination.

## 9. RESEARCH METHODS

### 9.1. Study Design

This study is a retrospective comparative cohort study of pregnant women who receive ABRYSVO compared with an unexposed pregnant comparator group. As our primary focus is on drawing causal inferences from observational data, we aim to emulate a hypothetical pragmatic randomised trial. This trial would assess the safety of administering one dose of ABRYSVO in pregnant women who receive the vaccine between 24-36 weeks of gestation compared to pregnant women who do not receive ABRYSVO.(6)

In this hypothetical randomised trial, individuals become eligible from 24 weeks of gestation. However, the timing of vaccination can vary. Therefore, participants will be enrolled in a sequence of "weekly trials" based on their gestational age at the time of vaccination. As we

cannot truly randomise participants, we emulate this feature by carefully addressing confounding biases through techniques such as matching and Inverse Probability Weighting (IPW) . Additionally, we will stratify our analyses by immunocompromised status and high-risk pregnancies.

The emulation of target trial conditions will help to reduce bias due to censoring, immortal time, competing events and confounding, improve the interpretability of estimands, and highlight any remaining challenges with the data.(7)

The study will make use of multiple secondary sources of data from electronic health records and claims data that can be linked on an individual level to birth registries or outcomes. Currently, it is not known how maternal immunisation will be organised in each of the participating countries, since NITAGs are still making recommendations, therefore, it is not presently known whether selected data sources will capture the main exposure of interest. Progress Reports will be conducted every 6 months in the first year, and every 12 months thereafter to assess the coverage of ABRYSVO in pregnancy and compare this with national statistics, to ensure comprehensive capture and avoid exposure misclassification in the comparator group.

At Time zero, the day that an individual fulfils eligibility criteria (see Section 9.2.1 and enters the cohort, ABRYSVO-exposed women will be matched (1:1) with an unexposed woman on gestational age (same week of gestation), calendar time (same week), maternal age (year of birth), immunocompromised status, and high-risk pregnancy. A non-exposed comparator group has been chosen since ABRYSVO is the only currently approved maternal vaccine for the prevention of RSV in offspring.

A main analytic concern in this study of late pregnancy is the gestational age at Time zero, which has a direct impact on the prevalence of preterm birth. Therefore, we will match firmly on gestational age, and we will emulate a series of separate target trials with different eligibility criteria according to gestational age, i.e, 24, 25, 26.... 36 weeks. Exposed persons in each trial will be matched to eligible control persons who are unexposed to ABRYSVO on the date of vaccination and who have the same gestational age. When treatment crossover occurs, follow-up is censored, and the person now vaccinated with ABRYSVO can be included in the exposed cohort and matched to a non-vaccinated woman. In addition, women will also be matched on immunocompromised status and high-risk pregnancy status.

Study populations are displayed in Table 1. We aim to include as many eligible pregnancies as possible and will require only that women are eligible for ABRYSVO and have at least one day of follow-up. For analyses of birth outcomes, we will restrict to pregnancies that have follow-up duration to cover the full term of pregnancy.

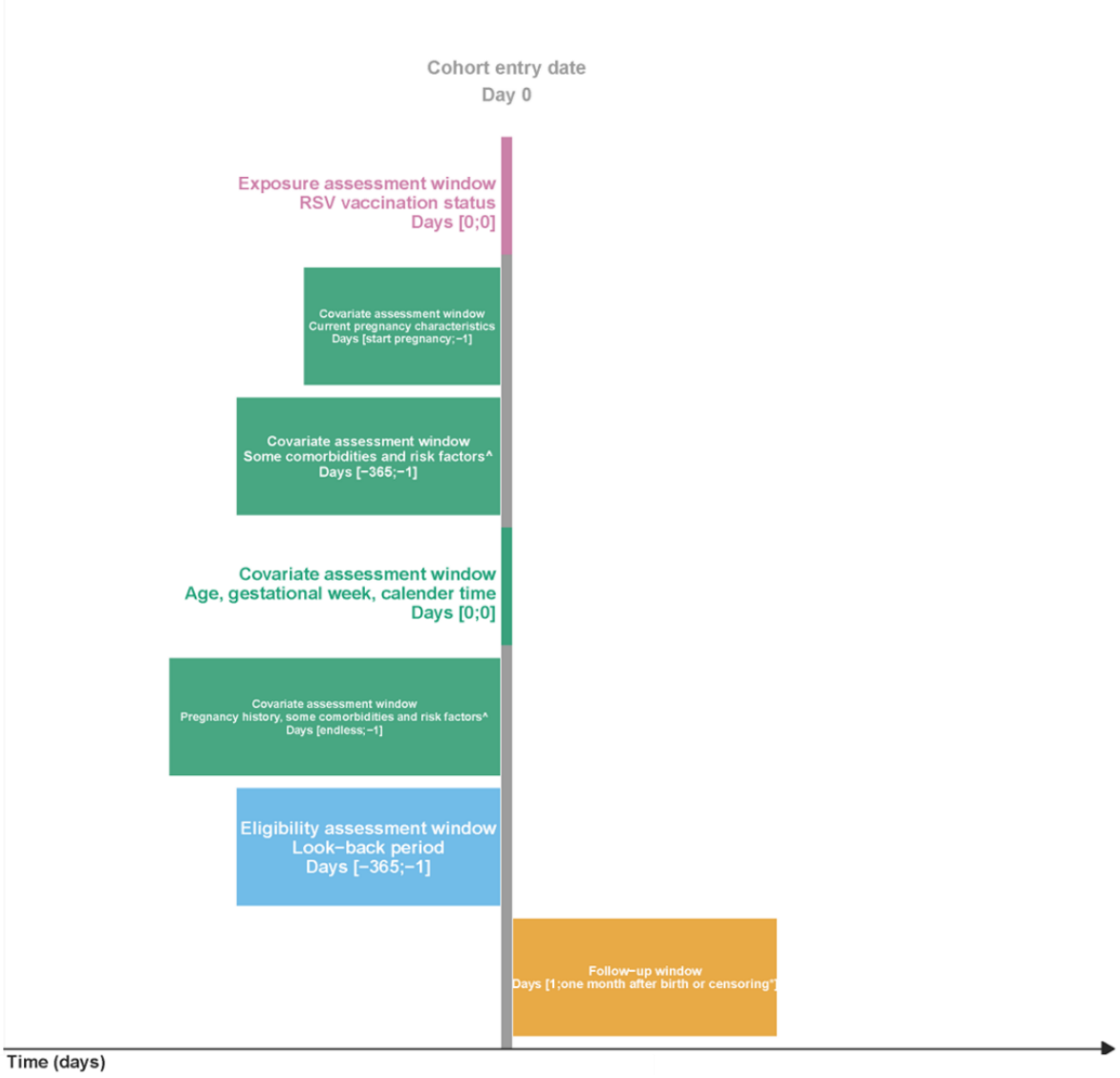
## 9.2. Setting

**Table 1. Study populations per objective**

| Study population | Objective | Description |
|---|---|---|
| Women who are at least 24 weeks pregnant with a maximum of 36 weeks of gestation and eligible for ABRYSVO after the launch date of ABRYSVO. | Primary | We will select females from the data sources, who are pregnant at or beyond the 24th week of gestation after the launch of ABRYSVO. We will use the ConcePTION pregnancy algorithm (PrA) to estimate the start and end date of pregnancy, or DAP-specific algorithms if they exist. We will include ongoing pregnancies to avoid selection bias towards pregnancies that ended prematurely. In some data sources, pregnancy is only observed when pregnancy has ended, in that instance we will include only pregnancies that have at least 10 months of administrative follow-up from the last menstrual period. These 10 months cover the gestational period plus a month to identify outcomes in offspring at birth. |
| Women who are at least 24 weeks pregnant with a maximum of 36 weeks of gestation and eligible for ABRYSVO after the launch date of ABRYSVO and are immunocompromised at Time zero. | Secondary | From the primary cohort we will select matched exposed and non-exposed pairs who are immunocompromised at Time zero. |
| Women who are at least 24 weeks pregnant with a maximum of 36 weeks of gestation and eligible for ABRYSVO after launch date of ABRYSVO and are classified as having a high-risk pregnancy at Time zero. | Secondary | From the primary cohort we will select matched exposed and non-exposed pairs who are classified as having a high-risk pregnancy at Time zero. |
| Women who are at least 24 weeks pregnant after launch of ABRYSVO by week of gestation with a maximum of 36 weeks of gestation. | Secondary | From the primary cohort we will select matched exposed and non-exposed pairs by week of gestation at Time zero. |

Figure 1 provides an overview of the data that will be assessed for eligibility to enrol in the study, and the timing.

**Figure 1. Schematic illustration of study design**




*Censoring includes death, disenrollment or migration, end of data availability in the data source, treatment crossover (unexposed becoming exposed) or occurrence of a given outcome.
^ Chronic comorbidities and risk factors will be assessed from database entry to receipt of ABRYSVO while time-varying comorbidities and risk-factors from a minimum of 1 year (365 days) and a maximum of 10 years prior to Time zero to receipt of ABRYSVO

Figure based on Schneeweiss et al.(8)

### 9.2.1. Inclusion Criteria

The target population will comprise pregnant women at or beyond the 24$^{th}$ week of gestation who have at least 12 months of look-back period in the data source and received ABRYSVO during pregnancy or were unexposed during pregnancy. A woman may have more than one pregnancy. Pregnancies in birth registers are only recorded at birth. To avoid selection of

shorter-term pregnancies when pregnancies are identified only at birth, women must have at least 10 months of administrative follow-up from the last menstrual period (LMP) in the data source unless they died, for all outcomes in those data sources.(7) These 10 months cover the gestational period plus a month to identify outcomes in offspring at birth.

Participants must meet all the following inclusion criteria to be eligible for inclusion in the study:

1. Women (no age restriction) identified to be pregnant
2. Date of (LMP+24 weeks) is after the start of the study period (24 August 2023)
3. Enrolled in the healthcare system for at least 12 months (to ensure records exist) prior to Time zero
4. Vaccinated with ABRYSVO, during mid/late pregnancy (24 weeks of gestation or beyond with a maximum of 36 weeks of gestation), or not vaccinated during pregnancy at matched Time zero (comparator)
5. At least one day of follow-up for maternal outcomes
6. At least 10 months of follow-up after LMP for birth and pregnancy outcomes

### 9.2.2. Exclusion Criteria

Participants meeting the following criteria will not be included in the study:

1. Less than 12 months of look back period at Time zero.
2. Birth registry ID not linkable to other required databanks.
3. Exposure to ABRYSVO prior to current pregnancy or before 24$^{th}$ week gestation (vaccination in a prior pregnancy is permitted).
4. Exposure to any other RSV vaccine at any time during current pregnancy

After application of all the eligibility criteria, the study population will include pregnant women who have received ABRYSVO, and unexposed pregnant women.

### 9.2.3. Follow Up

Time zero is the day that an individual fulfils eligibility criteria and enters the cohort. At Time zero, ABRYSVO-exposed women will be matched (1:1) with unexposed women on gestational age (same week of gestation), calendar time (same week), maternal age (year of birth), immunocompromised status, and high-risk pregnancy.

Follow-up of the exposed and unexposed women will start at Day 1, and end at the earliest of 1 month after birth, maternal death, disenrollment or migration, end of data availability in the data source, or treatment crossover (unexposed becoming exposed). Follow-up of the exposed and unexposed women will also end when the individual receives any other RSV vaccine during current pregnancy (i.e., they will be censored). In addition, follow-up for each outcome in women will end at the occurrence of a given outcome.

Treatment crossover (protocol violation) is when the formerly unexposed matched pregnant woman receives vaccination with ABRYSVO during follow-up. We will censor the unexposed woman upon treatment violation, but not the exposed woman when treatment crossover occurs, to maintain power, but we will correct for selective censoring by using censoring weights. In a sensitivity analysis, we will censor both exposed and non-exposed matched pregnant women, when treatment violation occurs in the formerly unexposed person. When an unvaccinated woman gets vaccinated, she is eligible for inclusion in the vaccinated cohort.

Follow-up of offspring to assess birth outcomes will last until the earliest of one month of age (to ensure assessment of low birth weight), death, disenrollment or migration, or end of data availability in the data source. In addition, follow-up for each outcome in infants will end at the occurrence of the given outcome.

### 9.2.4. Study Period

Data collection will start on 15 January 2025 and capture data retrospectively from 24 August 2023 (the day after European Commission approval) onwards. Data extraction will be conducted for the Progress Reports, and the number of exposures will trigger reporting (Table 2). The study period over which inclusion is possible is from 24 August 2023 until the last data availability. Therefore, the end date of the study period may vary across DEAPs, using the most up-to-date data available by September 2028. Then, validation will occur until end of data collection scheduled on March 2029.

**Table 2. Dates of end of data availability for each Progress Report.**

| Data Source | VID | SIDIAP | EpiChron | NHR | DHR | PHARMO[1] | SNDS | CPRD |
|---|---|---|---|---|---|---|---|---|
| Progress Report 1 (June 2025) | October 2024 | December 2024 | October 2024 | December 2023 | December 2024 | April 2025 (unlinked) Dec 2023 (linked) | NA | October 2024 |
| Progress Report 2 (December 2025) | October 2024 | June 2025 | April 2025 | December 2024 | December 2024 (same data as PR1) | October 2025 (unlinked) December 2024 (linked) | NA | March 2025 |
| Progress Report 3 (June 2026) | October 2025 | December 2025 | October 2025 | December 2024 | December 2025 | April 2026 (unlinked) December 2024 (linked) | NA | October 2025 |
| Progress Report 4 (June 2027) | October 2026 | December 2026 | October 2026 | December 2025 | December 2026 | April 2027 (unlinked) December 2025 (linked) | NA | October 2026 |
| Progress Report 5 (June 2028) | October 2027 | December 2027 | October 2027 | December 2026 | December 2027 | April 2028 (unlinked) December 2026 (linked) | NA | October 2027 |

**Table 2. Dates of end of data availability for each Progress Report.**

| Data Source | VID | SIDIAP | EpiChron | NHR | DHR | PHARMO[1] | SNDS | CPRD |
|---|---|---|---|---|---|---|---|---|
| Final Study Report (Sep 2029) | October 2028 | December 2028 | October 2028 | December 2027 | December 2028 | April 2029 (unlinked) December 2027 (linked) | NA | October 2028 |

1 Unlinked data originates from the in-house general practitioner (GP) and outpatient pharmacy, while linked data is connected to the perinatal registry.
Abbreviations: The Valencia Health system Integrated Database (VID); The Information System for Research in Primary Care (Sistema d'Informació per al Desenvolupament de la Investigació en Atenció Primària (SIDIAP); EpiChron Research Group, Aragon Health Research Institute (IIS Aragón) (EpiCHron); Norwegian Health Registers (NHR); Danish Health Registers (DHR); PHARMO Data Network (PHARMO); The Système National des Données de Santé (SNDS); The Clinical Practice Research Datalink (CPRD)

## 9.3. Variables

### 9.3.1. Pregnancy

**Identification of pregnancies**

Identification of pregnancies and pregnancies start date, varies across data sources. In several data sources that link with birth registries, pregnancies are only identified when they end, since records are generated at birth. During the ConcePTION project an algorithm was created that can also identify ongoing pregnancies, using different types of data such as diagnostic data and procedures that relate to pregnancy.(9)This algorithm was applied in several published EMA-requested studies and is tailored to each DAP.(10)

The algorithm allows the identification of pregnancies from 4 streams of information:

- stream PROMPTS: uses data source-specific information from birth registries, terminations registries, and spontaneous abortion registries: the existence of one of such record implies that a pregnancy has ended.
- stream EUROCAT: records of the EUROCAT table in the Common Data Model (CDM).
- stream CONCEPTSETS: diagnostic codes from the EVENTS or procedure codes from the PROCEDURES or codes from the EVENTS file referring to an end or an ongoing pregnancy.
- stream ITEMSETS: variables from ordinary healthcare that are only populated when a woman is pregnant. The resulting sets of pregnancies of the same person are then compared with each other, to identify which pregnancies are the same, recorded on multiple occasions.

The algorithm first identifies pregnancies from any possible records and subsequently establishes the start and end date of pregnancy by processing all available information in a hierarchical manner. Hierarchy is based on how the identification of the start and end dates of the pregnancy was performed.

VAC4EU(11,12)has adopted the ConcePTION algorithm to determine the start and end date of a pregnancy, but data sources that have their own validated algorithms can use those as well (Table 3). We aim to include all pregnancies (ongoing and ended at the end of follow-up) for the analyses of maternal and pregnancy outcomes. To avoid selection of shorter-term pregnancies when pregnancies are identified only at birth, women must have at least LMP+10 months follow-up. For birth outcomes we will limit the analysis to pregnancies that completed in a livebirth or non-live birth after 20 weeks of gestation.

Upon use of ongoing pregnancies, we include pregnancies that either have an unknown outcome or end after the end of follow-up. Unknown outcomes of completed pregnancies may be due to lag time in data update or elected/spontaneous non-recorded abortions. Since the timing of ABRYSVO vaccination should occur after the period of spontaneous abortions, we assume unknown outcomes will mostly be lag times in data updates.

**Table 3. Data elements and algorithms used to identify pregnancies for this study**

| Data Source | Algorithm for LMP identification (ConcePTION or DAP algorithm) | End of pregnancy identification algorithm (ConcePTION or DAP algorithm) | Inclusion of ongoing pregnancies algorithm (ConcePTION or DAP algorithm) | Streams of information used for ConcePTION algorithm | Birth register linkage delay |
|---|---|---|---|---|---|
| **VID** | ConcePTION PrA | ConcePTION PrA | ConcePTION PrA | Population database, hospital registry and metabolopathies database (Mother-child linkage) | No |
| **SIDIAP** | ConcePTION PrA | ConcePTION PrA | ConcePTION PrA | ASSIR variables (Attention to sexual and reproductive health), Mother-child linkage (70%) | No |
| **EpiChron** | ConcePTION PrA | ConcePTION PrA | ConcePTION PrA | Mother-child linkage | No |
| **NHR** | ConcePTION PrA | ConcePTION PrA | ConcePTION PrA | Medical birth registry | Every June the registry has updated data for the prior year |
| **DHR** | ConcePTION PrA and/or own depending on source of data | ConcePTION PrA and/or own depending on source of data | NA but will explore inclusion of ongoing pregnancies from GP records ConcePTION PrA and/or own depending on source of data | Can potentially use all except EUROCAT, subject to additional development | No |

**Table 3. Data elements and algorithms used to identify pregnancies for this study**

| Data Source | Algorithm for LMP identification (ConcePTION or DAP algorithm) | End of pregnancy identification algorithm (ConcePTION or DAP algorithm) | Inclusion of ongoing pregnancies algorithm (ConcePTION or DAP algorithm) | Streams of information used for ConcePTION algorithm | Birth register linkage delay |
|---|---|---|---|---|---|
| **PHARMO** | LMP from Perined register | Own (because of linkage to Perined Perinatal Registry) | NA (because of linkage to Perinatal Registry) | NA (because of linkage to Perinatal Registry) | 1.5-year lag time (compared to 1 year lag time for in-house databases of the PHARMO data network) |
| **SNDS** | LMP available in each pregnancy inpatient stay (monitoring, delivery...) | Own (Blotière et al., 2018) and CONCEPTION PrA | CONCEPTION PrA | 1. Hospital diagnoses and GHM data (Diagnosis Related Groups – Groupes homogenes de malades)<br>2. In and out patients acts and procedures (CCAM – Classification Commune des Actes Medicaux)<br>3. In and out patient laboratory analyses (NABM – Nomeclature des Actes de Biologie Medicale) | NA (no linkage with birth registry), pregnancy data are available only in inpatient data (data of year N-1 are available from Q3 year N) |
| **CPRD** | LMP - based on the algorithm used by CPRD to generate the CPRD Aurum Pregnancy Register. | Own - based on the algorithm used by CPRD to generate the CPRD Aurum Pregnancy Register. | Own - based on the algorithm used by CPRD to generate the CPRD Aurum Pregnancy Register. | Own - based on the algorithm used by CPRD to generate the CPRD Aurum Pregnancy Register. | Approximately 2 months. |

*Pregnancy Algorithm (PrA); The Valencia Health system Integrated Database (VID); The Information System for Research in Primary Care (Sistema d'Informació per al Desenvolupament de la Investigació en Atenció Primària (SIDIAP); EpiChron Research Group, Aragon Health Research Institute (IIS Aragón) (EpiCHron); Norwegian Health Registers (NHR); Danish Health Registers (DHR); PHARMO Data Network (PHARMO); The Système National des Données de Santé (SNDS); The Clinical Practice Research Datalink (CPRD)*

## Description of specific DAP specific algorithms and information

### Pregnancy identification in SNDS (France)

Algorithms are available in SNDS to identify pregnancies. Following the publication by Blotière (2018), the pregnancy identification algorithm identifies pregnancies based on

discharge diagnoses and medical procedures associated with pregnancy outcomes (live births, stillbirths, elective abortions, therapeutic abortions, spontaneous abortions, and ectopic pregnancies) recorded in the French national insurance database (DCIR) or the French hospital discharge database (PMSI). In the Blotière (2018) study, when records indicated different outcome dates within a certain timeframe, the later record was retained (ie, 28 weeks for births, 6 weeks for terminations). Records with unknown women identifiers were removed (some records cannot be linked to other records in the data source), as were duplicate records. Then, pregnancy termination codes that appeared during a pregnancy episode ending in a delivery were removed; pregnancy terminations in the first 10 weeks after a delivery were also removed. Finally, pregnancy outcomes were categorised into live births, stillbirths, spontaneous and other types of abortions, and abnormal products of conception. Information on time since LMP, gestational age, the date of the first prenatal medical examination, dates of the ultrasounds, and date of the pregnancy outcome were used to estimate the dates of the beginning and end of pregnancy.

Linkage between maternal and neonatal data for births occurring at or later than 22 weeks of gestation is possible within the PMSI using a common identifier that is recorded for both the delivery stay and the birth stay.

**CPRD Aurum Pregnancy Register:**

The CPRD Aurum Pregnancy Register is derived from the primary care data and contains a list of all pregnancy episodes within the CPRD Aurum database, approximately 17 million pregnancies. The CPRD Aurum Pregnancy Register is developed using an algorithm and contains a number of data variables including the start and end of pregnancy, trimester dates and the outcome of the pregnancy.

The ability to study exposures before and during pregnancy, maternal/foetal complications, and outcomes of pregnancy in the CPRD depends crucially on the identification of pregnancy episodes. Some important examples are pharmacoepidemiology studies (drug and vaccine safety during pregnancy and maternal vaccine uptake and effectiveness). Because the precise time-period during which a woman is pregnant can be difficult to ascertain in the data, an algorithm has been developed to identify and maximise the use of records relating to the timing and duration of pregnancy, the type of pregnancy outcome (live birth, stillbirth or pregnancy loss), and additional features pertaining to the pregnancy.

A list of more than 6,000 pregnancy-related SNOMED, Read and local EMIS® codes and numunitids, categorised according to the type of code (antenatal, pregnancy outcome [including delivery and pregnancy loss codes], postnatal, etc.), are used to identify patients who had a pregnancy. Pregnancy-related records are extracted from the Observation file and the EMIS Diary Table of all female patients between the ages of 11 and 49 years. Delineating unique pregnancy episodes involves first identifying the end of each pregnancy (when an

outcome was recorded) and estimating the pregnancy end date. The end date is then used as a point of reference from which to estimate the start of the pregnancy, in combination with additional data (when available) on gestational age, the estimated date of delivery, conception, or first day of a woman's last menstrual period (LMP).

**CPRD Mother-Baby Link**

CPRD has developed a probabilistic mother-baby link algorithm, based on data recorded in the primary care medical record. This links likely mother-baby pairs within the CPRD Aurum database, based on household number plus maternity information from the mother's primary care record, the infant's month of birth and care records of newly registered babies.

CPRD holds a practice-specific household number that can be used to ascertain whether people are living within the same household. This is primarily based on residence but, the existence of this variable allows us to link members of families together, and particularly mothers with their children. Furthermore, because both pregnancy and delivery information are recorded during the long follow-up time within CPRD primary care data, we are able to follow some children from conception rather than just from birth. This means the CPRD primary care data can be used to undertake the sort of studies that require information in all three trimesters as well as beyond birth.

**PHARMO-Perined linkage**

Perined is a Dutch nationwide registry in which medical data around pregnancy and birth are included from pregnancies with a gestational age of at least 16 weeks (including terminated pregnancies and stillborn). It is a linked database combining medical registries from four professional groups that provide perinatal care: general practitioner, midwives, gynaecologists and neonatologists/paediatricians. Among the items reported are maternal demographics and medical conditions, pregnancy complications and details concerning labour, birth and neonatal outcomes. Linking the records is a complex operation—especially when it comes to records that originate from different data sets. Probabilistic linkage based on matching data is performed in the absence of unique identification of mother and/or child. There is a firm basis for deciding whether two records describe the same case or have a high resemblance. The established registry reflects virtually all deliveries in the Netherlands (~99% agreement with the municipal administration), that is, including home as well as hospital births. The frequency of data collection and processing is four times a year. The average lag time of the data is half a year.

PHARMO is a population-based network of databases combining subnational data from different primary and secondary healthcare settings in the Netherlands. These different data sources, including data from general practices, inpatient and outpatient pharmacies, clinical laboratories, hospitals, the cancer registry, pathology registry and perinatal registry, are linked on a patient level through validated algorithms. Data are retrieved directly from the

source, that is, the electronic medical records of the healthcare providers who agree to contribute to PHARMO. All patients registered at the contributing healthcare providers are included unless the patient requested to opt out. To ensure the privacy of the data in the PHARMO Database Network, the collection, processing, linkage and anonymisation of the data are performed by the foundation 'Stichting Informatievoorziening voor Zorg en Onderzoek' (STIZON). STIZON is an independent ISO/IEC 27001 certified foundation, that acts as a trusted third party (TTP) between the data sources and the PHARMO Institute. STIZON also acts as a TTP for the linkage between Perined and PHARMO. This specific linkage is primarily based on the birth date of the mother and child, their gender and their zip codes. In case multiple possible links are established, these determinants are supplemented with hospital admission records around delivery as well as obstetrician or gynaecologist-prescribed medication. Furthermore, home codes that indicate mother and child live on the same address are used to verify established pairs and improve linkage specificity.

### 9.3.2. Exposure

The exposure of interest is ABRYSVO (RSVpreF) vaccination. Depending on the data source, vaccination information will be obtained from pharmacy dispensing records, general practice records, immunisation registers, vaccination records, medical records, or other secondary data sources. We will consider a single administration of one dose, as recommended during pregnancy. Outcome-specific exposure windows are described in Table 5.

### 9.3.3. Outcomes

Outcomes of interest will include prespecified pregnancy outcomes as described in Table 4. The outcome-specific exposure windows will be defined as shown in Table 5. The outcomes will be ascertained using coded diagnoses, procedures, medicinal products, and information in other databanks.

**Table 4. Outcomes of interest**

| Outcomes | Clinical definition of outcomes | Pregnancies among which the outcome will be ascertained | Outcome type |
|---|---|---|---|
| **Preterm birth** | Preterm birth will be defined as babies born alive before 37 weeks of pregnancy. We will further subcategorise preterm birth, based on gestational age (13):<br>• **Extremely preterm**: less than 28 weeks<br>• **Very preterm**: 28 to less than 32 weeks<br>• **Moderate to late preterm**: 32 to less than 37 weeks | Pregnancies ending with live births | Pregnancy |

## Table 4. Outcomes of interest

| Outcomes | Clinical definition of outcomes | Pregnancies among which the outcome will be ascertained | Outcome type |
|---|---|---|---|
| | During validation we want to identify if the preterm birth was iatrogenic (delivery is initiated for maternal of foetal conditions) or spontaneous. | | |
| **Time from vaccination to birth** | Time between ABRYSVO vaccination and birth in days. | Pregnancies ending with live and non-live births | Pregnancy |
| **Stillbirth** | Stillbirth(14) is defined by the Brighton collaboration as foetal death occurring before birth after a selected predefined duration of gestation. The death of the foetus could have occurred before onset of labour (antepartum) or at delivery (intrapartum).<br>WHO defines stillbirth as the death of a foetus that has reached a birth weight of 500 gram, or if birth weight is unavailable, gestational age of 22 weeks or crown-to-heel length of 25 cm.<br>There are several definitions for the minimum gestational age:<br>• WHO/ICD/EMA = 22 weeks of gestation<br>• ACOG/CDC = 20 weeks of gestation<br>• RCOG (UK) = 24 weeks of gestation<br>We will use the ACOG definition in this study. | All pregnancies reaching 24 weeks of gestational age | Pregnancy |
| **Low birth weight** | Low birth weight(15) is defined as weight at birth of <2500 grams (up to and including 2499 grams). It can be caused by foetal growth restriction, prematurity or both. | Pregnancies ending with live births | Birth |
| **Small for gestational age (SGA)** | SGA(16) is defined as a birth weight below the 10$^{th}$ percentile for gestational age and sex. SGA can be caused by placental dysfunction, referred to as Foetal Growth Restriction (FGR), or it can be due to a constitutionally small foetus without any pathological causes. Other possible causes include congenital malformations or infections. | Pregnancies ending with live births | Birth |
| **Placental abruption** | Placental abruption (abruptio placentae) is defined as premature separation of the placenta from the uterus before delivery, which can cause maternal haemorrhage and foetal compromise. | All pregnancies reaching 20 weeks of gestational age | Maternal |
| **Hypertensive disorders in pregnancy** | The following hypertensive disorders in pregnancy will be considered:(17)<br>• **Gestational hypertension** | All pregnancies reaching 24 weeks of gestational age | Maternal |

## Table 4. Outcomes of interest

| Outcomes | Clinical definition of outcomes | Pregnancies among which the outcome will be ascertained | Outcome type |
|---|---|---|---|
| | Defined as hypertension (systolic blood pressure greater than or equal to 140 mm Hg and/or diastolic blood pressure greater than or equal to 90 mm Hg) arising de novo at ≥20 weeks' gestation in the absence of proteinuria or other findings suggestive of pre-eclampsia.<br>• **Preeclampsia/HELLP/eclampsia**<br>Defined as gestational hypertension accompanied by one or more of the following new-onset conditions at ≥20 weeks' gestation:<br>1. Proteinuria<br>2. Other maternal end-organ dysfunction, including neurological complications, pulmonary oedema, haematological complications, renal insufficiency, impaired liver function<br>3. Uteroplacental dysfunction<br>Preeclampsia superimposed on chronic (existing) hypertension / use of antihypertensives prior to LMP will also be included. HELLP (Haemolysis, Elevated Liver Enzyme, Low Platelet) is a serious manifestation of pre-eclampsia and will be assessed if available in the data sources. | | |
| **Guillain-Barré Syndrome (GBS)** | GBS is defined as an immune-mediated polyradiculoneuropathy frequently preceded by an infection with Campylobacter jejuni or nonspecific infections, and, rarely, by a vaccination. | All pregnancies | Maternal |

Abbreviations: ACOG, American College of Obstetricians and Gynaecologists; CDC, Centers for Disease Control and Prevention; EMA, European Medicines Agency; GBS, Guillain-Barré Syndrome; HELLP, Haemolysis Elevated Liver Enzyme Low Platelet; ICD, International Classification of Diseases; LMP, last menstrual period; RCOG, Royal College of Obstetricians and Gynaecologists; WHO, World Health Organization.

## Table 5. Outcome-specific exposure windows

| Outcome | Exposure risk window for outcomes | Comment |
|---|---|---|
| **Pregnancy outcomes** | | |
| **Preterm birth** | From Time zero to before Week 37 of gestation (36 weeks and 6/7 days) | Because the outcome occurs before Week 37, only exposure up to end of gestational Week 36 is investigated |
| **Stillbirth** | From Time zero to end of pregnancy | Stillbirth starts from the 20$^{th}$ week of gestation |

**Table 5. Outcome-specific exposure windows**

| Outcome | Exposure risk window for outcomes | Comment |
|---|---|---|
| **Birth outcomes** | | |
| **Low birth weight** | From Time zero to end of pregnancy | |
| **SGA** | From Time zero to end of pregnancy | |
| **Maternal outcomes** | | |
| **Hypertensive disorders in pregnancy** | From Time zero or gestational age of 20 Weeks or longer (whichever is latest) | Hypertensive disorders due to pregnancy start from the 20th week of gestation |
| **GBS**** | From Time zero + 21 days, From Time zero + 42 days | |
| **Placental abruption** | From Time zero to end of pregnancy + 14 days* | Placental abruption starts from the 20th week of gestation |

Abbreviations: GA, gestational age; GBS, Guillain-Barré Syndrome; RSVpreF, RSV prefusion F vaccine; SGA, small for gestational age. *The definite diagnosis is made after birth, when the placenta is examined(18). **The analysis is performed over two different risk windows, presence of a GBS diagnosis 21 days after Time zero, and presence of a GBS diagnosis 42 days after Time zero

### 9.3.4. Covariates

*Demographics:*

- Age at Time zero

*High-risk pregnancy:*

High-risk pregnancies will be defined as pregnancies in which women, or their offspring have a history of any of the following conditions in the current pregnancy (before Time zero):

- Obesity
- Hypertension
- Pre-eclampsia/HELLP/eclampsia
- HELLP
- Multifoetal pregnancy
- Diabetes
- Gestational diabetes

and/or any of the following conditions in previous pregnancies:

- Gestational diabetes
- Preeclampsia/HELLP/eclampsia
- Stillbirth or late miscarriage
- Small for gestational age or foetal growth restriction

- Congenital anomaly

*Immunocompromised status*

Individuals must meet at least one of the following criteria at index or in the period prior to the index date (unless otherwise noted) to be eligible for inclusion in the immunocompromised population:

- Medical conditions:
  a. Diagnosed with symptomatic HIV/AIDS
  b. Diagnosed with hematologic malignancy (e.g., chronic lymphocytic leukaemia, non-Hodgkin lymphoma, multiple myeloma, acute leukaemia)
  c. Diagnosed with solid malignancy
  d. Diagnosed with rheumatologic/inflammatory conditions (e.g., Sjogren's syndrome, Systemic Lupus Erythematosus (SLE), psoriatic arthritis, rhematic arthritis, arthritis spondylarthritis, polymyalgia rheumatica, demyelination multiple sclerosis, polymyalgia rheumatica, Inflammatory Bowel Disease (IBD), autoimmune thyroiditis) and have evidence of treatment with chemotherapy or immune modulators (see below)
- Immunosuppressive treatments:
  a. Organ transplant recipients or islet transplant recipients taking immunosuppressive therapy
  b. CAR-T-cell therapy or hematopoietic stem cell transplant recipients taking immunosuppressive therapy
  c. Rheumatologic/inflammatory conditions treated with immunosuppressive therapy
  d. Active treatment (at Time zero) with various immunomodulatory agents (e.g., , alkylating agents, antimetabolites, transplant-related immunosuppressive drugs, cancer chemotherapeutic agents classified as severely immunosuppressive, TNF blockers, and other biologic agents that are immunosuppressive or immunomodulatory).

  Note: It is recommended that pregnant women between 24-34 weeks gestational age who are at immediate risk of preterm delivery (eg. premature labor occurring within the next 7-10 days) immediately receive a single course of systemic corticosteroids. This type of steroid use will be excluded from the definition of immunocompromised pregnant woman.
- Specific medical procedures:
  a. Organ transplant recipients or islet transplant recipients
  b. CAR-T-cell therapy or hematopoietic stem cell transplant recipients

*Other maternal vaccinations prior to Time zero when available*

- Influenza (inactivated) (yes/no)
- SARS-CoV-2 (yes/no)
- Tetanus, Diphtheria and Pertussis (Tdap) (yes/no)

*Risk factors for outcomes*

Table 6 provides the risk factors for each of the outcomes of interest that will be measured when available.

**Table 6. Risk factors for the outcomes of interest**

| **PRETERM BIRTH**(19,20) | |
|---|---|
| **Risk factors** | **Covariate assessment window** |
| Advanced maternal age (≥35 years) or early maternal age (<20 years) | At Time zero |
| *Race/ethnicity:* African American, Afro-Caribbean | From database entry to Time zero |
| Smoking during pregnancy, substance abuse/dependence during pregnancy | From start of pregnancy (LMP) to Time zero |
| *Current pregnancy:* nulliparity, multifoetal pregnancy, Assisted Reproductive Technology (ART), short uterine cervix (<25 mm in second trimester), gestational hypertension, preeclampsia/HELLP (Haemolysis, Elevated Liver Enzyme, Low Platelet)/eclampsia, gestational diabetes, premature rupture of membrane, placenta previa, antepartum haemorrhage | From start of pregnancy (LMP) to Time zero, for ART from 365 days prior LMP |
| *Prior pregnancy history of* preterm birth, abortion, caesarean delivery | From database entry to Time zero |
| Birth space less than 2 years | From database entry to Time zero |
| *Morbidities:* anaemia, asthma, obesity (pre-pregnancy BMI >30 kg/m$^2$), pre-existing diabetes, chronic hypertension, depression, thyroid disease, anomalies of the uterus (e.g., presence of a uterine septum) | Chronic comorbidities: From database entry to Time zero<br>Time-varying comorbidities: From 365 days prior to Time zero |
| *Infections:* HIV, urinary tract infections, chlamydia, toxoplasmosis, trichomonas vaginalis, malaria, COVID-19 | Chronic infections: From database entry to Time zero<br>Acute infections: From start pregnancy (LMP) to Time zero |
| *Medicines:* antidepressants, benzodiazepines, selective serotonin receptor inhibitors, antibiotics, NSAIDs | From start of pregnancy (LMP) to Time zero |
| **STILLBIRTH**(21,22) | |
| **Risk factors** | **Covariate assessment window** |
| Advanced maternal age (≥35 years) or early maternal age (<20 years) | Age at Time zero |
| *Race/ethnicity:* Black, African American | From database entry to Time zero |
| Smoking, substance abuse/dependence | From start of pregnancy (LMP) to Time zero |
| *Current pregnancy:* nulliparity, multifetal pregnancy, ART, gestational hypertension, preeclampsia/HELLP/eclampsia, gestational diabetes, FGR, congenital anomaly, premature rupture of membrane, antepartum haemorrhage, placental abruption | From start of pregnancy (LMP) to Time zero, for ART from 365 days prior LMP |
| *Prior pregnancy history of:* stillbirth, pregnancy loss, miscarriage, preterm birth, SGA | From database entry to Time zero |

## Table 6. Risk factors for the outcomes of interest

| | |
|---|---|
| *Morbidities:* obesity (pre-pregnancy BMI >30 kg/m$^2$), pre-existing diabetes, chronic hypertension, chronic kidney disease, thyroid disorders, SLE, sickle-cell disease | Chronic comorbidities: From database entry to Time zero<br>Time-varying comorbidities: From 365 days prior to Time zero |
| *Infections:* HIV, Escherichia coli, Klebsiella, Group B Streptococcus, Enterococcus, Mycoplasma/Ureaplasma, Haemophilus influenzae, Chlamydia | Chronic infections: From database entry to Time zero.<br>Acute infections: From start pregnancy (LMP) to Time zero |
| **HYPERTENSIVE DISORDERS IN PREGNANCY**(17,23) | |
| **Risk factors** | **Covariate assessment window** |
| Advanced maternal age (≥40 years) | At Time zero |
| *Race/ethnicity:* African American | From database entry to Time zero |
| Smoking (protective) | From start of pregnancy (LMP) to Time zero |
| *Current pregnancy:* nulliparity, multifetal pregnancy, ART | From start of pregnancy (LMP) to Time zero |
| *Prior pregnancy history of:*<br>preeclampsia/HELLP/eclampsia, placental abruption, stillbirth, FGR | From database entry to Time zero |
| *Morbidities:* obesity (pre-pregnancy BMI >30 kg/m$^2$), pre-existing diabetes, chronic hypertension, chronic kidney disease (inc. kidney transplanted women), SLE antiphospholipid antibody syndrome, rheumatoid arthritis, sickle cell disease, PCOS, multiple sclerosis | Chronic comorbidities: From database entry to Time zero<br>Time-varying comorbidities: From 365 days prior to Time zero |
| *Infections:* urinary tract infections | Chronic infections: From database entry to Time zero.<br>zero. Acute infections: From start pregnancy (LMP) to Time zero |
| **PLACENTAL ABRUPTION**(18) | |
| **Risk factors** | **Covariate assessment window** |
| Advanced maternal age (≥35 years) or early maternal age (<20 years) | At Time zero |
| Smoking, substance abuse/dependence | From start of pregnancy (LMP) to Time zero |
| *Current pregnancy:* multifetal pregnancy, gestational hypertension, preeclampsia/HELLP/eclampsia, gestational diabetes, polyhydramnios, antepartum haemorrhage, short umbilical cord (less than 35 cm), abdominal trauma, ART | From start of pregnancy (LMP) to Time zero, for ART from 365 days prior LMP. For short umbilical cord from start of pregnancy to end of pregnancy. |
| *Prior pregnancy history of:* premature rupture of membranes, placental abruption, abnormal placentation, stillbirth, caesarean delivery, placenta previa, antepartum haemorrhage, SGA, miscarriage, chorioamnionitis | From database entry to Time zero |
| *Co-morbidities:* chronic hypertension, trombophilia, anaemia, diabetes | From database entry to Time zero |

## Table 6. Risk factors for the outcomes of interest

| **GUILLAIN-BARRÉ SYNDROME**(24) | |
|---|---|
| **Risk factors** | **Covariate assessment window** |
| *Co-morbidities:* HIV, mycoplasma pneumonia | Chronic comorbidities: From database entry to Time zero<br>Time-varying comorbidities: From 365 days prior to Time zero |
| *Infections:* Campylobacter jejuni, CMV, EBV, influenza, Zika virus | Chronic infections: From database entry to Time zero<br>Acute infections: From start pregnancy (LMP) to Time zero |
| *Vaccinations:* Influenza, SARS-CoV-2 | From start of pregnancy (LMP) to Time zero |
| **SMALL FOR GESTATIONAL AGE**(25,26) | |
| **Risk factors** | **Covariate assessment window** |
| Advanced maternal age (≥35 years) or early maternal age (<20 years) | At Time zero |
| *Race/ethnicity:* Black | From database entry to Time zero |
| Smoking, substance abuse/dependence | From start of pregnancy (LMP) to Time zero |
| *Current pregnancy:* nulliparity, multifetal pregnancy, ART, gestational hypertension, preeclampsia/HELLP/eclampsia, gestational diabetes, FGR, congenital anomaly, placental abruption | From start of pregnancy (LMP) to Time zero, for ART from 365 days prior LMP |
| *Prior pregnancy history of:* SGA | From database entry to Time zero |
| *Co-morbidities:* anaemia, pre-existing diabetes, chronic hypertension, chronic kidney disease, SLE, sickle-cell disease, anomalies of the uterus (e.g., presence of a uterine septum) | Chronic comorbidities: From database entry to Time zero<br>Time-varying comorbidities: From 365 days prior to Time zero |
| *Infections:* HIV, CMV, rubella, toxoplasmosis | Chronic infections: From database entry to Time zero<br>Acute infections: From start of pregnancy (LMP) to Time zero |
| **LOW BIRTH WEIGHT**(27) | |
| **Risk factors** | **Covariate assessment window** |
| Advanced maternal age (≥35 years) or early maternal age (<20 years) | At Time zero |
| *Race/ethnicity:* Black | From database entry to Time zero |
| Smoking, substance abuse/dependence | From start of pregnancy (LMP) to Time zero |
| *Current pregnancy:* nulliparity, multifetal pregnancy, preterm birth, gestational hypertension, preeclampsia/HELLP/eclampsia, gestational diabetes, FGR, congenital anomaly | From start of pregnancy (LMP) to Time zero |
| *Prior pregnancy history of:* preterm birth, low birth weight | From database entry to Time zero |
| *Co-morbidities:* anaemia, pre-existing diabetes, chronic hypertension, chronic kidney disease | Chronic comorbidities: From database entry to Time zero<br>Time-varying comorbidities: From 365 days prior to Time zero |

**Table 6. Risk factors for the outcomes of interest**

| | |
|---|---|
| *Infections:* HIV, CMV, rubella, chickenpox, toxoplasmosis, chlamydia | Chronic infections: From database entry to Time zero<br><br>Acute infections: From start of pregnancy (LMP) to Time zero |

Abbreviations: ART, assisted reproductive technology; BMI, body mass index; CMV, cytomegalovirus; EBV, Epstein-Barr virus; FGR, foetal growth restriction; GBS, Guillain Barré syndrome; HIV, human immunodeficiency viruses; NSAIDS, non-steroidal anti-inflammatory drugs; PCOS, polycystic ovary syndrome; SGA, small for gestational age; SLE, Systemic Lupus Erythematosus.

## 9.4. Data Sources

The setting for this study will include data sources from the VAC4EU multinational network. The VAC4EU study network comprises research organisations, public health institutes, and data access providers under the condition of being qualified and able to provide either access to relevant data and/or relevant expertise to the post-marketing monitoring of vaccines. The characteristics of each of the potentially participating DAPs are summarised below and in Table 7.

**Table 7. Characteristics of potentially participating data sources**

| Data source | Country (region) | Diagnoses recordings | Vaccines | Medical birth registry |
|---|---|---|---|---|
| **VID** | Spain (Valencia) | GP, specialist, hospital | Vaccine register | Yes |
| **SIDIAP** | Spain (Catalunya) | GP, hospital | Vaccine register | Mother-Child linkage table |
| **EpiChron** | Spain (Aragon) | GP, hospital | Vaccine registry | Yes |
| **NHR** | Norway | GP, specialists, hospital | Vaccine register | Yes |
| **DHR** | Denmark | Hospital | Vaccine register | Yes |
| **PHARMO** | Netherlands | GP, hospital | GP vaccination (depending on the NITAG recommendations and national immunisation programme (NIP) roll-out) | Yes |
| **SNDS** | France | Hospital | Vaccination claims | No |
| **CPRD** | United Kingdom | Mainly GP. Specialist or hospital via hospital or specialist letters to GP. | Vaccination may be recorded by GP, or automatically populated in GP medical records based on NHS vaccine register. | Yes, Mother- Baby linked data |

### 9.4.1. VID (ES)

The Valencia health system integrated database (VID) is a set of multiple, public, population-wide electronic databases for the Valencia Region, the fourth most populated Spanish region, with ~5 million inhabitants and an annual birth cohort of 48000 new-borns, representing 10.7% of the Spanish population and around 1% of the European population. The VID provides exhaustive longitudinal information including sociodemographic and administrative

data (sex, age, nationality, etc.), clinical (diagnoses, procedures, diagnostic tests, imaging, etc.), pharmaceutical (prescription, dispensation) and healthcare utilisation data from hospital care, emergency departments, specialised care (including mental and obstetrics care), primary care and other public health services. It also includes a set of associated population databases and registries of significant care areas such as cancer, rare diseases, vaccines, congenital anomalies, microbiology and others, and public health databases from the population screening programmes. All electronic health systems in the VID use the ICD-9-CM and the ICD-10-CM. All the information in the VID databases can be linked at the individual level through a single personal identification code. The databases were initiated at different moments in time, but all in all the VID provides comprehensive individual-level data fed by all the databases from 2008 to date. The Foundation for the Promotion of Health and Biomedical Research of Valencia Region (FISABIO) is Data Access Provider for Valencia Integrated Databases (VID).

### 9.4.2. SIDIAP (ES)

The Information System for Research in Primary Care (Sistema d'Informació per al Desenvolupament de la Investigació en Atenció Primària (SIDIAP) in Catalonia, Spain, is a primary care database set up by the Institute of Research in Primary Care (Institut Universitari D'Investigació en Atenció Primària Jordi Gol [IDIAP Jordi Gol]) and Catalan Institute of Health (Institut Català de la Salut). The database collects information from 278 primary health care centers and includes more than 5.8 million patients covered by the Catalan Institute of Health (approximately 78% of the Catalan population) and is highly representative of the Catalan population.
SIDIAP data comprise the clinical and referral events registered by primary care health professionals (i.e, GPs, paediatricians, and nurses) and administrative staff in electronic medical records, comprehensive demographic information, community pharmacy invoicing data, specialist referrals, and primary care laboratory test results. SIDIAP can also be linked to other data sources, such as the hospital discharge database, on a project-by-project basis. Health professionals gather this information using International Classification of Diseases, 10th Revision (ICD-10) codes, ATC codes, and structured forms designed for the collection of variables relevant to primary care clinical management, such as country of origin, sex, age, height, weight, body mass index, tobacco and alcohol use, blood pressure measurements, and blood urine test results. Concerning vaccines, information on all routine childhood and adult immunisations is included in addition to the antigen and the number of administered doses.

SIDIAP is listed under the ENCePP resources databases. SIDIAP was characterised in the IMI-ADVANCE project and considered fit for purpose for vaccine coverage, benefits, and risk assessment. After EMA approval, the protocol must be evaluated by the SIDIAP Scientific Committee and by the IDIAPJGol Ethics Committee, the approval can take 4-6 weeks. The timeframe for data availability after the approval by the two local Committees is one month. An algorithm to identify pregnancies has been previously used within SIDIAP. The algorithm uses diagnosis codes recorded in primary healthcare records during pregnancy and information recorded in the sexual and reproductive healthcare registries, including LMP, gestational week, expected date of delivery, actual date of delivery or termination, and pregnancy outcomes. Approximately 50% to 60% of pregnant women in Catalonia are

attended in the sexual and reproductive healthcare centres that contribute data to SIDIAP. Approximately 70% of infant records can be linked to maternal records and used for research.

### 9.4.3. EpiChron (ES)

The Spanish National Health System is organised at a regional level. Aragon is one of the regions, with approximately 1.3 million inhabitants. The Aragon data sources to be used in this study, which cover approximately 98% of the reference population, are the following:

- The user database (BDU) with sociodemographic information
- Individuals' electronic medical records from primary care (OMI-AP) and hospital care (Minimum Basic Data Set, CMBD, with data on hospital discharges, and PCH database with data on visits to the emergency room)
- Individuals' pharmacotherapeutic history with prescriptions and dispensation of drugs in community pharmacies (Receta Electrónica database).

### 9.4.4. Norwegian Health Registers (NHR) (NO)

The core data that University of Oslo (UiO) has access to are the health care administrative data banks of the entire Norwegian population, which represents approximately 5.3 million inhabitants, with about 56000 deliveries yearly. Norway has a universal public healthcare system, consisting of primary healthcare services and specialist healthcare services. Many population-based health registries were established in the 1960s, with use of unique personal identifiers facilitating linkage between registries. The mandatory national health registries were established to maintain national functions. They are used for health analysis, health statistics, improving the quality of healthcare, research, administration and emergency preparedness. Since January 2004, all pharmacies in Norway have been obliged to send data electronically to the Norwegian Institute of Public Health on all prescribed drugs (irrespective of reimbursement) dispensed to individuals in ambulatory care.

Linked data from the following national health registries are available:

- The Medical Birth Registry (MBRN)
- The National Patient Register (NPR)
- The Norwegian Immunisation Registry
- The National Prescription Registry (NorPD)
- Vaccine registry (SYSVAK)

Information about all Norwegian National Registries can be found here: www.fhi.no/en/more/access-to-data/about-the-national-health-registries2/. UiO is Data Access Provider for Norwegian linked registry data.

### 9.4.5. Danish Health Registers (DHR) (DK)

Denmark has a tax-funded healthcare system ensuring equal access to healthcare for all its residents. All hospital-based encounters including visits to outpatient specialist clinics in Denmark are recorded.(28) The administrative registry Danish Civil Registration System contains data on the unique personal identifier (the CPR-number), sex, and dates of birth, immigration, emigration, and death. The CPR-number is assigned to every Danish resident

upon birth or immigration. The linkage of registers at an individual level is possible via CPR-number, which is used in all Danish registers. Danish registers have nationwide coverage and a virtually complete capture of hospital-based encounters of 5.9 million Danish residents.

Linked data from the following registries are available:

- Danish Civil Registration System (CRS): identifier for linkage, age, sex, births, deaths, migrations
- Danish National Prescription Registry(29): outpatient dispensing of medicines in community pharmacies, including dispensing date, ATC code, product code and amount
- Danish National Health Service Register: records general practitioner contacts including vaccinations and pregnancy-related primary care visits, these will be used to identify ongoing pregnancies.
- Danish National Patient Registry (DNPR)(30): records diagnoses and procedures from all hospital encounters including specialist outpatient clinics. This includes diagnoses for, and pregnancies ending in abortive outcomes, as well as some medicines administered in hospitals
- Danish Vaccination Registry all vaccines
- Danish Medical Birth registry (MBR)(31): data on all livebirths (any gestational age), live or stillbirths from week 22 onwards
- Danish Hospital Medicines Register: selected data on medicines administered in hospitals

Department of Clinical Epidemiology, Aarhus University will be the Data Access Provider for the Danish registries. Data will be linked, using a unique pseudonymised identifier on the servers of the Danish Health Data Authority (SDS). Individual-level data will be analysed by uploading and running analytic scripts on the SDS servers. Aggregate data that does not allow backtracking to individuals in accordance with the data regulation will be used for reporting.

### 9.4.6. PHARMO (NL)

The PHARMO Data Network is a population-based network of electronic health records databases. The longitudinal nature of the PHARMO Data Network system enables the follow-up of more than 4 million (25%) residents of a well-defined population in the Netherlands for an average of 10 years.

The network combines data from different primary and secondary healthcare settings in the Netherlands. These data sources include data from general practices, in- and out-patient pharmacies, clinical laboratories, hospitals, the cancer registry, the pathology registry and the perinatal registry. Data sources are linked at a patient level through validated algorithms. For the purpose of this present study, it is expected that data sources will include data from the Perinatal Registry, GP and out-patient pharmacies. These data sources are described in brief below. The eventual selection of data sources will depend on the delivery route of the

vaccine in combination with the anticipated overlap between the catchment areas required to assess the outcomes of interest.

The Netherlands Perinatal Registry is maintained by Perined and comprises data on pregnancies, births and neonatal outcomes of births in the Netherlands, voluntarily collected by perinatal caregivers, mainly for benchmarking. For research purposes the data are linked with the PHARMO Data Network via the TTP, resulting in the PHARMO Perinatal Research Network (PPRN). Records include information on mothers (e.g. maternal age, obstetric history, parity), pregnancy (e.g. mode of conception, mode of delivery) and children (e.g. birth weight, gestational age, Apgar score). Diagnoses and symptoms are coded according to the Perinatal Registry code lists.

The general practitioner (GP) data comprise electronic patient records registered by GPs. The records include information on diagnoses and symptoms, laboratory test results, referrals to specialists and healthcare product/drug prescriptions. The prescription records include information on type of product, prescription date, strength, dosage regimen, quantity and route of administration. Drug prescriptions are coded according to the WHO Anatomical Therapeutic Chemical (ATC) Classification System. Diagnoses and symptoms are coded according to the International Classification of Primary Care (ICPC), which can be mapped to ICD codes, but can also be entered as free text. GP data cover a catchment area representing 3.2 million residents (~20% of the Dutch population).

The out-patient pharmacy data comprise general practitioner or specialist-prescribed healthcare products dispensed by out-patient pharmacies including community pharmacies as well as hospital-based out-patient pharmacies. The dispensing records include information on the type of product, date, strength, dosage regimen, quantity, route of administration, prescriber specialty and costs. Drug dispensing is coded according to the WHO Anatomical Therapeutic Chemical (ATC) Classification System. Out-patient pharmacy data cover a catchment area representing 4.2 million residents (~25% of the Dutch population).

The medical records capture information on vaccines provided by the GP, and COVID-19 vaccines. Linkage with vaccine registers may be needed and conducted ad hoc, depending on the health care professional that will vaccinate pregnant women.

### 9.4.7. SNDS (FR)

The Système National des Données de Santé (SNDS) is the French nationwide healthcare database. It currently covers the overall French population (about 67 million persons) from birth (or immigration) to death (or emigration), even if a subject changes occupation or retires.(32,33) Using a unique pseudonymised identifier, the SNDS merges all reimbursed outpatient claims from all French health care insurance schemes (SNIIRAM database), hospital-discharge summaries from French public and private hospitals (PMSI database), and the national death registry. SNDS data are available since 2006 and contains information on:

- General characteristics: gender, year of birth, area of residence, deprivation index, etc.
- Death: month, year and cause.
- Long-term disease registration associated with an ICD-10 diagnostic code.

- Outpatient reimbursed healthcare expenditures with dates and codes (but not the medical indication nor result): visits, medical procedures, nursing acts, physiotherapy, lab tests, dispensed drugs, vaccines and medical devices, etc. For each expenditure, associated costs, prescriber and caregiver information (specialty, private/public practice) and the corresponding dates are provided.
- Inpatient details: primary, related and associated ICD-10 diagnostic codes resulting from hospital discharge summaries with the date and duration of the hospital stay, the performed medical procedures (but no results), lab tests (but no results) and the related costs. Drugs included in the diagnosis-related group cost are not captured. However, expensive drugs (i.e., the one charged in addition to the group cost) are.
- Mother and child linkage: there is a link to identify and track the newborn in the national hospital discharge summary database (PMSI) during the birth stay for deliveries with a gestational age ≥22 weeks. This linkage is possible for live births, stillbirths, and therapeutic abortions after 22 weeks. Follow-up of infants after birth is possible through linkage of the infant to the social security numbers of the parents.

Bordeaux PharmacoEpi (BPE), a research platform of the University of Bordeaux specialised in real world studies, will be Data Access provider for SNDS data. Outpatient data (SNIIRAM) are uploaded to the SNDS throughout the year. It is known that a lag of around 6 months is required to obtain 90% of dispensings. Inpatient data (PMSI) are uploaded in one time, at the end of the following year. Hence, we consider that complete SNDS data of year Y are available in January of the year Y+2. SNDS access is regulated: each study involving a human being with or without data extraction from the SNDS requires approval from the Comité Ethique et Scientifique pour les Recherches, les Etudes et les Evaluations dans le domaine de la Santé (CESREES) to assess scientific quality of the study, and authorisation from the Commission Nationale de l'Informatique et des Libertés (CNIL), the French data protection authority, and thereafter, an agreement with the SNDS data holder (CNAM) is needed for data extraction.

### 9.4.8. CPRD (UK)

The Clinical Practice Research Datalink (CPRD) from the UK collates the computerised medical records of GPs in the UK who act as the gatekeepers of health care and maintain patients' life-long electronic health records. Accordingly, GPs are responsible for primary health care and specialist referrals, and they also store information about specialist referrals and hospitalisations. General practitioners act as the first point of contact for any non-emergency health-related issues, which may then be managed within primary care and/or referred to secondary care, as necessary. Secondary care teams also provide information to GPs about their patients, including key diagnoses.

The data recorded in the CPRD include demographic information, prescription details, clinical events, preventive care, specialist referrals, hospital admissions, and major outcomes, including death. Most of the data is coded by GPs using Read or SNOMED codes, and available in CPRD Aurum as MedCode ID's or ProdCode ID's. Data validation with original records (specialist letters) is also available via the CPRD Prove Plus service.

The population in the data bank is generalisable to the UK population based on age, sex, socioeconomic class, and national geographic coverage CPRD Aurum versions is used. There are currently approximately 46.6 million individuals (acceptable for research purposes) -16 million of whom are active (i.e, still alive and registered with the GP practice)- in over 1700 primary care practices (https://cprd.com/Data). Data include demographics, all GP/health care professional consultations (e.g., phone calls, letters, e- mails, in surgery, at home), diagnoses and symptoms, laboratory test results, treatments (including all prescriptions), all data referrals to other care providers, hospital discharge summary (date and based on Read/SNOMED codes), hospital clinic summary, preventive treatment and immunisations, and death (date and cause). For a proportion of the CPRD panel practices (> 80%), the GPs have agreed to permit the CPRD to link at the patient level to Hospital Episode Statistics (HES) data. Additional CPRD-linked datasets include Death Registration data from the Office for National Statistics, which includes information on the official date and causes of death (using ICD codes), the CPRD Aurum Ethnicity Record, the Index of Multiple Deprivation (IMD) patient or practice level linked datasets and the algorithm based linked datasets, CPRD Aurum Pregnancy Register and the CPRD Aurum Mother-Baby link.

### 9.5. Study Size

In this study, the duration of observation is determined by the Progress Reports (monitoring) of exposure to ABRYSVO during pregnancy. The number of exposures triggering the first interim report analysis is 600 vaccinated women based on 80% power, a 2% prevalence rate of outcome of interest and targeting a minimal detectable risk ratio of 2.5.If the combined number of vaccinated participants across all sites is below 600, the interim analysis will be deferred until this threshold is met. However, reaching this threshold earlier than expected will not accelerate the timing of the report; the analysis will proceed according to the predefined schedule. The study will include all pregnant women (including immunocompromised pregnant women and women with high-risk pregnancies) who meet the study inclusion criteria and who receive ABRYSVO at 24 weeks of gestation or later up to 36 weeks of gestation (or matched comparator) as identified in the data source during the study period. It is currently unknown how many women will be vaccinated during pregnancy, as it depends heavily on the advice of various NITAGs. Table 8 provides an overview of the status of the NITAG advice in different countries that are represented in this study.

**Table 8. Overview of NITAG and national guidelines recommendations regarding inclusion of RSV vaccination in maternal immunisation schedule**

| Country | NITAG advice/ national guidelines recommendations |
|---|---|
| **Spain** | Currently, no vaccination recommendations of pregnant women for 2025-2026 season.<br>https://www.sanidad.gob.es/areas/promocionPrevencion/vacunaciones/comoTrabajamos/sincitial.htm<br>https://www.aragon.es/-/vacunacion-vrs-adultos |

**Table 8. Overview of NITAG and national guidelines recommendations regarding inclusion of RSV vaccination in maternal immunisation schedule**

| Country | NITAG advice/ national guidelines recommendations |
|---|---|
| | https://canalsalut.gencat.cat/ca/salut-a-z/v/vacunacions/tardor/ |
| **Norway** | Approved/recommended but not part of a national immunisation program: "ABRYSVO can be considered for pregnant women between gestational weeks 24 and 36 to protect infants in the first 6 months of life. The effect appears to be best with vaccination in gestational weeks 30 to 36. A minimum interval of two weeks between Abrysvo and the whooping cough vaccine is recommended."<br>RSV Vaccine Handbook for Health Professionals<br>https://www.fhi.no/va/vaksinasjonshandboka/vaksiner-mot-de-enkelte-sykdommene/rs-virusvaksine/<br>Norwegian institute of public health (NIPH): https://www.fhi.no/va/vaksinasjonsveilederen-for-helsepersonell/vaksinasjon-i-ulike-livsfaser/vaksinasjon-av-gravide-og-ammende/?term=<br>Scientific Reference Group for National Immunisation Programs / NIPH:<br>https://www.fhi.no/en/va/innforing-av-nye-vaksiner/scientific-reference-group-for-national-immunisation-programs/<br>The evaluation process (health technology assessment) to determine whether it should be included in the immunisation program is currently undergoing by Norwegian Medical Products Agency. The status can be tracked here: https://www.dmp.no/offentlig-finansiering/metodevurdering-av-medisinske-produkter/metodevurdering-av-vaksiner/vaksiner-under-vurdering |
| **Denmark** | The Danish government har decided that pregnant women will be offered a RSV vaccine in their 32nd week of pregnancy as part of a seasonal programme with vaccination between May 1st and January 31st January each year. The vaccine will be administered free of charge at routine prenatal visits at general practitioners, and approximately 32,000 pregnant women annually are expected to participate.<br>The vaccination programme commenced on 1 October 2025. Pregnant women in week 33-36 were offered a catch-up programme at commencement of the programme:<br>https://www.ism.dk/nyheder/2025/september/vaccinationstilbud-fremrykkes-gravide-faar-tilbud-om-rs-vaccine-allerede-til-efteraaret<br>https://www.ism.dk/nyheder/2025/august/nyt-vaccinationsprogram-skal-forebygge-alvorlig-sygdom-hos-spaedboern |
| **The Netherlands** | Maternal RSV vaccination is available for purchase, and is indicated for vaccination between 24 and 36 weeks of pregnancy. The vaccination can be requested via the GP, vaccination department, or travel vaccination clinic at the Municipal Public Health Services (GGDs)<br>https://www.rivm.nl/en/rsv/rsv-vaccination-during-pregnancy<br>The Dutch National Immunisation Programme (NIP) includes the RSV immunisation for babies as of September 2025. Babies born from 01 April 2025 are eligible to receive immunisation with nirsevimab.<br>https://rijksvaccinatieprogramma.nl/vaccinaties/rs-virusprik<br>The rationale for including nirsevimab in the NIP is based on the recommendation provided by the Gezondheidsraad in Q2 2024, as described below:<br>"The committee has a preference for the use of immunisation with antibodies. There are three reasons for this:<br>In immunisation with nirsevimab, seasonal timing of offering the antibodies allows a large proportion of children to be protected against RSV. With maternal vaccination, fewer children can be protected because a proportion are born out of season and efficacy has declined by the time they enter their first |

**Table 8. Overview of NITAG and national guidelines recommendations regarding inclusion of RSV vaccination in maternal immunisation schedule**

| Country | NITAG advice/ national guidelines recommendations |
|---|---|
| | RSV season. These children could then be administered antibodies, but that means setting up two programmes. The committee prefers the use of one agent. More health gains could then be achieved with nirsevimab.<br><br>Another advantage of immunisation with nirsevimab is that preterm infants can also be protected. With maternal vaccination, there is a chance that premature infants may be insufficiently protected against RSV after birth. If there are less than 2 weeks between vaccination and delivery, insufficient maternal antibodies have reached the foetus. These children may still be receiving nirsevimab, but the maternal vaccination will then have been in vain.<br><br>Both agents offer newborns and infants good protection against RSV, but the safety of nirsevimab is more certain than the safety of maternal vaccination."<br>https://www.healthcouncil.nl/documents/advisory-reports/2024/02/14/immunisation-against-rsv-in-the-first-year-of-life |
| **France** | Recommendation from HAS (Haute Autorité de Santé) in June 2024. ABRYSVO is recommended between 32 and 36 weeks of pregnancy<br><br>https://www.has-sante.fr/upload/docs/application/pdf/2023-09/note_de_cadrage_recommandation_vaccinale_contre_les_infections_a_vrs_chez_les_femmes_enceintes.pdf<br><br>https://www.has-sante.fr/upload/docs/application/pdf/2024-06/recommandation_vaccinale_contre_les_infections_a_vrs_chez_les_femmes_enceintes_2024-06-12_16-22-54_898.pdf |
| **UK** | The Joint Committee on Vaccination and Immunisation (JCVI) has advised that Abrysvo® (Pfizer RSV Pre-F vaccine) should be offered to all pregnant women from week 28 gestation, in every pregnancy. Vaccination should ideally be offered in week 28 or soon after to maximise the likelihood that a baby will be optimally protected from birth.<br><br>https://assets.publishing.service.gov.uk/media/686fbfcf2557debd867cbf9d/Green_Book_Chapter27a_RSV_14July2025.pdf<br><br>https://www.gov.uk/government/publications/vaccine-update-issue-347-july-2024-rsv-special/vaccine-update-issue-347-july-2024-rsv-special<br><br>https://www.nhs.uk/vaccinations/rsv-vaccine/<br><br>Since 1st September 2024, pregnant women can get a free RSV vaccination on the NHS. It was advised that all women who are at least 28 weeks pregnant on 1 September 2024 should be offered a single dose of the RSV vaccine, through commissioned services. After that, pregnant women will become eligible as they reach 28 weeks gestation, and remain eligible up to birth. The ideal opportunity to offer vaccination would be at the 28-week antenatal contact (ANC), following prior discussion at the 20-week ANC. The vaccine is recommended during every pregnancy. |

Maternal immunisation programs in Europe are not mandatory but vary highly. Figure 2 provides an overview of the different vaccination programs for pregnant women in Europe in 2024.

**Figure 2. Vaccination programs for pregnant women in Europe**

| Country | Influenza | Pertussis | Coronavirus | Tetanus | Diphtheria |
|---|---|---|---|---|---|
| Belgium[EU] | 2nd–3rd trimester | 24th–32nd week | 1st–3rd trimester | 24th–32nd week | 24th–32nd week |
| Spain[EU] | 1st–3rd trimester | From 27th week | 1st–3rd trimester | From 27th week | From 27th week |
| Bulgaria[EU] | 2nd–3rd trimester | 27th–36th week | | 2nd–3rd trimester | 2nd–3rd trimester |
| Ireland[EU] | 1st–3rd trimester | 2nd–3rd trimester | 1st–3rd trimester | 2nd–3rd trimester | 2nd–3rd trimester |
| Italy[EU] | 1st–3rd trimester | 3rd trimester | 1st–3rd trimester | 3rd trimester | 3rd trimester |
| Finland[EU] | 1st–3rd trimester | From 16th to 32nd week | 1st–3rd trimester | | |
| Estonia[EU] | 1st–3rd trimester | 2nd–3rd trimester | | | |
| Croatia[EU] | 1st–3rd trimester | 2nd–3rd trimester | | | 2nd–3rd trimester |
| Germany[EU] | 2nd–3rd trimester* | 2nd–3rd trimester | 2nd trimester | | 3rd trimester** |
| Norway | 2nd–3rd trimester* | From 24th week | 2nd–3rd trimester | 2nd–3rd trimester | 2nd–3rd trimester |
| Denmark[EU] | 2nd–3rd trimester* | 24th–32nd week** | 1st–3rd trimester | | |
| Netherlands[EU] | 2nd–3rd trimester | From 22nd week | | From 22nd week | From 22nd week |
| Luxemburg[EU] | 1st–3rd trimester | 13th–26th week | From 10th week | | |
| Portugal[EU] | 2nd–3rd trimester | 20th–36th week | 1st––3rd trimester | | |
| Iceland | 1st–3rd trimester | 2nd–3rd trimester | 1st–3rd trimester | | |
| Switzerland | 1st–3rd trimester | 13th–26th week | From 13th week | | |
| Sweden[EU] | 2nd–3rd trimester | From 16th week | From 12th week | | |
| Austria[EU] | 2nd–3rd trimester* | 27th–36th week | 2nd–3rd trimester | | |
| Czech Republic[EU] | 1st–3rd trimester | 3rd trimester | From 13th week | | |
| France[EU] | 1st–3rd trimester | 2nd–3rd trimester | 1st–3rd trimester | | |
| Romania[EU] | 1st–3rd trimester | 2nd–3rd trimester | | | |
| Ukraine | 1st–3rd trimester | 3rd trimester | | | |
| Cyprus[EU] | 1st–3rd trimester | 27th–36th week | | | |
| Greece[EU] | 1st–3rd trimester | 27th–36th week | | | |
| Poland[EU] | 1st–3rd trimester | 27th–36th week | | | |
| Liechtenstein | 1st–3rd trimester | 2nd trimester | | | |
| Slovenia[EU] | 1st–3rd trimester | From 24th week | | | |
| United Kingdom | 1st–3rd trimester | 2nd–3rd trimester | | | |
| Serbia | 1st–3rd trimester | 3rd trimester | | | |
| Lithuania[EU] | 1st–3rd trimester | | 1st–3rd trimester | | |
| Slovakia[EU] | 1st–3rd trimester | | 1st–3rd trimester | | |
| Malta[EU] | 2nd–3rd trimester* | | From 12th week | | |
| Moldova | | 3rd trimester | | | |
| Albania | 1st–3rd trimester | | | | |
| Belarus | 1st–3rd trimester | | | | |
| Hungary[EU] | 1st–3rd trimester | | | | |
| Latvia[EU] | 1st–3rd trimester | | | | |
| Monaco | 1st–3rd trimester | | | | |
| Russia | 2nd–3rd trimester* | | | | |

Figure adapted from Properzi et al. (34)

Table 9 provides information on annual number of births and maternal vaccination coverage for other vaccines. This provides some indication of the willingness of pregnant women to be vaccinated in Europe and the UK.

**Table 9. Estimates of maternal vaccination coverage**

| Country | Data source | Estimated births per year (*1000) in database | Vaccination coverage for pertussis in pregnancy | Vaccination coverage for influenza during pregnancy | Vaccination coverage for COVID during pregnancy (at least one dose) |
|---|---|---|---|---|---|
| Spain | VID | 45 | 84% | 50% | unknown |
| Spain | SIDIAP | 45 | 84% | 50% | unknown |
| Spain | EpiChron | 8 | unknown | unknown | |
| Denmark | Danish National Registries | 60 | unknown | unknown | 56% |
| Norway | Norway National Registries | 54 | unknown | unknown | 50% |
| Netherlands | Perined | 35 | 70%(35) | unknown | 30-50% |
| France | SNDS | 70 | 47% | 7% | unknown |
| UK | CPRD | 100 | 70%(36) | 44%(36) | 22%(37) |

*SIDIAP, Sistema d'Informació per al Desenvolupament de la Investigació en Atenció Primària; VID, Valencia Integrated Database; SNDS, Système National des Données de Santé; Perined, (merger organization of PAN [Perinatal Audit Netherlands] and PRN [Perinatal Registry Netherlands]); CPRD, Clinical Practice Research Datalink*

Table 10 provides the estimated prevalence of pregnancy outcomes and the incidence of GBS in various European data sources.

**Table 10. Prevalence of pregnancy outcomes and incidence of GBS in various European data sources (preterm birth, stillbirth and low birth weight is DAP specific or otherwise from Peristat)**

| Country | Data Source | Preterm birth (% of live births) | Stillbirth >24 wks /1000 live births | Low birth weight (<2500 g) | Placental abruption (38) | Hypertensive disorders of pregnancy (based on CONSIGN(11)) | SGA (39) | GBS (ACCESS study(40)) |
|---|---|---|---|---|---|---|---|---|
| Spain | VID | 7.1% | 3.0 | 7.9% | 0.4 - 1% | NA | NA | NA |
| Spain | SIDIAP | 7.1% | 3.0 | 7.9% | | 1.0% | NA | 1 to 1.5/100,000 person-years |
| Spain | EpiChron | 6.2 % | 4.0 | 6.4% | | 3.2 % | NA | |
| Denmark | Danish National Registries | 5.8% | 2.2 | 4.5% | | NA | NA | |
| Norway | Norway National Registries | 6.1% | 2.5 | 4.4% | | 3.8% | 3.9% | |
| Netherlands | Perined | 6.6% | 3.0 | 5.6% | | NA | NA | |
| France | SNDS | 6.9% | 3.6 | 7.1% | | NA | 8.8% | |

**Table 10. Prevalence of pregnancy outcomes and incidence of GBS in various European data sources (preterm birth, stillbirth and low birth weight is DAP specific or otherwise from Peristat)**

| **Country** | **Data Source** | **Preterm birth (% of live births)** | **Stillbirth >24 wks /1000 live births** | **Low birth weight (<2500 g )** | **Placental abruption** (38) | **Hypertensive disorders of pregnancy (based on CONSIGN**(11 )**)** | **SGA** (39) | **GBS (ACCESS study**(40)**)** |
|---|---|---|---|---|---|---|---|---|
| UK | CPRD | 7.8% | 3.3 | 7.4% | | NA | NA | |
| SIDIAP, Sistema d'Informació per al Desenvolupament de la Investigació en Atenció Primària; SNDS, Système National des Données de Santé; Perined, (merger organisation of PAN [Perinatal Audit Netherlands] and PRN [Perinatal Registry Netherlands]); CPRD, Clinical Practice Research Datalink; NA, not available. | | | | | | | | |

**Power and sample size**

Minimal detectable risks were calculated based on the assumption that at least every unvaccinated pregnant woman could be compared with one vaccinated pregnant woman (i.e, a ratio of 1:1 unexposed to exposed). The desired alpha level is 5%, and RR values of 1.5, 2.0, 2.5 and 4.0 were considered. For the GBS outcome we calculate the power obtainable assuming a maximum sample size of 30,000 exposed pregnant women, with an incidence rate (i.e, risk) of 1/100,000 person-years (PY) in the unexposed group (Table 11). For the pregnancy and birth outcomes, we calculated the required number of exposed persons to obtain a power of 80% under different RR values, assuming prevalence rates (i.e, risk in the unexposed group) between 0.2% and 5.0%. To detect a RR of 1.5 with 95% CI for preterm birth approximately 1200 pregnancies ending in livebirth would need to be included in each data source.

**Table 11. Power and Sample Size Estimates for GBS and Pregnancy/Birth Outcomes**

| **Risk Ratio (RR)** | **RR=1.5** | **RR=2.0** | **RR=2.5** | **RR=4.0** |
|---|---|---|---|---|
| **GBS**<br>(Incidence rate 1/100,000 PY, Maximum number exposed 30,000, 1:1 ratio unexposed:exposed) | | | | |
| Power to detect | 0.0341 | 0.0406 | 0.0461 | 0.0628 |
| **Pregnancy and Neonatal Outcomes (Sample Size)**<br>(Power of 80%, 1:1 ratio unexposed:exposed, rounded-up to nearest hundred) | | | | |
| Prevalence 0.2% (e.g. stillbirth) | 38600 | 11300 | 5700 | 1900 |
| Prevalence 1% | 7600 | 2300 | 1200 | 400 |
| Prevalence 2% | 3800 | 1100 | 600 | 200 |
| Prevalence 3% | 2500 | 800 | 400 | 100 |

**Table 11. Power and Sample Size Estimates for GBS and Pregnancy/Birth Outcomes**

| Risk Ratio (RR) | RR=1.5 | RR=2.0 | RR=2.5 | RR=4.0 |
|---|---|---|---|---|
| Prevalence 4% | 1900 | 600 | 300 | 100 |
| Prevalence 5% | 1500 | 500 | 300 | 100 |
| Prevalence 6% (e.g. preterm birth, low birth weight) | 1200 | 350 | 200 | 100 |

Estimates based on the "Cohort Power" tab of Episheet, by K. Rothman and O. Miettinen.

Table 12 provides the estimated prevalence of immunocompromised pregnant women and high-risk pregnancies. The proportion of pregnant women with immunocompromised status is estimated to be around 3-5%. However, research findings often pertain to specific populations and settings. In the CONSIGN study, which includes pregnant women with and without COVID-19 and utilizes some of the VAC4EU data sources, the risks of HIV and immunosuppressive use are outlined below. There is some variation between data sources, but approximately 3-4% of women use immunosuppressants, which may include those treated for a threatening preterm birth. It is estimated that around 10-15% of pregnancies are considered high-risk. Again, this can vary based on the population, setting and the definition of high-risk pregnancy used. In the VAC4EU data sources in the CONSIGN study, the prevalence of a history of adverse pregnancy outcomes was around 7-9% in most data sources and 2% in Norway.

**Table 12. Prevalence of immunocompromised status in pregnancy and high-risk pregnancy in various European data sources (based on CONSIGN study)**

| Data Source | VID | SIDIAP | EpiChron | NHR | DHR | PHARMO | SNDS[1] | CPRD |
|---|---|---|---|---|---|---|---|---|
| HIV | 2/11,908 (0.02%) | NA | 0/3,568 (0%) | 4/4,696 (0.09%) | NA | NA | 10/4,060 (0.2%) | NA |
| Use of immunosuppressants | 359/11,908 (3.0%) | NA | 149/3,568 (4.2%) | 149/4,696 (3.2%) | NA | NA | 835/4,060 (20.6%) | NA |
| Prior history of adverse pregnancy outcomes[2] | 939/11,908 (7.9%) | NA | 308/3,568 (8.6%) | 83/4,696 (1.8%) | NA | NA | 270/4,060 (6.7%) | NA |

1 SNDS contains hospital data only
2 Gestational diabetes, hypertensive disorders, stillbirth. spontaneous abortions, SGA, FGR, major congenital malformations.

### 9.6. Data Management

The study will be conducted in a distributed manner using the UMCU and VAC4EU tools, procedures, and pipeline. This pipeline can be viewed from a programming perspective (see Figure 3) or tool perspective (see Figure 4). Figure 4 specifies the data sets (D) and transformation processes (T), programming follows this pipeline, with involvement of different types of experts.

**Figure 3. Data Management from the data transformation perspective**

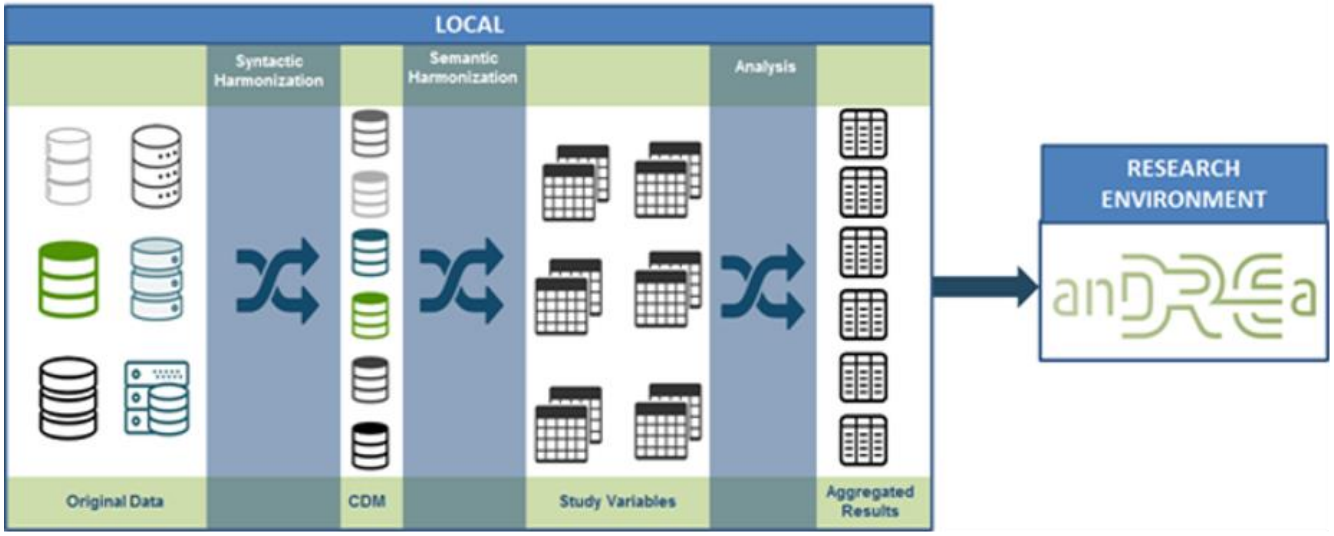
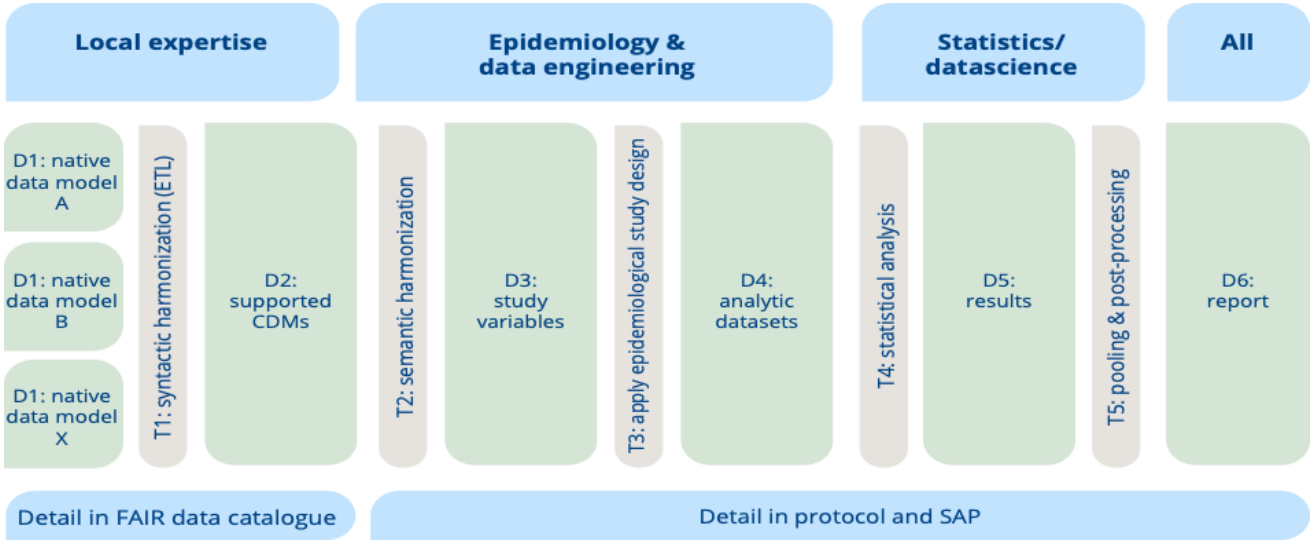



**Figure 4. Data Management from a systems and location perspective**




*D1: Original data can be in any native format*

The RWD-RWE pipeline used by VAC4EU starts with data banks that are controlled by the DAP, these can be in any format. This stays local. The ETL design is shared in a searchable FAIR VAC4EU catalogue. The VAC4EU FAIR Molgenis data catalogue is a meta-data management tool designed to contain searchable meta-data describing organisations that can provide access to specific data sources.

*T1: Syntactic harmonisation (ETL)*

T1: Syntactic harmonisation is conducted through an extraction, transformation, and loading (ETL) process of native data into the requested CDM. To harmonise the structure of the data sets stored and maintained by each data partner, a shared syntactic foundation is used. The ETL process has various structured steps as described by Thurin et al (2021)(41):

- DAPs are asked to share the data dictionaries of their data banks (selected tables and variable names/structure)
- Metadata (descriptive data about the data sources and databanks) & data dictionaries, are uploaded in FAIR data catalogue (Molgenis).

*D2: Common data model*

For this project, the CDM (D2) is the ConcePTION common data model. The CDM version that is used is v2.2, which is available as an open-source CDM. In this CDM, data are represented in a common structure, but the values of the data remain in their original language (e.g. codes will have either ICD9/10/ICPC/SNOMED values).

*T2: Semantic harmonisation*

During the T2 step, many data transformations occur related to the completion of missing features in the data. Based on the relevant diagnostic medical codes and keywords, as well as other relevant concepts (e.g., medications), one or more phenotype algorithms are constructed (typically one sensitive, or broad, algorithm and one specific, or narrow, algorithm) to operationalise the identification and measurement of each event. In this step we conduct time anchoring (observation periods, look back periods), clean the data such as the dose of vaccines, sort on record level, aggregate across multiple records, and combine concepts for implantation of algorithms, and rule-based creation of study variables.

In this phase of the creation of study variables, semantic mapping is conducted. This semantic mapping across different vocabularies is conducted as part of the R-study script using different functionalities. To reconcile differences between different terminologies and native data availability, machine-readable code lists are used that comprise the terminologies that are used in the network (e.g. ICD-9, ICD10, SNOMED, ICPC and DAP specific adaptations). This is combined with the BRIDGE metadata file that defines risk windows, look-back periods, and algorithms for each study variable (Cid Royo et al., 2023)(42).

*D3: Study variables*

D3 datasets are interim data sets with information on study variables for each study participant, the unit may be a person, a medicine, or episode of time. The design of these datasets is described in codebooks. Examples of D3 datasets are the outputs of the ConcePTION pregnancy algorithm, functions that define smoking. Multiple functions/packages exist within the VAC4EU, for different study variables.

*T3: Application of epidemiological design*

In the T3 step epidemiological designs are applied such as sampling, matching (on specific variables and/or propensity scores), and selection based on inclusion and exclusion criteria using the study variables in the D3 datasets. The designs will be implemented for the various study objectives using R-scripts, and these may use the existing functions (R-cran) or functions that have been developed in the VAC4EU community (e.g. matching).

*D4: Analytical data set*

D4 is an analytical dataset, and multiple D4 data sets may be produced based on the objectives of the study. The format is described initially in a code book for communication between programmers and statisticians.

*T4: Statistical analysis*

This step in the data transformation pipeline will produce statistical estimates such as descriptives (counts, percentages), distributions (mean, percentiles), rates (prevalence, incidence), regression coefficients, or other relevant estimates. This will be conducted using R.

*D5: Results*

D5 is the set of estimands, tables or aggregate data that is transferred from the DAPs to the Digital Research Environment (DRE). The aggregated results produced by these scripts at the DAPs site will be uploaded to the UMCU DRE for post-processing, pooling and visualisation (Figure 3). The DRE is a cloud-based, globally available research environment where data are stored and organised securely and where researchers can collaborate. The DRE is made available through UMCU. The DRE applies double authentication where researchers can collaborate using data that are stored and organised securely.(43) UMC Utrecht is responsible for data processing and data security.

All researchers who need access to the DRE will be granted access to study-specific secure workspaces by UMCU. Access to the workspaces will be possible only after double authentication using an identification code and password together with the user's mobile phone for authentication.

Uploading of files will be possible for all researchers with access to the workspace within the DRE. Downloading of files will be possible only after requesting and receiving permission from a workspace member with an "owner" role, who will be a UMCU team member.

*T5: Post-processing/pooling.*

In this step, the result from different DAPs is pooled and converted into tables and figures for reporting.

*Scripting and deployment*

The analytical R scripts that produce the T2-T4 steps are produced on UMCU-RWE GitHub for version control. Links to the latest script will be distributed to DAPs for local deployment. Any issues can be notified on the private GitHub, and the data engineers who are responsible for the R code will work with the local DAP to resolve issues if they occur.

After the final report is accepted the script will be made publicly available through GitHub and get a digital object identifier through Zenodo.

### 9.7. Data Analysis

Detailed methodology for summary and statistical analyses of data collected in this study will be documented in a statistical analysis plan (SAP), which will be dated, filed and maintained by the sponsor. The SAP will be annotated and may modify plans in the initial protocol, and any major modifications of the primary endpoint definition will be reflected in protocol amendments.

#### 9.7.1. Descriptive Analyses

**Periodic assessment**

Each Progress Report will present the total number of pregnancies, ABRYSVO exposed pregnancies and gestational week at vaccination (to the extent available), and type of information that has been used to identify the pregnancies.

**Interim /final reports**

Description of baseline characteristics for ABRYSVO exposed and comparator cohorts will be reported as means, standard deviations, medians and other quartiles for continuous variables and as counts and proportions for categorical variables. Missingness of lifestyle factors will also be described, as well as the duration of the look-back period.

To describe the comparability of matched cohorts, we will estimate standardised differences between ABRYSVO exposed and matched non-exposed cohorts for each baseline characteristic. For categorical variables with more than 2 levels, we will calculate an overall standardised difference across all levels.

For pregnancy and birth outcomes, risk, prevalence and 95% CIs will be reported, for the time interval between vaccination and delivery, median and distributions will be provided.

#### 9.7.2. Unadjusted Outcome Measures

In the study population, unadjusted risk, incidence and prevalence ratios or differences will be estimated comparing the incidence or prevalence between ABRYSVO exposed cohort and the comparator cohort, with 95% CI.

Subgroup analyses will be conducted for immunocompromised status, high risk pregnancies, and weeks of gestation for secondary analyses.

#### 9.7.3. Adjustment For Baseline Imbalances

The ABRYSVO exposed and unexposed comparator cohorts will be matched 1:1 at Time zero on several time-related variables (age of mother, gestational week, and calendar time) as well as immunocompromised status and high-risk pregnancy. This will create some balance of important confounding variables. Other characteristics and risk factors for the different outcomes may remain unbalanced. Propensity score methods will be used to adjust for

confounders that remain imbalanced. The primary analysis may suffer from selective censoring due to treatment crossover in the unexposed and will require inverse probability censoring weights.

Time from vaccination to birth will be analysed using regression analyses, or in the case of censoring, time-to-event analyses, with gestational age at the time of vaccination as a covariate in the model. Additionally, the cumulative distribution of the interval for exposed versus unexposed groups will be plotted. More details on these issues and the detailed analysis will be provided in the SAP.

### 9.7.4. Sensitivity Analyses

Sensitivity analyses will include:

- A modification of the study period, to ensure that short pregnancies that start the study observation period are not selectively incorporated into the study population; this analysis will stop the accrual of pregnancies earlier to allow at least 10 months of data between LMP and the last observed data point.
- An exploration of the potential impact of treatment crossover by censoring the matched pair when the unexposed woman later receives a vaccination with ABRYSVO.
- Excluding medically indicated (iatrogenic) preterm births

### 9.7.5. Meta-Analysis

Analyses will be conducted separately within each data source based on a common R-script that will be provided by UMC Utrecht. Using the main estimates from each data source, appropriate random-effects meta-analytic methods will be used to obtain a combined effect estimate. The heterogeneity across data sources will be checked, and a forest plot will be produced with the data sources and the pooled estimate. In the situation where there are zero events, we will also report and meta-analyse incidence rates separately. Incidence rates can be zero and yield valid standard errors.

### 9.7.6. Small Cells Count Policy

Table 13 shows the small cell count rules for each data source that will be considered for the report.

**Table 13. Masking requirements for small cell counts**

| Country-DAP | Numbers to be masked | Text to be used in redactions | Possible to share with regulators | Comments |
|---|---|---|---|---|
| **ES-VID** | NA | NA | NA | NA |
| **ES-SIDIAP** | 1-4 | 1≤n<15 | Yes | Not applicable |
| **ES-EpiChron** | 1-4 | 1<n<15 | Yes | |

**Table 13. Masking requirements for small cell counts**

| Country-DAP | Numbers to be masked | Text to be used in redactions | Possible to share with regulators | Comments |
|---|---|---|---|---|
| **NO-NHR** | 1-5 | <5 | No | |
| **DK-DHR** | 1-4 | <5 | No | Numbers should also be masked if they allow computation of small counts from surrounding data, such are proportions of confidence limits, or other complementary data that allow back-calculation of small counts between 1 and 4. Zeros can be reported. |
| **NL-PHARMO** | No results may be displayed for N (denominator) below 5 (note: cell counts below 5 can be displayed, as long as the (sub)cohort of interest includes at least 5 patients. | | Yes | Not applicable |
| **FR-SNDS** | 1-10 | 1≤n≤10 | No | A statement about cell suppression is required |
| **UK-CPRD** | 1-5 | <5 | Yes | CPRD allows an exemption from the small cell suppression requirement for regulatory submissions to medicines regulatory agencies to inform policy decisions on the condition that the small cells will be suppressed if the regulators wish to publish the results in the interest of transparency |

## 9.8. Quality Control

## 9.9. Limitations Of The Research Methods

Key limitations of this study as foreseen at the moment of writing the protocol are listed below:

- *Identification of RSV vaccination (ABRYSVO).* At this time of preparation of this protocol, it is not certain how maternal immunisation programs for RSV in each of the countries represented in this study will be implemented. which directly impacts the ascertainment of exposure. Some data sources that are included capture vaccines provided through the national immunisation program (e.g., DK, NO, VID, SIDIAP), but others only capture claims (SNDS) or vaccines provided by GP (e.g. PHARMO, CPRD). As part of the feasibility assessment, we will assess exposure to *ABRYSVO* in each of the data sources and benchmark with national estimates. Only data sources that capture ABRYSVO F exposure accurately will be included in the comparative analyses of outcomes between exposed and unexposed.

- *Comparator group.* We will use a non-exposed comparator group because there is presently no other marketed maternal vaccine for RSV. Depending on the uptake of the *ABRYSVO* vaccine, it may be possible for crossover to occur whereby the non-exposed pregnant woman in the comparator group becomes vaccinated with *ABRYSVO*. In this instance, the vaccinated woman in the comparator group will be censored. This may lead to selective censoring, which may be avoided by censoring the entire pair. This will be conducted in a sensitivity analysis. For the main analysis we will maintain maximum power by not censoring the exposed and adjust for selective censoring by inverse probability for censoring weights.

- *Channelling and confounding*. The lack of use of an active comparator facilitates potential confounding since those who received the vaccine may have different healthcare-seeking behaviour and risk of outcomes than those who do not get vaccinated. Confounding will be addressed by design (matching) and by adjustment/matching using propensity scores.

- *Pregnancies detected while still ongoing*. To increase power, we will include all pregnancies that can be identified and that comply with eligibility criteria, including pregnancies that may have an unknown outcome. Some pregnancies with unknown outcome cannot plausibly be ongoing, especially if the expected end date would fall within the observed follow-up period. This would mean that the outcome would inadvertently not be captured or delayed in the data source. In data sources that capture births through birth registers, lack of information might be assumed to represent foetal loss. We will compare the rate of pregnancies, which should have an end of pregnancy within the follow-up period, between the comparator groups, to inspect this imbalance.

- To ensure that short pregnancies that start later in the study period are not selectively incorporated in the study population we will conduct a sensitivity analysis that will only include pregnancies with at least 10 months of follow-up after LMP.

- *Outcome misclassification.* This study will use previously collected health care data to identify outcomes of interest, using diagnostic codes/algorithms or observations in birth registers. Diagnostic codes may be misclassified. To be specific we will use code lists from VAC4EU and codes that have been tagged as narrow (specific/incident). These tags aim to reduce the false positive rate. Validation studies of some events (e.g., GBS) are ongoing at the moment for different VAC4EU studies, and PPVs will be available for potential use. For preterm birth, validation may be needed since preterm birth may be either spontaneous or iatrogenic for other circumstances. We will conduct a sensitivity analysis excluding medically indicated iatrogenic preterm births. If the LMP is estimated incorrectly, gestational age may be misclassified and therefore also preterm birth, this cannot be verified, but we assume

it will be non-differential. If pregnancy end date is imputed (i.e., earlier than actual date), the proposed diagnostic window for placental abruption could fail to capture some cases.

### 9.10. Other Aspects

Not applicable.

## 10. PROTECTION OF HUMAN PARTICIPANTS

### 10.1. Participant Information

This study involves data that exist in a deidentified/pseudonymised structured format and contain no patient personal information.

### 10.2. Patient Consent

As this study involves deidentified/pseudonymised structured data, which are subject to the General Data Protection Regulation; obtaining informed consent from patients by Pfizer is not required.

### 10.3. Institutional Review Board (IRB)/ Ethics Committee (EC)

There must be prospective approval of the study protocol, protocol amendments, and other relevant documents (e.g., informed consent forms if applicable) from the relevant IRBs/ECs or data source governance committees. All correspondence must be retained. Copies of IRB/EC approvals or waivers must be forwarded to Pfizer.

### 10.4. Ethical Conduct Of The Study

The study will be conducted in accordance with legal and regulatory requirements, as well as with scientific purpose, value, and rigor and follow generally accepted research practices described in the following paragraphs:

The study will be conducted according to the guidelines for Good Pharmacoepidemiology Practice (GPP) (International Society for Pharmacoepidemiology)(44) and has been designed in line with the *ENCePP Guide on Methodological Standards in Pharmacoepidemiology revision 11*,(45) the UK MHRA *guidance on the use of real-world data in clinical studies to support regulatory decisions*(46) and the FDA guidance "*Considerations for the Use of Real-World Data and Real-World Evidence To Support Regulatory Decision-Making for Drug and Biological Products*".(47)

The ENCePP Checklist for Study protocols is included for this protocol (Annex 2.).

The study is a PASS and will comply with the definition of the non-interventional study referred to in the International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use tripartite guideline Pharmacovigilance E2E (48) and provided in the EMA *Guideline on Good Pharmacovigilance Practices (GVP) module VIII*. (49) The study will comply with the study reporting requirements specified in module VIII Section VIII.B.6.3.1, Progress Reports and Section VIII.B.6.3.2, Final Study Report of the Guideline of Good Pharmacovigilance practices. In alignment with the EMA

GVP Module VIII Section VIII.B.2, “Study Registration” the study and its protocol will be registered in the HMA-EMA Catalogue of RWD studies(50) before the start of data collection. At completion, the final report or its summary will be posted.

All partners are ENCePP centers and members of the VAC4EU international association, an ENCePP-listed network. VAC4EU adheres to the general principles of transparency and scientific independence in the *ENCePP Code of Conduct.*(51)

## 11. MANAGEMENT AND REPORTING OF ADVERSE EVENTS/ADVERSE REACTIONS

This study involves data that exist as structured data by the time of study start. In these data sources, it is not possible to link (i.e, identify a potential association between) a particular product and medical event for any individual. Thus, the minimum criteria for reporting an adverse event (AE) (i.e, identifiable patient, identifiable reporter, a suspect product, and event) cannot be met.

## 12. PLANS FOR DISSEMINATING AND COMMUNICATING STUDY RESULTS

As per EMA GVP Module VIII, the study and its protocol will be registered in the HMA-EMA Catalogue of RWD studies prior to the start of data collection. Progress and Final Reports will be posted as well. The study protocol and reports will be submitted to the FDA and the EMA as agreed in the RMP/PVP. Results will be delivered in report form.

Planned Reports:
Progress Reports: every 6 months beginning in June 2025 through June 2026, and then annually through June 2028.

Interim Study Report: 31 December 2026

Final Study Report: 28 September 2029

Study results will be published following guidelines, including those for authorship, established by the International Committee of Medical Journal Editors (ICMJE). When reporting the results of this study, the appropriate Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) checklist will be followed. Independent publication rights will be granted to the research team in line with Section VIII.B.5., Publication of study results, of the EMA *Guideline on Good Pharmacovigilance Practices (GVP) Module VIII: Post-Authorisation Safety Studies*.

Upon study completion and finalisation of the study report, the results of this PASS will be submitted for publication, preferably in a relevant peer-reviewed journal. Communication via other appropriate scientific venues will be considered.

In the event of any prohibition or restriction imposed (e.g. clinical hold) by an applicable competent authority in any area of the world, or if the responsible parties are aware of any new information which might influence the evaluation of benefits and risks of a Pfizer product, Pfizer should be informed immediately.

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## 14. LIST OF TABLES



## 15. LIST OF FIGURES



## 16. ANNEX 1. LIST OF STANDALONE DOCUMENTS

None.

# 17. ANNEX 2. ENCEPP CHECKLIST FOR STUDY PROTOCOLS

| |
|---|
| **Study title:** A Post-Authorisation Safety Study of ABRYSVO (Respiratory Syncytial Virus Stabilised Prefusion F Subunit Vaccine) in Pregnant Women and their Offspring in a Real World Setting in Europe and UK |

| |
|---|
| **EU PAS Register® number:** To be registered before the start of data collection<br>**Study reference number (if applicable):** Not applicable |

| **Section 1: Milestones** | **Yes** | **No** | **N/A** | **Section Number** |
|---|---|---|---|---|
| 1.1 Does the protocol specify timelines for | | | | 6 |
| 1.1.1 Start of data collection[1] | ☒ | ☐ | ☐ | |
| 1.1.2 End of data collection[2] | ☒ | ☐ | ☐ | |
| 1.1.3 Progress report(s) | ☒ | ☐ | ☐ | |
| 1.1.4 Interim report(s) | ☒ | ☐ | ☐ | |
| 1.1.5 Registration in the HMA-EMA Catalogue of RWD studies | ☒ | ☐ | ☐ | |
| 1.1.6 Final report of study results. | ☒ | ☐ | ☐ | |

Comments:

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| |

| **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) | ☒ | ☐ | ☐ | 7 |
| 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) | ☒ | ☐ | ☐ | 9.2 |
| 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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[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 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) | ☒ | ☐ | ☐ | 9.5 |
| 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)) | ☒ | ☐ | ☐ | 9.5 |
| 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) | ☐ | ☐ | ☒ | |

Comments:

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| **Section 4: Source and study populations** | **Yes** | **No** | **N/A** | **Section Number** |
|---|---|---|---|---|
| 4.1 Is the source population described? | ☒ | ☐ | ☐ | 9.2 |
| 4.2 Is the planned study population defined in terms of: | | | | |
| 4.2.1 Study time period | ☒ | ☐ | ☐ | 9.2.4 |
| 4.2.2 Age and sex | ☐ | ☐ | ☒ | |
| 4.2.3 Country of origin | ☐ | ☒ | ☐ | |
| 4.2.4 Disease/indication | ☒ | ☐ | ☐ | 9.2.1 |
| 4.2.5 Duration of follow-up | ☒ | ☐ | ☐ | 9.2.3 |
| 4.3 Does the protocol define how the study population will be sampled from the source population? (e.g. event or inclusion/exclusion criteria) | ☒ | ☐ | ☐ | 9.2.1 and 9.2.3 |

Comments:

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| **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) | ☒ | ☐ | ☐ | 9.3.2 |
| 5.2 Does the protocol address the validity of the exposure measurement? (e.g. precision, accuracy, use of validation sub-study) | ☐ | ☐ | ☒ | |
| 5.3 Is exposure categorised according to time windows? | ☒ | ☐ | ☐ | 9.3.3 |

| **Section 5: Exposure definition and measurement** | **Yes** | **No** | **N/A** | **Section Number** |
|---|---|---|---|---|
| 5.4 Is intensity of exposure addressed? (e.g. dose, duration) | ☒ | ☐ | ☐ | 9.3.3 |
| 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? | ☒ | ☐ | ☐ | 9.1 |

Comments:

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| **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? | ☐ | ☐ | ☒ | |
| 6.2 Does the protocol describe how the outcomes are defined and measured? | ☒ | ☐ | ☐ | 9.3.3 |
| 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, health care services utilisation, burden of disease or treatment, compliance, disease management) | ☐ | ☐ | ☒ | |

Comments:

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| **Section 7: Bias** | **Yes** | **No** | **N/A** | **Section Number** |
|---|---|---|---|---|
| 7.1 Does the protocol address ways to measure confounding? (e.g. confounding by indication) | ☒ | ☐ | ☐ | 9.7.3 |
| 7.2 Does the protocol address selection bias? (e.g. healthy user/adherer bias) | ☒ | ☐ | ☐ | 9.2 |
| 7.3 Does the protocol address information bias? (e.g. misclassification of exposure and outcomes, time-related bias) | ☒ | ☐ | ☐ | 9.2 |

Comments:

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| **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, sub-group analyses, anticipated direction of effect) | ☒ | ☐ | ☐ | 9.7.2 |

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) | ☒ | ☐ | ☐ | 9.4 |
| 9.1.2 Outcomes? (e.g. clinical records, laboratory markers or values, claims data, self-report, patient interview including scales and questionnaires, vital statistics) | ☒ | ☐ | ☐ | 9.4 |
| 9.1.3 Covariates and other characteristics? | ☒ | ☐ | ☐ | 9.4 |
| 9.2 Does the protocol describe the information available from the data source(s) on: | | | | |
| 9.2.1 Exposure? (e.g. date of dispensing, drug quantity, dose, number of days of supply prescription, daily dosage, prescriber) | ☒ | ☐ | ☐ | 9.4 |
| 9.2.2 Outcomes? (e.g. date of occurrence, multiple event, severity measures related to event) | ☒ | ☐ | ☐ | 9.4 |
| 9.2.3 Covariates and other characteristics? (e.g. age, sex, clinical and drug use history, co-morbidity, co-medications, 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) | ☒ | ☐ | ☐ | 9.4 |

Comments:

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| **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 |

| **Section 10: Analysis plan** | **Yes** | **No** | **N/A** | **Section Number** |
|---|---|---|---|---|
| 10.2 Is study size and/or statistical precision estimated? | ☒ | ☐ | ☐ | 9.5 |
| 10.3 Are descriptive analyses included? | ☒ | ☐ | ☐ | 9.7.1 |
| 10.4 Are stratified analyses included? | ☒ | ☐ | ☐ | 4 |
| 10.5 Does the plan describe methods for analytic control of confounding? | ☒ | ☐ | ☐ | 9.9 |
| 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? | ☒ | ☐ | ☐ | 9.8.1 |
| 10.8 Are relevant sensitivity analyses described? | ☒ | ☐ | ☐ | 9.7.4 |

Comments:

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| **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) | ☒ | ☐ | ☐ | 9.6 |
| 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? | ☒ | ☐ | ☐ | 9.9 |
| 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). | ☒ | ☐ | ☐ | 9.9 |
| 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? | ☒ | ☐ | ☐ | 10.3 |
| 13.2 Has any outcome of an ethical review procedure been addressed? | ☒ | ☐ | ☐ | 10.3 |
| 13.3 Have data protection requirements been described? | ☒ | ☐ | ☐ | 10.2 |

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: | Cynthia de Luise<br>Safety Surveillance Research Worldwide Medical and Safety, Pfizer, Inc., New York, NY | |
| Date: dd/Month/year | 14 March 2024 | |
| Signature: |  | |

# 18. ANNEX 3. ADDITIONAL INFORMATION

## Annex 3. Checklist for Reporting In Perinatal Pharmacoepidemiology

| # | Element | Yes | No | N/A | Section Number |
|---|---|---|---|---|---|
| **Source of information on beginning and end of pregnancy** | | | | | |
| 1 | Source of information for start of pregnancy (e.g., electronic algorithm, ultrasound) | ☒ | ☐ | ☐ | 9.3.1 |
| 2 | Source of information for pregnancy outcome date (e.g., recorded codes for spontaneous abortion, date estimated using algorithm) | ☒ | ☐ | ☐ | 9.3.1 |
| **Composition of the study population** | | | | | |
| 3 | Multifetal pregnancies included in study population? | ☒ | ☐ | ☐ | 9.3.4 |
| 4 | More than one pregnancy per woman included in study population? | ☒ | ☐ | ☐ | 9.2.1 |
| 5 | Fetuses with chromosomal abnormalities included in study population? | ☒ | ☐ | ☐ | 9.9.2 (Not part of the exclusion criteria) |
| 6 | Fetuses with major malformations included in study population? | ☒ | ☐ | ☐ | 9.9.2 (Not part of the exclusion criteria) |
| 7 | Fetuses with minor malformations included in study population? | ☒ | ☐ | ☐ | 9.9.2 (Not part of the exclusion criteria) |
| 8 | Non-live births included in denominator? | ☒ | ☐ | ☐ | 9.3.3 (Specified per outcome what denominator is) |
| **Mother-infant and father-infant linkage** | | | | | |
| 9 | If mother-infant linkage was implemented, was the process described? | ☒ | ☐ | ☐ | 9.3.1 (Described per data source) |
| 10 | If mother-infant linkage was implemented, was the success rate reported? | ☒ | ☐ | ☐ | 9.3.1 (Described per data source) |
| 11 | If mother-infant linkage was implemented, was the information taken from maternal versus infant files? | ☒ | ☐ | ☐ | 9.3.1 (Described per data source) |
| 12 | If father-infant linkage was implemented, was the process described? | ☐ | ☐ | ☒ | Not implemented |
| 13 | If father-infant linkage was implemented, was the success rate reported? | ☐ | ☐ | ☒ | Not implemented |
| **Analytical aspects** | | | | | |
| 14 | Unit of analysis for pregnancy outcomes | ☒ | ☐ | ☐ | 9.3.3 |
| 15 | Unit of analysis for fetal or infant outcomes | ☒ | ☐ | ☐ | 9.3.3 |

| # | Element | Yes | No | N/A | Section Number |
|---|---|---|---|---|---|
| 16 | Gestational age at start of follow | ☒ | ☐ | ☐ | 9.2.1 |
| 17 | Was intrafamily correlation considered? | ☐ | ☒ | ☐ | To obtain power, analyses are not restricted to one pregnancy per women. However, correlation between pregnancies within a patient is not considered. |

Abbreviation: N/A=not applicable.

# Document Approval Record

| | |
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