# PASS information

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|---|---|
| Title | Monitoring safety of Spikevax in pregnancy: an observational study using routinely collected health data in five European countries |
| Protocol version identifier | Version 1.2 |
| Current date of protocol | 27 September 2021 |
| EU PAS register number | Protocol will be registered before start of the data collection |
| Active substance | COVID-19 mRNA-1273 vaccine (nucleoside modified) |
| Medicinal product | COVID-19 Vaccine Moderna/Spikevax |
| Product reference | EMEA/H/C/005791 |
| Procedure number | MEA 034 |
| Marketing authorisation holder(s) | Moderna Biotech Spain, S.L.<br>Calle Monte Esquinza 30<br>28010 Madrid<br>Spain |
| Joint PASS | No |
| Research question and objectives | The overarching research question is: is there a greater risk or prevalence of pregnancy complications, adverse pregnancy outcomes, or adverse neonatal outcomes following pregnancies exposed to Spikevax compared with pregnancies unexposed to Spikevax?<br>Primary objectives:<br>• To determine whether exposure to the Spikevax during pregnancy is associated with an increased risk of:<br>a. Pregnancy complications<br>b. Adverse pregnancy outcomes<br>c. Major congenital malformations in the offspring (overall and organ-specific if feasible)<br>d. Adverse neonatal outcomes |

| | |
|---|---|
| | Secondary objectives<br>• To describe utilization of Spikevax in pregnancy |
| Country(-ies) of study | Denmark, Italy, Norway, Spain, United Kingdom |
| Authors | |

Marketing authorisation holder(s)

| | |
|---|---|
| Marketing authorisation holder(s) | ModernaTX, Inc. |
| MAH contact person | |

# 1. Table of contents

# 2. List of abbreviations

| Abbreviation | Explanation |
|---|---|
| ACCESS | vACCine COVID-19 monitoring readinESS |
| AE | Adverse event |
| AESI | Adverse event of special interest |
| ARDS | Acute respiratory distress syndrome |
| ATC | Anatomical Therapeutic Chemical |
| BMI | Body mass index |
| CONSIGN | COVID-19 infectiOn aNd medicineS In preGNancy |
| CDC | Centers for Disease Control and Prevention |
| CDM | Common data model |
| CI | Confidence interval |
| COVID-19 | Coronavirus disease 2019 |
| COPD | Chronic obstructive pulmonary disease |
| CPRD | Clinical Practice Research Datalink |
| DAP | Data access provider |
| DRE | Digital Research Environment |
| DSRU | Drug Safety Research Unit |
| EEA | European Economic Area |
| EMA | European Medicines Agency |
| ENCePP | European Network of Centres for Pharmacoepidemiology and Pharmacovigilance |
| ETL | extraction, transformation, and loading |
| EU | European Union |
| EUROCAT | European network of population-based registries for the epidemiological surveillance of congenital malformations |
| GDPR | General Data Protection Regulation |
| GVP | Guideline on good pharmacovigilance practices |
| ICD-9CM | International Classification of Diseases, 9th Revision, Clinical Modification |
| ICPC | International Classification of Primary Health Care |
| ICD-10 | International Classification of Diseases, 10th Revision |
| ICD-10CM | International Classification of Diseases, 10th Revision, Clinical Modification |
| ISPE | International Society for Pharmacoepidemiology |
| MAH | Marketing Authorisation Holder |
| MHRA | Medicines and Healthcare products Regulatory Agency |
| mRNA | Messenger ribonucleic acid |
| PASS | postauthorisation safety study |
| PRAC | Pharmacovigilance Risk Assessment Committee |
| RMP | Risk Management Plan |

| Abbreviation | Explanation |
|---|---|
| SGA | Small for gestational age |
| SAP | Statistical Analysis Plan |
| SARS-CoV-2 | severe acute respiratory syndrome coronavirus 2 |
| STROBE | Strengthening the Reporting of Observational Studies in Epidemiology |
| TOPFA | Termination of Pregnancy for Fetal Anomaly |
| TBD | To be determined |
| UK | United Kingdom |
| US | United States |
| VAC4EU | Vaccine monitoring Collaboration for Europe |

# 3. Responsible parties

| Center | Role | Address | Main Contact Person |
|---|---|---|---|
| Moderna Tx | Sponsor | | |
| Aarhus University, Denmark | Lead Scientific Center | | |
| Julius Clinical Research | Lead Operating Center | | |
| Aarhus University, Denmark | Data Access Provider | | |
| University of Oslo, Norway | Data Access Provider | | |
| ARS Toscana, Italy | Data Access Provider | | |

| | | | |
|---|---|---|---|
| IDIAP JGolSpain | Data Access Provider, Spain | | |
| DSRU, UK | Data Access Provider | | |

## Signatory Approval

Reviewed and Approved by

| | | | |
|---|---|---|---|
| Daina Esposito | DocuSigned by: Daina Esposito<br>Signer Name: Daina Esposito<br>Signing Reason: I approve this document<br>Signing Time: 03-Nov-2021 \| 07:32 EDT<br>EE68054F1F2644EEBA6C523EF7E30974 | Senior Director, Global Safety Epidemiologist, PV | 03-Nov-2021 \| 07:33 E |
| Moderna, Study Lead | **Signature** | **Title** | **Date** |
| Marie Caby-Tosi | DocuSigned by: Marie Caby-Tosi<br>Signer Name: Marie Caby-Tosi<br>Signing Reason: I approve this document<br>Signing Time: 01-Nov-2021 \| 10:55 EDT<br>3D343A0A6E0B43E1B2B998FF74A14C27 | EEA/UK QPPV | 01-Nov-2021 \| 10:55 E |
| Moderna, EU QPPV | **Signature** | **Title** | **Date** |
| Henrik Toft Sørensen | | | |
| Aarhus University, Principal Investigator | **Signature** | **Title** | **Date** |

## Signatory Approval

Reviewed and Approved by

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| Daina Esposito | DocuSigned by: Daina Esposito Signer Name: Daina Esposito Signing Reason: I approve this document Signing Time: 03-Nov-2021 \| 07:32 EDT EE68054F1F2644EE8A6C523EF7E30974 | Senior Director, Global Safety Epidemiologist, PV | 03-Nov-2021 \| 07:33 E |
| Moderna, Study Lead | **Signature** | **Title** | **Date** |
| Marie Caby-Tosi | DocuSigned by: Marie Caby-Tosi Signer Name: Marie Caby-Tosi Signing Reason: I approve this document Signing Time: 01-Nov-2021 \| 10:55 EDT 3D343A0A6E0B43E1B2B998FF74A14C27 | EEA/UK QPPV | 01-Nov-2021 \| 10:55 E |
| Moderna, EU QPPV | **Signature** | **Title** | **Date** |
| Henrik Toft Sørensen | Henrik Toft Sørensen | Professor, Chair | 04-Nov-2021 |
| Aarhus University, Principal Investigator | **Signature** | **Title** | **Date** |

# 4. Abstract

**Title**

Monitoring safety of Spikevax in pregnancy: an observational study using routinely collected health data in five European countries

mRNA-1273-P904, Protocol Draft Version 1.1, 19 August 2021

Professor Vera Ehrenstein, Aarhus University, Denmark

**Rationale and background**

The novel coronavirus SARS-CoV-2 (severe acute respiratory syndrome coronavirus 2) causes coronavirus disease 2019 (COVID-19) and has led to a global pandemic. A mass vaccination campaign is currently underway in Europe. The mRNA-1273 vaccine, currently known as Spikevax,[1] combines Moderna's mRNA (messenger ribonucleic acid) delivery platform with the stabilized SARS-CoV-2 spike immunogen, developed by NIAID.

**Research question and objectives**

The overarching research question is: is there a greater risk or prevalence of pregnancy complications, adverse pregnancy outcomes, or adverse neonatal outcomes following pregnancies exposed to Spikevax compared with pregnancies unexposed to Spikevax?

Primary objectives:

- To determine whether exposure to the Spikevax during pregnancy is associated with an increased risk of:
    a. Pregnancy complications
    b. Adverse pregnancy outcomes
    c. Major congenital malformations in the offspring (overall and organ-specific if feasible)
    d. Adverse neonatal outcomes

Secondary objectives

- To describe utilization of Spikevax in pregnancy

Depending on the outcome, either a prevalence design (all endpoints except pregnancy-related death and neonatal death) or cohort design (pregnancy-related death and neonatal death) will be used to address each objective.

**Study design**

The maternal and pregnancy outcomes will be addressed using the prevalence study design; neonatal outcomes and pregnancy related death in the cohort design. In the routinely collected data, pregnancies are typically identifiable on the date of pregnancy end, either in a birth or in an abortive outcome. All identifiable pregnancies will be included, and their start and end dates will be determined based on the LMP or gestational age at end, depending on data availability. Outcomes examined in this design include gestational diabetes, hypertensive disorders of pregnancy, pregnancy-related death, fetal growth restriction/small for gestational age, spontaneous abortion, stillbirth, preterm birth, major congenital malformations, microcephaly, neonatal death, and termination of pregnancy for foetal anomaly (TOPFA).

**Population**

This study will be multi-database, utilizing routinely collected health data of various types in five European countries: Denmark, Italy, Norway, Spain, and the United Kingdom. Pregnancies ending between 6 January 2021 (date of the earliest approval of the COVID-19 Moderna Vaccine in Europe) and 31 December 2022 will be identified and classified according to the exposure to the COVID-19 Moderna Vaccine, overall and according to the trimester of exposure. The study period may be extended if the size of the study population is insufficient to study specific outcomes of interest.

The study population will encompass all pregnancies, identifiable in the databases, ending in a live or still birth, a spontaneous abortion, or an induced abortion, as identifiable in the participating databases. In Denmark and Norway, all pregnancies ending in a live or still birth, as well as pregnancies leading to a hospital encounter due to termination will be identifiable.

**Variables**

Members of the analysis populations (pregnancies, births, depending on the outcome) will be described with respect to available demographic characteristics, medical history, medication use, receipt of other vaccines, and characteristics of the exposed pregnancy. Pregnancies and births will be classified according to the exposure status Spikevax, overall and by trimester.

The outcomes of interest will include pregnancy complications, adverse pregnancy outcomes, and adverse neonatal outcomes.

Covariates will include maternal pre-pregnancy demographic and clinical characteristics, such as age, smoking, body mass index, chronic morbidities and medication use.

**Data sources**

This study is planned as analysis of routinely collected health data in secondary automated electronic data sources in Denmark, Italy, Norway, Spain, and the UK, selected based on availability of the required routinely collected data, including information on vaccine brand and frequency of data updates.

**Study size**

It is estimated that the number of live births available for analysis will range between 20,000 to 100,000 depending on a data source.

**Data analysis**

Counts and percentages will be presented for categorical variables (woman's age at conception in categories). Means, standard deviations, medians and interquartile ranges will be presented for continuous variables (woman's age at conception). The proportion of missing data will be described when appropriate. For pregnancy complications and adverse pregnancy outcomes, pregnancy will be the unit of observation; for neonatal outcomes, a newborn will be the unit of observation. For the outcomes of congenital malformations and stillbirth, the number at risk will be the total number of live or stillborn children.

Prevalence of each outcome will be computed as number of observations with a given outcome divided by the total number of observations at risk. Prevalence of each outcome will be compared for exposed vs. unexposed pregnancies according to predefined exposure categories and using, whenever necessary, plausible exposure risk windows. For example, for assessing the outcome of congenital malformations, maternal gestational diabetes and hypertensive disorders, births or pregnancies will be classified based on their exposure in the first (or second, if relevant) trimester. For all other neonatal outcomes, exposure any time in pregnancy and per trimester may be considered.

For neonatal deaths, 28-day mortality risks will be computed and compared among live-born neonates. For pregnancy-related death, maternal mortality will be evaluated at any time while pregnant or up to 1 year after pregnancy end.

All relevant analyses will be stratified by country, maternal age, sex, calendar time, trimester and seasonality if applicable.

**Milestones**

Data collection will continue through 31 March 2023 with a final study report planned by December 2023.

## 5. Amendments and updates

Write "None" or indicate any substantial amendment and update to the study protocol after the start of data collection in a table as indicated below.

| Number | Date | Section of study protocol | Amendment or update | Reason |
|---|---|---|---|---|
| 1 | Date | Text | Text | Text |
| 2 | Date | Text | Text | Text |
| … | Date | Text | Text | Text |

# 6. Milestones

| Milestone | Planned date* |
|---|---|
| Start of data collection | 31 December 2021 |
| End of data collection/data cut for Final report of study results | 31 March 2023 |
| Study progress report 1 | 31 March 2022 |
| Study progress report 2 | 31 December 2022 |
| Study progress report 3 | 30 June 2023 |
| Registration in the EU PAS register | Upon approval |
| Final report of study results | 31 December 2023 |

* Subject to data queues by data custodians; progress report will contain information on study progress and data updates whenever available.

# 7. Rationale and background

The novel coronavirus SARS-CoV-2 (severe acute respiratory syndrome coronavirus 2) causes coronavirus disease 2019 (COVID-19) and has led to a global pandemic. A mass vaccination campaign is currently underway in Europe.

The mRNA-1273 vaccine candidate was co-developed by the Cambridge, Massachusetts-based biotechnology company Moderna, Inc., and the United States (US) National Institute of Allergy and Infectious Diseases (NIAID), part of the National Institutes of Health. The vaccine, currently known as Spikevax,[1] combines Moderna's mRNA (messenger ribonucleic acid) delivery platform with the stabilized SARS-CoV-2 spike immunogen, developed by NIAID.

The completed COVE Phase 3 efficacy multicentre trial in United States (US) showed 94.1% efficacy of the Spikevax at preventing COVID-19 illness, including severe disease. Aside from transient local and systemic reactions, no safety concerns were identified. Pregnant women were not eligible to participate in that trial.[2] Preliminary findings from an observational study in the US were not indicative of obvious safety signals among pregnant persons who received mRNA COVID-19 vaccines, but the study indicated the need for longitudinal follow-up in a large number of women.[3]

Spikevax was authorised across the European Union (EU), following conditional marketing authorisation by the European Commission on 6 January 2021[4] and was approved on 08 January 2021 by the United Kingdom (UK) Medicines and Healthcare products Regulatory Agency (MHRA).[5] Currently, Spikevax is indicated for active immunisation to prevent COVID-19 caused by SARS-CoV-2 in individuals 18 years of age and older.[1] According to the 28 May update the UK Joint Committee on Vaccination and Immunisation recommends that is that COVID-19 vaccines should be offered to pregnant women at the same time as the rest of the population, in line with the age group roll out.[6] At the same time, a multinational cohort study showed that COVID-19 infection in pregnancy was associated with increased in severe maternal morbidity and mortality and with neonatal complications.[7] Thus, an uptake of COVID-19 vaccination among pregnant women should be expected. Indeed, as of 21 July 2021 the Danish Health Authority recommended vaccination of pregnant women in second or third trimester, citing similar recommendations in 20 countries. Vaccination of some or all pregnant women is recommended in Denmark[8] and Spain, permitted in the UK, and permitted with qualifications in Italy, according to Covid-19 Maternal Immunization Tracker, provided by Johns Hopkins University.[9]

Use of COVID-19 Moderna Vaccine in pregnancy and its effect on the mother and the neonate are currently not fully understood.[10] This postauthorisation safety study (PASS), aims to describe use of Spikevax use in pregnancy and to examine any potential association between Spikevax vaccination and pregnancy complications, and adverse pregnancy and neonatal outcomes. This study is a Category 3 Required Pharmacovigilance Activity in the RMP. Safety of the Spikevax in the general population is examined in a separate, dedicated PASS (reference number mRNA-1273-P904)

# 8. Research question and objectives

The overarching research question is: is there a greater risk or prevalence of pregnancy complications, adverse pregnancy outcomes, or adverse neonatal outcomes following pregnancies exposed to Spikevax compared with pregnancies unexposed to Spikevax?

## *8.1. Primary objectives*

- To determine whether exposure to the Spikevax during pregnancy is associated with an increased risk of:
    a. Pregnancy complications
    b. Adverse pregnancy outcomes
    c. Major congenital malformations in the offspring (overall and organ-specific if feasible)
    d. Adverse neonatal outcomes

## *8.2. Secondary objectives*

- To describe utilization of Spikevax in pregnancy, overall and by trimester of pregnancy

Depending on the outcome, either a prevalence design (all endpoints except pregnancy-related death and neonatal death) or cohort design (pregnancy-related death and neonatal death) will be used to address each objective.

# 9. Research methods

This protocol is prepared based on the methodology developed as part of the European Medicines Agency's infrastructure to support the monitoring of the efficacy and safety of COVID-19 treatments and vaccines when used in day-to-day clinical practice, specifically the CONSIGN project (COVID-19 infectiOn aNd medicineS In preGNancy). This project is ongoing and all Data Access Providers (DAPs) participating in this study also contribute to CONSIGN. The CONSIGN project is collecting data on the impact of COVID-19 in pregnancy in order to guide decision-making about vaccine indications, vaccination policies and treatment options for COVID-19 in pregnant women. CONSIGN will analyse existing data sources (e.g. electronic health records, hospital data) and cohorts of pregnant women to provide information on the effect of infection and its treatments in different trimesters of pregnancy and on neonates.[11]

## *9.1. Study design*

### 9.1.1 Prevalence study

The pregnancy complications, adverse pregnancy outcomes (except pregnancy-related death), and neonatal outcomes (except neonatal death) will be addressed using the prevalence study

design. In the routinely collected data, pregnancies are identifiable on the date of pregnancy end, either in a birth or in an abortive outcome. All identifiable pregnancies will be included, and their start and end dates will be estimated based on the first day of the last menstrual period (LMP) or gestational age at end, depending on data availability. Outcomes examined in this design include gestational diabetes, hypertensive disorders of pregnancy, fetal growth restriction/small for gestational age, abortive outcomes, stillbirth, preterm birth, major congenital malformations, microcephaly (head circumference), and ectopic pregnancy..

Risk of adverse and pregnancy outcomes will be compared in births exposed and unexposed to Spikevax. The measure of association will be prevalence ratio.

### 9.1.2 Cohort study

For the outcomes neonatal death, and pregnancy-related death, and postpartum bleeding, a cohort design will be employed.

Risk of neonatal (28-days postnatally) death will be compared in liveborn neonates exposed and unexposed to Spikevax in utero or during the periconceptional period. The measure of association will be the risk ratio.

Pregnancy-related deaths will be assessed by comparing deaths among pregnant women exposed and unexposed to Spikevax between 30 days before LMP and delivery date. A given pregnancy will be considered exposed from the recorded date of the first Spikevax dose receipt. The measure of association will be mortality rate ratio.

## *9.2. Setting*

This study will be multi-database, utilizing routinely collected health data of various types in five European countries: Denmark, Italy, Norway, Spain, and the United Kingdom. Pregnancies ending between 06 January 2021 (date of the earliest approval of the COVID-19 Moderna Vaccine in Europe) and up to 31 December 2022 will be identified and classified according to the exposure to Spikevax overall, and according to the trimester of exposure. The study period may be extended if the size of the study population is insufficient to study specific outcomes of interest. The source population comprises persons contributing to each participating database. The study databases are representatives of their source population (see Appendix 1 for details). Briefly, in Denmark and Norway, the registries have full population coverage with respect to the available routinely collected data. The regional databases in Italy (ARS) and Spain (SIDIAP) are representative of the underlying regional populations (Tuscany and Catalonia, respectively). The CPRD is broadly representative of the UK population.

### 9.2.1 Inclusion Criteria

The study population will include all pregnancies, identifiable in the databases, ending in a live or still birth, a spontaneous abortion, an induced abortion, or an ectopic pregnancy, as identifiable in the participating databases during the study period. In Denmark and Norway, all

pregnancies ending in a live or still birth, as well as pregnancies leading to a hospital encounter due to termination will be identifiable. All pregnancies will be eligible for inclusion.

#### *9.2.2 Exclusion Criteria*

Excluded will be pregnancies with exposure to known teratogenic medications/infections or chromosomal anomalies (for analysis of malformations) and pregnancies with unavailable information on data on pregnancy start or end. Main analyses will be restricted to women without exposure to COVID-19 vaccines other than Spikevax during pregnancy.

#### *9.2.3 Study Period*

In the prevalence study, there is no follow-up per se, as study population will be assembled based on existing (prevalent) outcomes.

In the cohort study, for the outcome of neonatal death, the maximum follow-up will be 28 days postnatally, censored at emigration or end of data. For the outcome pregnancy-related death, the maximum follow-up will be 1 year after pregnancy end,[12] censored by emigration or end of data availability.

### *9.3. Variables*

#### 9.3.1 Exposure

The exposure will be defined by a record of receipt of at least one dose of Spikevax during pregnancy.

For the purposes of timing of exposure, trimesters of pregnancy will be defined as follows:

- First trimester: from the first day of the last menstrual period (LMP) to LMP+97 days (both dates inclusive);
- Second trimester: from LMP+98 days to earliest of (LMP+202 days, pregnancy end) (both dates inclusive);
- Third trimester: from LMP+203 days (inclusive) until pregnancy end date (not included)

Pregnancies unexposed to Spikevax vaccine will be categorized as unexposed or as exposed to other COVID-19 vaccines and other non-COVID-19 vaccines (influenza, meningococcal disease, pneumococcal disease, rubella, shingles, tuberculosis), overall and trimester-wise. Pregnancies among women who received Spikevax before LMP will be enumerated and may be used as an additional comparator, group size permitting.

### 9.3.2 Outcome

#### 9.3.2.1 Primary outcomes

The following outcomes will be assessed, noting that outcome-specific analytic considerations such as the etiologically relevant exposure window and specific additional population restrictions (e.g., exclusion of women with teratogenic medication exposure or teratogenic infections for assessment of major congenital malformations) will be defined in the SAP.

- Pregnancy complications are:
    - Hypertensive disorders of pregnancy (preeclampsia, eclampsia, gestational hypertension)
    - Gestational diabetes
    - Bleeding during pregnancy
    - Postpartum haemorrhage
    - Pregnancy-related death

- Adverse pregnancy outcomes are:
    - Fetal death (spontaneous abortion or stillbirth)
    - Termination of pregnancy for fetal anomaly (TOPFA)
    - Any elective pregnancy termination
    - Ectopic pregnancy

- Adverse neonatal outcomes are:
    - Fetal growth restriction/small for gestational age (SGA), using sex- and gestational-age specific cutoffs[13]
    - Preterm birth (<37 full gestational weeks)
    - Low birth weight (<2500 g)
    - Major congenital malformations[14]
    - Microcephaly (based on head circumference)
    - Low 5-minute Apgar score
    - Neonatal death (death within 28 days of birth)

Where a signal is detected for the outcome of major congenital malformation as a composite, organ system-specific analyses will be conducted. Organ-specific major congenital malformations, according to the EUROCAT[14] classification are:

- Nervous system
- Eye
- Ear, face and neck
- Congenital heart defects
- Respiratory

- Oro-facial clefts
- Digestive system
- Abdominal wall defects
- Urinary
- Genital
- Limb
- Other

#### 9.3.2.2 Secondary outcomes

- Characteristics of Spikevax utilization according to predefined exposure categories:
    - Number and prevalence of exposed pregnancies/births any time during pregnancy/gestation;
    - Number and prevalence of pregnancies/births with one dose/two doses/more than two doses;
    - Number and prevalence of exposed pregnancies/births in each of the trimesters; trimester of first dose;
    - Maternal and newborn characteristics according to the exposure to Spikevax.

### 9.3.3 Covariates

The key covariates will include country of residence, calendar year of delivery, pregnant woman's age, smoking, alcohol use (whenever measured), marital status or other available socioeconomic measures, gravidity, parity, placenta previa, caesarean delivery, multifetal pregnancies, prior reproductive history (prior still birth, prior child SGA, prior pregnancy with preeclampsia) selected chronic comorbidities (cardiovascular diseases, respiratory diseases, type 2 and gestational diabetes, cancer, mental-health disorders, and autoimmune diseases [rheumatic diseases, systemic lupus erythematous, inflammatory bowel disease, multiple sclerosis, type 1 diabetes, thyroid disorders, medication use]), selected medication use, body mass index (BMI), and history of COVID-19 infection

Specific covariates' availability may vary by database and will be described in the SAP.

### 9.3.4 Subgroups

The following subgroups, study size permitting, will be specified to identify subpopulations of interest and additional subgroups may be added if identified during the study conduct.

- Maternal age (<30 years; 30-<40 years; >40 years).

- Trimester of exposure
- Maternal autoimmune diseases [rheumatic diseases, systemic lupus erythematous, inflammatory bowel disease, multiple sclerosis, type 1 diabetes]
- Indicators of immune suppression (if group size permits)
- Heterologous vaccine schedule (if group size permits)

### *9.4. Data sources*

This study will be based on electronic routinely collected data in five European countries (listed alphabetically): Denmark, Italy, Norway, Spain, and the United Kingdom. Table 1 provides overview of the data sources in each country. All databases have access to birth registry and allow for mother-child linkage. Additional description of the participating data sources is provided in Annex 3.

**Table 1 Summary of the data sources**

| Country | Denmark | Italy | Norway | Spain | UK |
|---|---|---|---|---|---|
| **Data access provider** | Aarhus University | ARS | University of Oslo | IDIAP | DSRU |
| **Type of data** | Record linkage | Record linkage | Record linkage | Record linkage & GP | GP medical record |
| **Data source name** | Danish registries | ARS | Norwegian registries | SIDIAP | CPRD |
| **Size of data in 2019** | 5.7 M | 3.5 M | 5.4 M | 5.8 M | 16 M |
| **Type of data** | | | | | |
| **Diagnosis coding** | ICD-10 | ICD-9CM/SNOMED | ICD-10CM/ICPC | ICD-10CM | ICD-10/READ/SNOMED |
| **Hosp. discharge Dx** | yes | Yes | yes | yes | yes |
| **Date of death** | yes | Yes | yes | yes | yes |
| **Emergency unit visit Dx** | yes | Yes | yes | yes | yes |
| **Outpatient specialist visit Dx** | Yes | No | yes | No./Yes referrals to specialists | yes |
| **Primary care Dx** | no | No | yes | yes | yes |
| **COVID-testing** | Yes | Yes (only positive results) | yes | yes | yes |
| **Medicines dispensing outp.(pharmacy)** | yes | Yes | yes | yes | no |
| **Medicines inpatient** | Some | Some | yes | no | no |

| | | | | | |
|---|---|---|---|---|---|
| **Medicines prescribing** | no | No | no | yes | yes |
| **COVID-19 Vaccine brand** | yes | Yes | yes | yes | yes |
| **Mother-child linkage** | yes | Yes- separate linkage | yes | yes | yes |
| **Linkage to birth register** | yes | Yes | yes | yes | Yes |

## *9.5. Study size*

Table 2 shows estimated number of live births expected annually from each participating database.

**Table 2 Estimated annual number of live births in each participating country/database**

| | Denmark | Italy | Norway | Spain | UK |
|---|---|---|---|---|---|
| Live/still births, per year | 60,000 | 25,000 | 60,000 | 45,000 | 10,000 |

In observational studies based on routinely collected data, where investigators do not control the study size, it is of interest to estimate the magnitude of an effect that can be ruled out with the available data and its precision.[15] Specifically, of interest is the magnitude of the upper 95% confidence limit that can be ruled out for an outcome, given the estimated size of the exposed/comparator groups and expected prevalence of the outcome. As proposed by Rothman and Greenland, study precision is expressed "by designing a study that gives an upper limit for the confidence interval that has a specified probability of being below a chosen value. The multiplier Z [in the calculations] is derived from the desired confidence level: Z is the value of the standard normal distribution such that the area under the curve from −Z to +Z equals the confidence level. Z is 1.96 for 95% confidence." (Rothman and Greenland, p. 600).[15]

**Table 3 Upper limit of 95% confidence interval (CI) that can be ruled out with 80% and 90% probability under different assumptions regarding proportion of vaccinated births and prevalence of outcome**

| Example country | Total births | Spikevax exposed births | Example outcome | Allocation ratio | Outcome prevalence in exposed | Outcome prevalence in comparator | Upper 95% CI limit, that can be ruled out with 80% probability | Upper 95% CI limit, that can be ruled out with 90% probability |
|---|---|---|---|---|---|---|---|---|
| **Denmark or Norway (largest number of births)** | 100,000 | 16667 | Cardiac malformations | 5 | 0.01 | 0.01 | 1.27 | 1.31 |
| | | 16667 | Any major malformation | 5 | 0.05 | 0.05 | 1.11 | 1.13 |
| | | 16667 | Small for gestational age | 5 | 0.1 | 0.1 | 1.07 | 1.09 |

| | | | | | | | | |
|---|---|---|---|---|---|---|---|---|
| | | 16667 | Spontaneous abortion | 5 | 0.2 | 0.2 | 1.05 | 1.06 |
| | | 9091 | Cardiac malformations | 10 | 0.01 | 0.01 | 1.36 | 1.43 |
| | | 9091 | Any major malformation | 10 | 0.05 | 0.05 | 1.14 | 1.17 |
| | | 9091 | Small for gestational age | 10 | 0.1 | 0.1 | 1.10 | 1.11 |
| | | 9091 | Spontaneous abortion | 10 | 0.2 | 0.2 | 1.06 | 1.07 |
| | | 4762 | Cardiac malformations | 20 | 0.01 | 0.01 | 1.51 | 1.61 |
| | | 4762 | Any major malformation | 20 | 0.05 | 0.05 | 1.20 | 1.23 |
| | | 4762 | Small for gestational age | 20 | 0.1 | 0.1 | 1.13 | 1.16 |
| | | 4762 | Spontaneous abortion | 20 | 0.2 | 0.2 | 1.09 | 1.10 |
| **UK (smallest number of births)** | 20,000 | 3333 | Cardiac malformations | 5 | 0.01 | 0.01 | 1.70 | 1.84 |
| | | 3333 | Any major malformation | 5 | 0.05 | 0.05 | 1.26 | 1.31 |
| | | 3333 | Small for gestational age | 5 | 0.1 | 0.1 | 1.17 | 1.20 |
| | | 3333 | Spontaneous abortion | 5 | 0.2 | 0.2 | 1.11 | 1.13 |
| | | 1818 | Cardiac malformations | 10 | 0.01 | 0.01 | 1.99 | 2.21 |
| | | 1818 | Any major malformation | 10 | 0.05 | 0.05 | 1.35 | 1.42 |
| | | 1818 | Small for gestational age | 10 | 0.1 | 0.1 | 1.23 | 1.27 |
| | | 1818 | Spontaneous abortion | 10 | 0.2 | 0.2 | 1.15 | 1.17 |
| | | 952 | Cardiac malformations | 20 | 0.01 | 0.01 | 2.52 | 2.92 |
| | | 952 | Any major malformation | 20 | 0.05 | 0.05 | 1.50 | 1.60 |
| | | 952 | Small for gestational age | 20 | 0.1 | 0.1 | 1.32 | 1.38 |
| | | 952 | Spontaneous abortion | 20 | 0.2 | 0.2 | 1.20 | 1.24 |
| Assumption: true prevalence ratio = 1 | | | | | | | | |

## *9.6. Data management*

This study, which will be conducted based on this common protocol, will use the Vaccine monitoring Collaboration for Europe (VAC4EU, https://vac4eu.org/) research environment based on a common protocol, and a common data model (CDM).[16] The work will be conducted using a distributed network of the participating data access providers (DAPs), all of whom have experience and have contributed to the CONSIGN project. The work will proceed according to Model C (Figure 1): each DAP will extract the data required for the study and transform their local patient level data into a CDM. It is proposed to use the ConcePTION CDM, which is publicly available[16] and is being specifically developed for multinational studies of medication safety in pregnancy. Extraction, transformation, and loading (ETL) design and instructions are available, as well as tools to check the quality of the data for the AESI estimated utilized for the ACCESS

background rate protocol. A common program to run quality checks, data transformation, and analysis will be prepared, verified and distributed to all DAPs. Aggregate results and summary estimates resulting from the programs will be returned to the coordinating center for pooled meta-analysis and reporting. The full approach will be developed and described in the Statistical Analysis Plan (SAP).

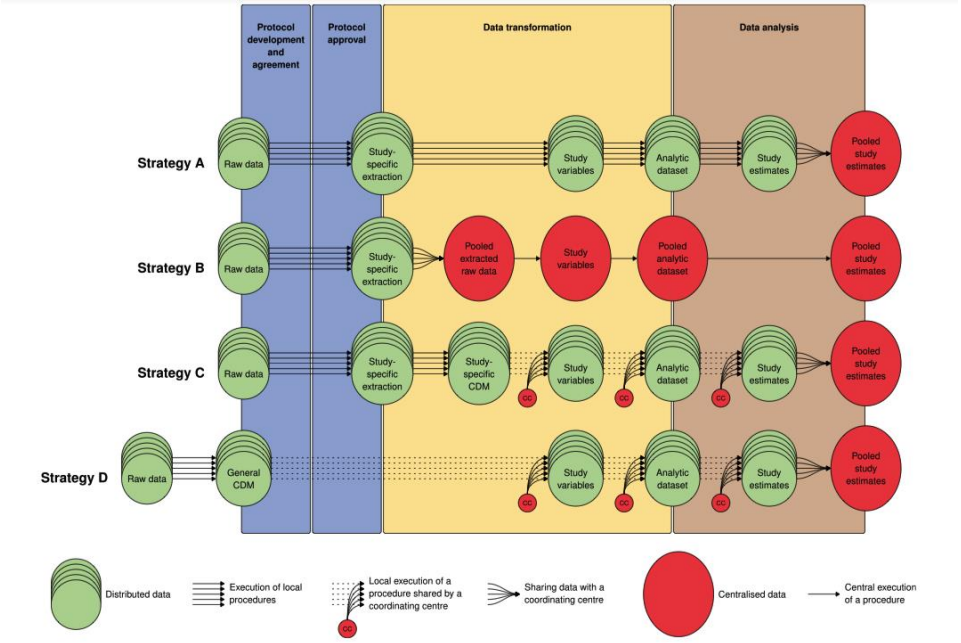



**Figure 1. Options for multi-database studies in Europe**[17]

## *9.7. Data analysis*

The details of the data analysis, including planned tables, figures, and listings for inclusion in the final study report will be provided in the SAP.

### 9.7.1 Descriptive analyses

Counts and percentages will be presented for categorical variables (age at conception in categories, sex). Means, standard errors, medians and ranges will be presented for continuous variables (age at conception). The proportion of missing data will be described when appropriate. For maternal outcomes, pregnancy will be the unit of observation; for neonatal outcomes, a newborn will be the unit of observation. For the outcomes of congenital malformations and stillbirth the number at risk will be the total number of live or stillborn children.

### 9.7.2 Measures of occurrence and measures of association

Prevalence of each outcome will be computed as number of observations with a given outcome divided by the total number of study population members. For neonatal death, a 28-day mortality risk will be the measure of occurrence among live-born infants. Prevalence/risks will be compared according to predefined exposure categories and using, whenever necessary,

plausible exposure risk windows. For example, for assessing the outcome of congenital malformations, births will be classified based on their exposure in the first trimester. For all other neonatal outcomes, exposure any time in pregnancy and per trimester may be considered.

Table 4 summarizes outcome-specific analysis populations and exposure windows.

**Table 4 Summary of outcome-specific analysis populations and relevant exposure windows**

| Outcome | Analysis population | Relevant exposure window |
|---|---|---|
| Hypertensive disorders of pregnancy (preeclampsia, eclampsia, gestational hypertension ) | All pregnancies | 1st or 2nd trimester |
| Gestational diabetes | All pregnancies | 1st or 2nd trimester |
| Bleeding during pregnancy | All pregnancies | 1st or 2nd trimester |
| Postpartum haemorrhage | All pregnancies | Any time during pregnancy |
| Pregnancy-related death | All pregnancies | Any time during pregnancy |
| Fetal death (spontaneous abortion or stillbirth) | A combined population of stillbirths, livebirths, and pregnancies ending in a spontaneous abortion | Any time during pregnancy |
| Termination of pregnancy for fetal anomaly (TOPFA) | All pregnancies | Any time during pregnancy |
| Any elective pregnancy termination | All pregnancies | Any time during pregnancy |
| Ectopic pregnancy | All pregnancies | Any time during pregnancy |
| Fetal growth restriction/small for gestational age (SGA) | Live births | Any time during gestation |
| Preterm birth (<37 full gestational weeks) | Live births | Any time during gestation |
| Low birth weight (<2500 g) | Live births | Any time during gestation |
| Major congenital malformations | Live or stillbirths/TOPFA (whenever available) without evidence of teratogenic exposure or infection or chromosomal anomaly | First trimester |
| Microcephaly (based on head circumference) | Live births without evidence of teratogenic exposure or infection or chromosomal anomaly | Any time during gestation |
| Low 5-minute Apgar score | Live births | Any time during gestation |
| Neonatal death (death within 28 days of birth) | Live births | Any time during gestation |

### 9.7.3 Methods to control/assess confounding

Crude and adjusted measures of association will be computed comparing the exposed vs the unexposed (prevalence ratios, risk ratios, mortality rate ratios). Adjustment will be performed by the covariates measured, with LMP as the anchor date. Covariates will be included in the

appropriate regression model: log-binomial regression for prevalences and risks and Cox proportional-hazards regression for incidence rate ratios. Candidate covariates for inclusion in the analyses will vary by database. A propensity-score based adjustment may be considered and will be described in a separate Statistical Analysis Plan. Table 5 shows country-specific availability of the covariates.

**Table 5 Proposed candidate covariates and data availability in participating databases**

| **Variable/data type** | **AVAILABILITY OF DATA IN THE DATABASE (either via diagnosis code or procedure or treatment proxy)** | | | | |
|---|---|---|---|---|---|
| | **DENMARK (NATIONAL REGISTRIES)** | **ITALY/ARS TOSCANA** | **NORWAY (NATIONAL REGISTRIES)** | **SPAIN/SIDIAP** | **UK/CPRD** |
| Pregnancy feasibility counts for interim reports | Hospital-based ICD-10 codes for pregnancy related diagnoses or codes for prenatal visits from the Insurance registry for primary care prenatal visits | Hospital-based ICD-10 codes for pregnancy related diagnoses or codes for prenatal visits from the Insurance registry for primary care prenatal visits | All pregnancies in Norway that last at least 12 weeks are captured in the Medical Birth Registry of Norway (mandatory notification to the registry, 100% coverage) | Most pregnancies will be identifiable in primary care; some might be missed without linkage to hospital data | Pregnancy information will be available in the main primary care dataset following primary care and/or secondary care contact with the patient. This will be based on Read and/or SNOMED codes. |
| Country of residence | YES | YES | YES | YES | YES |
| Calendar year of delivery | YES | YES | YES | YES | YES |
| Pregnant woman's age | YES | YES | YES | YES | YES |
| Marital or cohabiting status | YES | To be verified | YES | To be verified | YES |
| Smoking | YES | To be verified | YES | YES | YES |
| Alcohol use (also ICD codes) | YES, IF BASED ON ICD CODES | YES | YES, IF BASED ON ICD CODES | To be verified | YES |

| | | | | | |
|---|---|---|---|---|---|
| Marital status or other available socioeconomic measures | YES | YES | YES | YES Other available socioecomic measures | YES |
| Gravidity | YES | YES | YES | YES | YES |
| Parity | YES | YES | YES | YES | YES |
| Placenta previa | YES | YES | YES | YES | YES |
| Caesarean delivery | YES | YES | YES | YES | YES |
| Multifetal pregnancy | YES | YES | YES | YES | YES |
| Prior (before participating pregnancy) still birth | YES | YES | YES | To be verified | YES |
| Prior (before participating pregnancy) child SGA | YES | YES | YES | YES | YES |
| Prior (before participating pregnancy) pregnancy with preeclampsia | YES | YES | YES | To be verified | YES |
| Cardiovascular diseases (eg hypertension, migraine) | YES | YES | YES | YES | YES |
| Respiratory diseases (eg asthma COPD) | YES | YES | YES | YES | YES |
| Type 2 diabetes | YES | YES | YES | YES | YES |
| Gestational diabetes | YES | YES | YES | YES | YES |
| Cancer | YES | YES | YES | YES | YES |
| Mental-health disorders | YES | YES | YES | YES | YES |
| Rheumatic diseases | YES | YES | YES | YES | YES |
| Systemic lupus erythematous | YES | YES | YES | YES | YES |
| Inflammatory bowel disease | YES | YES | YES | YES | YES |
| Multiple sclerosis | YES | YES | YES | YES | YES |
| Type 1 diabetes | YES | YES | YES | YES | YES |

| | | | | | |
|---|---|---|---|---|---|
| Outpatient prescriptions/dispensings | YES | YES | YES | YES | NO |
| BMI or obesity | YES | YES | YES | YES | YES |
| History of COVID-19 infection | YES | YES | YES | YES | YES |
| HCRU measures (mother) | YES | YES | YES | YES | YES |

### 9.7.4 Subgroup analyses

All relevant analyses will be stratified by country, maternal age, sex, calendar time, trimester and seasonality if applicable and in subgroups specified in Section 9.3.4 where sample size permits.

### 9.7.5 Sensitivity analyses

The following sensitivity analyses of the primary outcomes will be conducted:

- Using the date of pregnancy start as (LMP – 30 days) as an alternative definition to correct for imprecisions in LMP determination
- Alternative comparators may be explored, including contemporaneous other vaccinations (eg. influenza) or pregnancies vaccinated before LMP
- Repeating the analysis to examine the association between receipt of Spikevax in the 2nd or 3rd (but not 1st) trimester and a given major congenital malformation outcome. This is a negative control exposure analysis because exposure beyond 1st trimester cannot plausibly cause malformations, and any observed association will be due to bias.[18]
- Different definitions of SGA will be examined:
    - birth weight below 2 standard deviations from sex- and gestational-week specific mean birth weight (a more specific definition, with expected prevalence of SGA of about 1%);
    - birth weight below 10th percentile of sex- and gestational-week specific mean birth weight (more sensitive definition, with expected prevalence of SGA of about 10%)

### 9.7.6 Data integration

Results will be presented separately for each data source and aggregate data will be pooled across data sources, if deemed justifiable given differences in data flow/population.

Meta-analysis may be conducted if/as appropriate using standard methods: heterogeneity will be assessed and visualizations such as forest plots be provided. Because of the expected variation in effect estimates of data-sources we recommend random effect models.[19]

### 9.7.7 Missing data

In routinely collected data, absence of a record is usually interpreted as absence of a condition. Missing data per se are rare, but may occur, e.g., in such variables as gestational age, smoking, BMI. The extent of missing data for each study variable will be reported. No imputation is planned.

## *9.8 Quality control*

The source electronic routinely collected data proposed for use in this study undergo standard curation and quality-check procedures by the data custodians. Standard operating procedures or internal process guidance at each research center will be adhered to for the conduct of the study. These procedures will include internal quality audits, rules for secure and confidential data storage, methods to maintain and archive project documents, quality-control procedures for programming, and standards for writing analysis plans. Routine procedures will include checking electronic files, maintaining security and data confidentiality, following analysis plans, and performing quality-control checks of all programs. Each partner should maintain any patient-identifying information securely on site according to internal standard operating procedures or guidance documents. Quality control for the central meta-analysis of the data will be described within project-specific documents.

This study will be conducted in accordance with the GVP, including the European Network of Centres for Pharmacoepidemiology and Pharmacovigilance (ENCePP) Code of Conduct.[20]

## *9.9 Limitations of the research methods*

An important limitation of the research method is that currently Spikevax is not indicated for use in pregnancy according to the current label, implying that at least at the initial study stages, the number of exposed pregnancies may be low, potentially affecting precision of the resulting estimates of association. Furthermore, owing to typical data flow in routinely collected data, only completed pregnancies (ending in a birth or an abortive outcome) are identifiable. Ongoing pregnancies cannot be identified. A further limitation is heterogeneity of the different data sources in their ability to identify all pregnancy outcomes of interest. Finally, unmeasured confounding due to non-comparability of vaccinated and non-vaccinated pregnancies (healthy or sick vaccinee), at least at the start of the vaccination of pregnant women, cannot be ruled out. If pregnant women with chronic diseases or those taking medication are more likely to be vaccinated, uncontrolled confounding by morbidity will produce an upward bias in the association between vaccination and some AESI, whenever these chronic diseases are themselves associated with adverse outcomes.

A potential misclassification of exposure timing (eg. if LMP is imprecise) may produce a downward bias, if an association exists.

Because, by definition, pregnancy and neonatal outcomes are prevalent outcomes, one cannot enumerate the cohort of conceptuses initiating the follow-up. Early pregnancies that end in a spontaneous abortion and do not lead to a health care record are not detectable in the available data sources. At the same time, shorter pregnancies may be overestimated in the study population because of being identified by pregnancy end.[21]

Finally, for the outcome major congenital malformations, the standard (EUROCAT)[14] definitions recommend follow-up until age 1 year, which will not be available for all neonates in currently defined study populations. This under ascertainment will lower the sensitivity of the outcome, which, if not related to vaccination status, should not bias associations

### *9.10 Other aspects*

Not applicable.

# 10 Protection of human subjects

The proposed studies are non-interventional studies re-using routinely collected health and administrative data. All data collected in the study will be de-identified with no breach of confidentiality with regard to personal identifiers or health information. Each data access provider should apply for an independent ethics committee or other review according to local regulations. Data protection and privacy regulations (GDPR) will be observed in collecting, forwarding, processing, and storing data from study participants. Whenever required by data protection regulations, implicit or explicit cell counts that potentially allow for identification of individuals (e.g., counts of 1-4 in most countries), appropriate masking methods will be applied. All participating investigators/data access providers will obtain all required governance approval for conducting this study. Only aggregate results will be shared. Security processes should be in place to ensure the safety of all systems and data. Every effort should be made to ensure that data are kept secure so that they cannot be accessed by anyone except the study team. Appropriate data storage and archiving procedures will be followed by each DAP and the coordinating center, with periodic backups.

# 11 Management and reporting of adverse events/adverse reactions

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

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

applicable.[20 22] According to the EMA Guideline on Good Pharmacovigilance Practices (GVP), Module VI – Management and Reporting of Adverse Reactions to Medicinal Products "All adverse events/reactions collected as part of [non-interventional post-authorization studies with a design based on secondary use of data], the submission of suspected adverse reactions in the form of [individual case safety reports] is not required. All adverse events/reactions collected for the study should be recorded and summarized in the interim safety analysis and in the final study report." Module VIII – Post-Authorization Safety Studies, echoes this approach The new legislation further states that for certain study designs such as retrospective cohort studies, particularly those involving electronic health care records, it may not be feasible to make a causality assessment at the individual case level.[10 23]

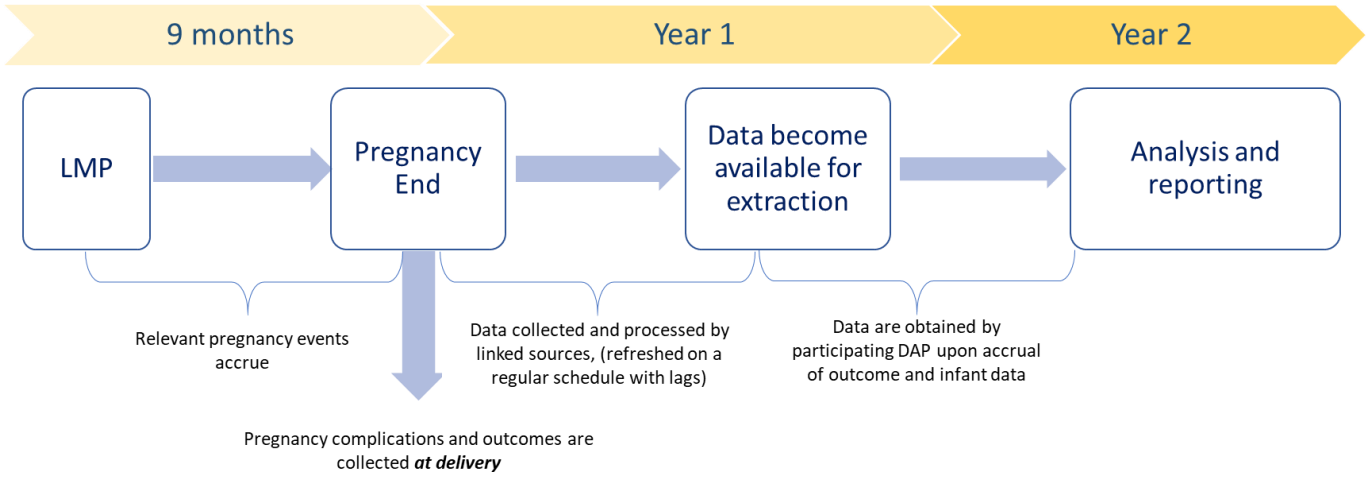
# 12 Plans for disseminating and communicating study results

GVP Module VIII: "For studies that are fully or partially conducted by investigators who are not employees of the marketing authorisation holder, the marketing authorisation holder and the investigator should agree in advance on a publication policy allowing the principal investigator to independently prepare publications based on the study results irrespective of data ownership. The marketing authorisation holder should be entitled to view the results and interpretations included in the manuscript and provide comments prior to submission of the manuscript for publication."[22]

The protocol and the final study report will be subject to mandatory publication in the EU PAS register and will comply with ENCePP or Code of Conduct, according to which study results will be published following guidelines, including those for authorship, established by the International Committee of Medical Journal Editors. When reporting results of this study, the appropriate Strengthening the Reporting of Observational Studies in Epidemiology (STROBE),[24] RECORD, and RECORD-PE[25 26] checklist will be followed, and recommendations on reproducible reporting of electronic health care data base studies should be followed.[27]

Owing to several limitations specific to routinely collected data on pregnancy, only one data extraction is feasible under this protocol. These limitations include: expected low initial number of Spikevax exposed pregnancies; the need to wait for pregnancy end to be identified; different timing of mother-child linkage in different databases; and less frequent (than other databases) data refreshes on birth registries with the largest number of observations and full population coverage (Denmark and Norway). Figure 2 illustrates the data pathway from pregnancy recording to availability for the analysis.

**Figure 2. Data pathway from pregnancy recording to availability for the analysis.**




To monitor the number of exposed pregnancies, and thus the feasibility of the pregnancy analysis, the number of Spikevax-exposed pregnancies will be approximated from the available pregnancy indicators, such as records of prenatal visits, or diagnostic codes associated with pregnancies. Such records, as a rule, will not be complete with respect to pregnancy outcomes, but are expected to conservatively estimate the number of pregnancies exposed to Spikevax that will be available for the final analysis. Table 6 summarizes the planned contents of the interim and final study reports.

**Table 6 Planned data extractions and contents of study reports.**

| **Milestone** | **Date** | **Pregnancy data available from each database** | | | | |
|---|---|---|---|---|---|---|
| | | Denmark | Italy | Norway | Spain | UK |
| START OF DATA COLLECTION (AT LEAST ONE DAP EXTRACTS DATA in study mRNA-1273-P904) | 31-Dec-21 | | | | | |
| **Study progress report 1**<br>Planned content: status update providing an overview of progress towards finalization of the study design, counts of pregnancies observed in study mRNA-1273-P904 (preliminary pregnancy counts from 31 December 2021 extraction) | 31-Mar-22 | | | | | |
| **Study progress report 2**<br>Planned content: status update providing an overview of project status, counts of pregnancies observed in study mRNA-1273-P904 (preliminary pregnancy counts from 31 December 2021 extraction) | 31-Dec-22 | | | | | |

| | | | | | | |
|---|---|---|---|---|---|---|
| **Study progress report 3**<br>Planned content: status update providing an overview of project status, application for data, initial steps towards execution of planned analyses, counts of pregnancies observed in study mRNA-1273-P904 (preliminary pregnancy counts from 31 December 2021 extraction) | 30-Jun-23 | | | | | |
| END OF DATA COLLECTION (ALL DAPS EXTRACT DATA FOR PREGNANCY ANALYSES) | 31-Mar-23 | | | | | |
| Estimated latest date of pregnancy end expected from the database at the end of data collection (31 Mar 23) | | | | | | |
| **Final report of study results (all per protocol analyses)** | 31-Dec-23 | 30-Oct-22 | 30-Oct-22 | 31-Dec-22 | 31-Dec-22 | 31-Dec-22 |

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# Annex 1. List of stand-alone documents

| Number | Document reference number | Date | Title |
|---|---|---|---|
| 1 | | 18 August 2021 | Pregnancy PASS Summary of Planned Tables and Figures20180818.docx |
| 2 | Number | Date | Text |
| … | Number | Date | text |

# Annex 2. ENCePP checklist for study protocols

Doc.Ref. EMA/540136/2009

ENCePP Checklist for Study Protocols (Revision 4)

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

| |
|---|
| Study title: Monitoring safety of Spikevax in pregnancy: an observational study using routinely collected health data in five European countries |

| |
|---|
| EU PAS Register® number:<br>Study reference number (if applicable): |

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

Comments:

| |
|---|
| |

[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 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) | ☐ | ☐ | ☒ | |
| 2.1.4 Which hypothesis(-es) is (are) to be tested? | ☒ | ☐ | ☐ | 9.5 |
| 2.1.5 If applicable, that there is no *a priori* hypothesis? | ☒ | ☐ | ☐ | 9.5 |

Comments:

| |
|---|
| Target population: NA because results are expected to inform safety for all vaccinees<br>Hypotheses are not stated, but explicitly the null hypothesis is that of no association between Spikevax and any of the pregnancy/neonatal outcomes. |

| **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? | ☒ | ☐ | ☐ | 9.4 |
| 3.3 Does the protocol specify measures of occurrence? (e.g., rate, risk, prevalence) | ☒ | ☐ | ☐ | 9.7 |
| 3.4 Does the protocol specify measure(s) of association? (e.g. risk, odds ratio, excess risk, rate ratio, hazard ratio, risk/rate difference, number needed to harm (NNH)) | ☒ | ☐ | ☐ | 9.7 |
| 3.5 Does the protocol describe the approach for the collection and reporting of adverse events/adverse reactions? (e.g. adverse events that will not be collected in case of primary data collection) | ☒ | ☐ | ☐ | 11 |

Comments:

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| **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 |
| 4.2.2 Age and sex | ☒ | ☐ | ☐ | 9.2 |
| 4.2.3 Country of origin | ☒ | ☐ | ☐ | 9.2 |
| 4.2.4 Disease/indication | ☒ | ☐ | ☐ | 9.2 |
| 4.2.5 Duration of follow-up | ☒ | ☐ | ☐ | 9.2, 9.7.2 |
| 4.3 Does the protocol define how the study population will be sampled from the source population? (e.g. event or inclusion/exclusion criteria) | ☐ | ☐ | ☒ | |

Comments:

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| No sampling is done per se, but some databases cover partial population of their respective countries. |

| **Section 5: Exposure definition and measurement** | **Yes** | **No** | **N/A** | **Section Number** |
|---|---|---|---|---|
| 5.1 Does the protocol describe how the study exposure is defined and measured? (e.g. operational details for defining and categorising exposure, measurement of dose and duration of drug exposure) | ☒ | ☐ | ☐ | 9.3.1 |
| 5.2 Does the protocol address the validity of the exposure measurement? (e.g. precision, accuracy, use of validation sub-study) | ☒ | ☐ | ☐ | 9.3.1 |
| 5.3 Is exposure categorised according to time windows? | ☒ | ☐ | ☐ | 9.3.1 |
| 5.4 Is intensity of exposure addressed? (e.g. dose, duration) | ☒ | ☐ | ☐ | 9.3.1 |
| 5.5 Is exposure categorised based on biological mechanism of action and taking into account the pharmacokinetics and pharmacodynamics of the drug? | ☒ | ☐ | ☐ | 9.6 |
| 5.6 Is (are) (an) appropriate comparator(s) identified? | ☒ | ☐ | ☐ | 9.3.1 |

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? | ☒ | ☐ | ☐ | 9.3.2 |
| 6.3 Does the protocol address the validity of outcome measurement? (e.g. precision, accuracy, sensitivity, specificity, positive predictive value, use of validation sub-study) | ☒ | ☐ | ☐ | 9.3.2 |
| 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) | ☒ | ☐ | ☐ | 9.3.1 |
| 7.2 Does the protocol address selection bias? (e.g. healthy user/adherer bias) | ☒ | ☐ | ☐ | 9.7.4 |
| 7.3 Does the protocol address information bias? (e.g. misclassification of exposure and outcomes, time-related bias) | ☒ | ☐ | ☐ | 9.7.4 |

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) | ☒ | ☐ | ☐ | 9.7.3 |

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) | ☒ | ☐ | ☐ | 9.7.5 |

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 |
| 10.2 Is study size and/or statistical precision estimated? | ☒ | ☐ | ☐ | 9.5 |
| 10.3 Are descriptive analyses included? | ☒ | ☐ | ☐ | 9.7.1 |
| 10.4 Are stratified analyses included? | ☒ | ☐ | ☐ | 9.7.3 |
| 10.5 Does the plan describe methods for analytic control of confounding? | ☒ | ☐ | ☐ | 9.3.1 |
| 10.6 Does the plan describe methods for analytic control of outcome misclassification? | ☐ | ☒ | ☐ | |
| 10.7 Does the plan describe methods for handling missing data? | ☒ | ☐ | ☐ | 9.7 |
| 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) | ☒ | ☐ | ☐ | 9.7.5 |
| 11.2 Are methods of quality assurance described? | ☒ | ☐ | ☐ | 9.8 |
| 11.3 Is there a system in place for independent review of study results? | ☒ | ☐ | ☐ | 12 |

Comments:

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| ENCePP publication of the study protocol and the study results is taken as independent review of study results. |

| **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 |

| **Section 12: Limitations** | **Yes** | **No** | **N/A** | **Section Number** |
|---|---|---|---|---|
| 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) | ☒ | ☐ | ☐ | 9.5 |

Comments:

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

Comments:

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| **Section 14: Amendments and deviations** | **Yes** | **No** | **N/A** | **Section Number** |
|---|---|---|---|---|
| 14.1 Does the protocol include a section to document amendments and deviations? | ☒ | ☐ | ☐ | 5 |

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: Prof. Vera Ehrenstein, MPH, DSc

Date: 25/06/2021

Signature: _____

# Annex 3. Additional information

# Appendix 1: Description of the participating data sources

## *Denmark: Danish population registries*

Denmark has a tax-funded health care system ensuring universal access to health care, and with this system health contacts are recorded in administrative and health registers. The records carry a unique personal identification number, called the CPR-number, assigned to every Danish resident, originally for taxation purposes. Linkage between registers at an individual level is possible because this CPR-number is used in all Danish registers. All registers have a nationwide coverage and an almost 100% capture of contacts covering information on currently 5.8 million inhabitants plus historical information. For the purpose of the study we will obtain information from the following registries. The Danish National Prescription Registry includes data on all outpatient dispensing of medications and vaccines at Danish pharmacies from 1995 and onwards, including dispensing date, ATC code, product code and amount. The Danish National Health Service Register includes data on primary care services, including general practitioner contacts, examinations, procedures, and vaccinations; psychologist or psychiatrist and other primary care provider visits; etc. From the Danish Civil Registration System, data on demographics (sex, date of birth) and censoring (migration, vital status). The Danish National Patient Registry contains diagnoses and procedures from all hospitalizations (including pregnancies ending in abortive outcomes). The Danish Medical Birth Registry records all live or still births at gestational week 22 or later. The Danish databases were characterized in the ADVANCE project and considered fit for purpose for vaccine coverage, benefits and risk assessment and could participate in near real-time monitoring. Use of the Danish Vaccination Registry will be involved to ascertain vaccinations outside GP offices and to ascertain vaccine brand. Danish health care and the flow of data into the registries have been described in a recent publication (https://www.ncbi.nlm.nih.gov/pubmed/31372058).

## *Italy: ARS database*

The Italian National Healthcare System is organized at regional level: the national government sets standards of assistance and a tax-based funding for each region, and regional governments are responsible to provide to all their inhabitants. Tuscany is an Italian region, with around 3.6 million inhabitants. The Agenzia Regionale di Sanita' della Toscana (ARS) is a research institute of the Tuscany Region. The ARS database comprises all information that are collected by the Tuscany Region to account for the healthcare delivered to its inhabitants. Moreover, ARS collects data from regional initiatives. All the data in the ARS data source can be linked with each other at the individual level, through a pseudo-anonymous identifier. The ARS database routinely collects primary care and secondary care prescriptions of drugs for outpatient use, and is able to link them at the individual level with hospital admissions, admissions to emergency care, records of exemptions from copayment, diagnostic tests and procedures,

causes of death, mental health services registry, birth registry, spontaneous abortion registry, induced terminations registry. A pathology registry is available, mostly recorded in free text, but with morphology and topographic SNOMED codes. Mother-child linkage is possible through the birth registry. Vaccine data is available since 2016 for children and since 2019 for adults. The ARS database was characterized in the ADVANCE project and considered fit for purpose for vaccine coverage, benefits and risk assessment when using the new vaccine registry (from 2019).

### *Norway: Norwegian population registries*

The core data that University of Oslo (UIO) has access to is the health care administrative databases of the entire Norwegian population, which amounts to approximately 5.3 million inhabitants. Norway has a universal public health care system, consisting of primary health care services and specialist health care 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. The most commonly used registries are administrated by The Norwegian Institute of Public Health, The Norwegian Directorate of Health and Statistics Norway. The Norwegian national identity number was introduced in the 1960s. This identifier is assigned to every person at birth or upon immigration; it is 11 digits long and encodes date of birth and sex. The code is included in all national registries, allowing accurate linkage among them. Information about all Norwegian National Registries can be found here: www.fhi.no/en/more/access-to-data/about-the-national-health-registries2/

### *Spain: SIDIAP*

The Information System for Research in Primary Care (Sistema d'Informació per al Desenvolupament de la Investigació en Atenció Primària' - SIDIAP; www.sidiap.org) was created in 2010 by the Catalan Health Institute (CHI) and the IDIAPJGol Institute. It includes information collected since 01 January 2006 during routine visits at 278 primary care centers pertaining to the CHI in Catalonia (North-East Spain) with 3,414 participating GPs. SIDIAP has pseudo-anonymized records for 5.7 million people (80% of the Catalan population) being highly representative of the Catalan population. The SIDIAP data comprises the clinical and referral events registered by primary care health professionals (GPs, pediatricians and nurses) and administrative staff in electronic medical records, comprehensive demographic information, community pharmacy invoicing data, specialist referrals and primary care laboratory test results. It 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 ICD-10 codes, ATC codes and structured forms designed for the collection of variables relevant for primary care clinical management, such as country of origin, sex, age, height, weight, body mass index, tobacco and alcohol use, blood pressure measurements, blood and urine test results. In

relation to vaccines, SIDIAP includes all routine childhood and adult immunizations, including the antigen and the number of administered doses. Encoding personal and clinic identifiers ensures the confidentiality of the information in the SIDIAP database. The SIDIAP database is updated annually at each start of the year. With the COVID-19 pandemic, there is the possibility to have shorter term updates in order to monitor the evolution of the pandemic. Recent reports have shown the SIDIAP data to be useful for epidemiological research. SIDIAP is listed under the ENCePP resources database www.encepp.eu/encepp/resourcesDatabase.jsp). The SIDIAP database was characterized in the ADVANCE project and considered fit for purpose for vaccine coverage, benefits and risk assessment.

### *United Kingdom: CPRD & HES*

The Clinical Practice Research Datalink (CPRD) from the UK collates the computerized medical records of general practitioners (GPs) in the UK who act as the gatekeepers of healthcare and maintain patients' life-long electronic health records. As such they are responsible for primary healthcare and specialist referrals, and they also store information stemming from specialist referrals, and hospitalizations. GPs 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 feedback 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. The majority of the data are coded in Read Codes. Validation of data with original records (specialist letters) is also available. The dataset is generalizable to the UK population based upon age, sex, socioeconomic class and national geographic coverage when GOLD & Aurum versions are used. There are currently approximately 42 million patients (acceptable for research purposes) – of which 13 million are active (still alive and registered with the GP practice) – in approximately 1,700 practices (https://cprd.com/Data). Data include demographics, all GP/healthcare professional consultations (phone, letter, email, in surgery, at home), diagnoses and symptoms, laboratory test results, treatments, including all prescriptions, all data referrals to other care, hospital discharge summary (date and Read and SNOMED codes), hospital clinic summary, preventive treatment and immunizations, death (date and cause). For a proportion of the CPRD panel practices (>80%), the GPs have agreed to permit CPRD to link at patient level to the Hospital Episode Statistics (HES) data. CPRD is listed under the ENCePP resources database, access will be provided by the DSRU. The CPRD was not yet characterized in the ADVANCE project, where the UK THIN and RCGP databases were used, but has been largely used in vaccine studies. The HES database contains details of all admissions to National Health System (NHS) hospitals in England; approximately 60% of GP practices in the CPRD are linked to the HES database. Not all patients in the CPRD have linked data (e.g. if they live outside England or if their GP has not agreed that their data should be used in this way). As with standard CPRD patients, HES data are limited to research-standard patients. CPRD records are linked to the HES using a combination of the patient's NHS number, gender and date of birth. The Drug Safety Research Unit (DSRU) is the leading UK centre for pharmacovigilance and pharmacoepidemiology

which has led and coordinated many large studies across the UK. The Unit has ample experience of monitoring the post-authorisation safety of vaccines, notably active surveillance on the H1N1 swine flu vaccine and an active surveillance study and six enhanced passive surveillance studies on the children's seasonal influenza vaccine. The DSRU works with the UK's National Institute for Health Research (NIHR) Clinical Research Network, which facilitates research in the National Health Service (NHS) and provides access to a large network of research-ready health care professionals, including GPs. The DSRU also has experience of study designs based on patient reported outcomes.