NON-INTERVENTIONAL STUDY PROTOCOL

TITLE	Moderna mRNA-1273 Observational Pregnancy Outcome Study
VERSION	1.2 01APR2021
CLIENT	Moderna Therapeutics 200 Technology Square Cambridge, MA 02139 USA
CONDUCTED BY	IQVIA 201 Broadway Cambridge, MA 02139 USA

This protocol contains confidential information that should only be disclosed to those persons responsible for execution and organization of the study and on condition that all such persons agree not to further disseminate it.

TABLE OF CONTENTS

Coordinating Center Investigator Signature Page

Study Title: Moderna mRNA-1273 Observational Pregnancy Outcome Study; Protocol mRNA-1273-P902, version 1.2 dated 01 April 2021.

I have read and understand the protocol and agree that it contains the ethical, legal and scientific information necessary to participate in this study. My signature confirms the agreement of both parties that the study will be conducted in accordance with the protocol and all applicable laws and regulations including, but not limited to good pharmacoepidemiology practices (GPP), and the ethical principles that have their origins in the Declaration of Helsinki and applicable privacy laws.

I will provide copies of this protocol as needed to all physicians, nurses, and other professional personnel responsible to me who will participate in the study. I will discuss the protocol with them to assure myself that they are sufficiently informed regarding the conduct of the study. I am aware that this protocol will need to be approved by an appropriate institutional review board (IRB) or independent ethics committee (IEC) prior to any patients being enrolled and that I am responsible for verifying whether that requirement is met. I agree to adhere to the attached protocol and if requested to provide copies of medical information for the purpose of verification of submitted information, I will comply.

Since the information in this protocol is confidential, I understand that its disclosure to any third parties, other than those involved in approval, supervision, or conduct of the study is prohibited. I will ensure that the necessary precautions are taken to protect such information from loss, inadvertent disclosure, or access by third parties.

Investigator:

_____

Print Name

_____ _____

Signature Date

_____

Print Name of Institution or Practice and Location

RETURN ORIGINAL TO IQVIA

RETAIN COPY

Client Signature Page

Reviewed and Approved by:

<Client>	**Signature**	**Title**	**Date**
<**Client**>	**Signature**	**Title**	**Date**
<Lead Epidemiologist>			
IQVIA	**Signature**	**Title**	**Date**
<Scientific Oversight>			
IQVIA	**Signature**	**Title**	**Date**

Informational Contacts

Client

Moderna will serve as the Client of this study. It is the responsibility of the Marketing Authorization Holder (MAH) to ensure proper monitoring of the study and compliance with all applicable regulatory guidelines and laws.

United States:

Moderna Therapeutics

200 Technology Square

Cambridge, MA 02139 USA

European Union:

Moderna Biotech Spain, S.L.
Calle Monte Esquinza 30
28010 Madrid
Spain

Protocol Authors

Moderna: David Martin, MD, MPH, Vice President, Pharmacovigilance at Moderna Therapeutics, Cambridge, MA, USA. (b) (6)

IQVIA: Eleonora Staines Urias, PhD, MSc. Sr Epidemiologist, Real World Solutions, IQVIA, Reading, UK. (b) (6)

Clinical research organization (CRO) responsible for the management of the study

IQVIA

201 Broadway

Cambridge, MA USA 01945

Phone: +1 617 621 1600

Fax: +1 617 621 1620

List of Abbreviations

AE	adverse event
BMI	body mass index
CC	coordinating center
CDC	Centers for Disease Control and Prevention
CI	confidence interval
CMA	conditional marketing authorization
CRO	contract research organization
CTP	Current Procedural Terminology
eCRF	electronic case report form
EDC	electronic data capture
EDD	estimated date of delivery
EMA	European Medicines Agency
EU	European Union
EUA	emergency use authorization
EUROCAT	European Surveillance of Congenital Anomalies
FDA	U.S. Food and Drug Administration
GPP	good pharmacoepidemiology practices
HCP	healthcare provider
HIPAA	Health Insurance Portability and Accountability Act of 1996
ICF	informed consent form
ICH	International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use
IEC	independent ethics committee
IRB	institutional review board
ISPE	International Society for Pharmacoepidemiology
IUGR	intrauterine growth restriction
LMP	last menstrual period
LNP	Lipid nanoparticle
MACDP	Metropolitan Atlanta Congenital Defects Program
MAH	marketing authorization holder

mRNA	messenger RNA
NICHD	National Institute of Child Health and Human Development
OB	Obstetrician
PCP	primary care provider
SAE	serious adverse event
SAP	statistical analysis plan
SDV	source data verification
SGA	small-for-gestational-age
SPR	Standardized prevalence ratio
US	United States

Study Synopsis

<table>
<tr><td colspan="4">Full Study Title: Moderna mRNA-1273 Observational Pregnancy Outcome Study</td></tr>
<tr><td>Phase:</td><td>Post marketing</td><td>Type:</td><td>Observational</td></tr>
<tr><td colspan="2">Number of Patients: 1,000 patients</td><td colspan="2">Duration of Patient Participation: up to 21 months (9 months of pregnancy and 12 months of infant follow-up)</td></tr>
<tr><td colspan="2">Number of Sites: one coordinating site per country in North America (US and Canada) and EU (including Germany, Italy, and Finland)</td><td colspan="2">Duration of study: approximately 3 years</td></tr>
<tr><td colspan="2">Name of Medicinal Product: COVID-19 Vaccine Moderna COVID-19 mRNA Vaccine (nucleoside modified)

EU Marketing Authorisation Number:
EU/1/20/1507/001</td><td colspan="2">Active substance: CX-024414 (single-stranded, 5’-capped messenger RNA (mRNA) produced using a cell-free in vitro transcription from the corresponding DNA templates, encoding the viral spike (S) protein of SARS-CoV-2)</td></tr>
<tr><td colspan="4">Milestones:
<table>
<tr><th>Milestone</th><th>Planned date</th></tr>
<tr><td>Registration in the EU PASS register</td><td>To be determined</td></tr>
<tr><td>Start of data collection</td><td>Q2 2021</td></tr>
<tr><td>End of data collection</td><td>Q3 2023</td></tr>
<tr><td>Study progress reports</td><td>According to agreed schedule</td></tr>
<tr><td>Interim reports</td><td>31 Jul 2021, 31 Jan 2022, 31 Jul 2022, 31 Jan 2023, 31 Jul 2023, 31 Jan 2024</td></tr>
<tr><td>Final study report</td><td>30 Jun 2024</td></tr>
</table></td></tr>
</table>

Background:

The 2019–20 coronavirus (COVID-19) global pandemic is caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), first identified in China in December 2019. Evidence of the impact of COVID-19 infection among pregnant women is currently evolving; however, it is known that pregnant women are at a higher risk of serious complications of COVID-19 than non-pregnant women, especially those with pre-existing conditions such as diabetes or high blood pressure (1, 2). Emerging information suggests that pregnant women with symptomatic COVID-19 were more likely to give birth prematurely (1).

mRNA-1273 is a messenger RNA (mRNA)-based vaccine against COVID-19 that encodes for a prefusion stabilized spike (S) glycoprotein of SARS-CoV-2 (3). The vaccine is administered as two separate doses (injections) into the deltoid muscle, occurring approximately 1 month apart. Findings from the Phase 3 COVE trial (NCT04470427) of mRNA-1273, among 30,000 enrollees, demonstrated 94.1% vaccine efficacy against COVID 19 and 100% efficacy against severe cases of COVID-19. mRNA-1273 was generally well-tolerated, and adverse events were more commonly reported after the second injection. Pregnant women were excluded from the COVE trial; however, women of childbearing potential could enroll in the trial with use of adequate contraception.

Rationale:

Although the Moderna COVID-19 vaccine (mRNA-1273) clinical trials have demonstrated a favorable risk-benefit profile, there are no studies on the effects on pregnancy and offspring associated with the administration of the Moderna COVID-19 vaccine during pregnancy, during lactation, and/or before conception.

The Moderna COVID-19 Vaccine Pregnancy Registry will collect and analyze information on the potential impact of exposure to the Moderna COVID-19 vaccine on pregnancy complications and birth outcomes for exposed pregnancies; the prevalence of major congenital malformations will be compared with the prevalence in the general population.

Objectives:

To evaluate outcomes of pregnancy in females exposed to the Moderna COVID-19 vaccine (mRNA-1273) during pregnancy. Specifically:

- To estimate the proportion of major congenital malformations in offspring of women exposed to the Moderna COVID-19 vaccine (mRNA-1273) at any point from 28 days prior to their last menstrual period (LMP) through pregnancy
- To compare the proportion of major congenital malformations in offspring of women exposed to the Moderna COVID-19 vaccine at any point from 28 days prior to LMP through pregnancy with the prevalence of birth defects in the general population in the EU and US (using European Surveillance of Congenital Anomalies [EUROCAT] and Metropolitan Atlanta Congenital Defects Program [MACDP], respectively, as external comparators)
- In women exposed to the Moderna COVID-19 vaccine during pregnancy
  - To estimate the proportion of pregnancy complications, including:
    - preeclampsia/eclampsia
    - pregnancy-induced hypertension
    - antenatal bleeding
    - preterm labor
    - gestational diabetes
    - dysfunctional labor
    - premature rupture of membranes
    - placenta previa
    - postpartum hemorrhage
    - small-for-gestational-age fetus/intrauterine growth restriction
    - non-reassuring fetal status
    - COVID-19 diagnosis
  - To estimate the proportion of spontaneous abortion, fetal death/stillbirth, elective termination, and preterm birth
- In infants of women exposed to the Moderna COVID-19 vaccine during pregnancy
  - To estimate the proportion of minor congenital malformations
  - To estimate the proportion of neonatal/infant adverse outcomes, including:
    - neonatal infections (including COVID-19)
    - neonatal encephalopathy
    - respiratory distress in the newborn
    - neonatal/infant death
  - To estimate the proportion of small-for-gestational age at birth and low birth weight, and describe postnatal growth (height, weight) and developmental milestones through the first year of life.

Study design:

The design of this prospective, observational pregnancy exposure registry is consistent with relevant guidelines and recommendations (4-7). The registry will collect primary data from pregnant women who have received the Moderna COVID-19 vaccine and their healthcare providers (HCPs) (e.g., primary care physician [PCP], obstetrician [OB], nurse midwife or pediatrician) from North America (United States [US] and Canada) and several European Union (EU) countries (including Germany, Italy, and Finland).

E-consent (where available) and patient-reported data will be obtained electronically or via the coordinating center (CC). The CC will be responsible for ensuring completion of informed consent (or obtaining consent if not enrolling electronically) and all HCP contacts during the study. Patients' data obtained via questionnaires administered to patients or from their HCPs will be recorded on electronic case report forms (eCRFs) by the CC; electronic questionnaire responses directly from patients may also be obtained, where possible.

Women who have been exposed to the Moderna COVID-19 vaccine during the 28 days prior to their LMP or at any time during pregnancy are eligible for enrollment into the exposed cohort. Administration of the Moderna COVID-19 vaccine as part of this observational study is at the discretion of the HCP in accordance with local clinical practice and national public health recommendations.

No internal comparator group will be included in this study due to methodologic and logistical challenges. Instead, an external population (e.g., MACDP and EUROCAT for congenital malformations and stillbirth and available published external comparator data for pregnancy/infant adverse outcomes) will be used to contextualize study outcomes.

Major congenital malformations and other pregnancy, maternal, fetal, and infant outcomes are outcomes of interest for this study. Data on risk factors, exposures, other therapeutic or environmental exposures, and adverse maternal, fetal, and infant outcomes will be collected from patients and their HCPs during pregnancy and through 1 year after birth (infant's HCP and/or the patient). Major and minor congenital malformations will be classified according to the MACDP and EUROCAT classification systems and evaluated by a committee of at least two qualified, independent teratologists using all available medical records.

The outcomes will be presented in comparison with existing external comparator data sources. The analysis will be adequately powered to detect an *a priori* clinically meaningful difference in the proportion of major congenital malformations between the Moderna COVID-19 vaccine exposed cohort and the prevalence of birth defects in the general population.

The study is voluntary, and exposure to the Moderna COVID-19 vaccine or any other COVID-19 vaccines during the study period will be according to national public health recommendations and local standard of care. Follow-up will cease if the patient is lost to follow-up, consent is withdrawn, death (mother and/or infant), study termination, or the study ends (whichever comes first). The total duration of per patient participation is up to

21 months (9 months of pregnancy + 12 months of infant follow-up) and the total expected duration of the study is approximately 3 years.

Study population:

Inclusion criteria

- Patient consent obtained prior to enrollment (written or verbal per local regulations or Ethics Committee requirements)
- Aged 18 years or older
- Currently pregnant
- The outcome of pregnancy (i.e., pregnancy loss or live birth) must not be known at entry
- Agrees to electronically sign the release of medical information form permitting the study to contact her healthcare providers (e.g., PCP, obstetrician, nurse midwife) and the infant's HCP (e.g., pediatrician) for medical information
- Received the Moderna COVID-19 vaccine at any point from 28 days prior to LMP throughout pregnancy

Exclusion criteria

- Has received any other COVID-19 vaccines at any point from 28 days prior to LMP throughout pregnancy
- Women currently participating in another investigational device or drug study, currently taking an investigational medicinal product, or having taken an investigational product within 28 days prior to LMP or during pregnancy

Data collection/Data Sources:

Pregnancy registry participation is voluntary for the patient. It is important to focus on minimizing burden on the patients and HCPs. Data collected are focused only on what is minimally required to meet the needs/objectives of the registry. Furthermore, processes are streamlined to minimize obligations and increase likelihood of participation and retention for both patients and HCPs.

The Registry CC is responsible for reviewing the informed consent form (ICF) (or ICF status if completed electronically) with the patient (if they do not already have a copy, a CC agent will refer them to the ICF that is part of the registry website or email them a copy). After the patient has reviewed ICF, they will provide "consent," (verbally or electronically if allowed by local regulations) which will be indicated in the electronic data capture (EDC). The CC will deliver the medical records release (and assent for the child) or will ensure the release for has been properly completed by the patient, if completed electronically.

Patients' data obtained via questionnaires administered to patients or their HCPs will be recorded on electronic case report forms (eCRFs) by the CC; electronic questionnaire responses obtained directly from patients may also be obtained, where possible.

Suspected major and minor congenital malformations will be evaluated by at least two qualified, independent teratologists using all available medical records. The classification of malformations according to EUROCAT and MACDP conventions will be based on the teratologists' adjudication. In the event of discordances between the teratologists, a third expert will be consulted to provide the final classification.

Study Entry:

- Documentation of informed consent when needed
- Reporter of information (patient, obstetrician)
- Patient demographics and characteristics (e.g., age of mother and father, education level, occupation/employment status, race/ethnicity, height, weight, body mass index [BMI]) where local regulations permit
- Patient, secondary contact, and HCP contact information. This information is confidential and remains at the CC, it is not recorded in the eCRF
- Lifestyle risk factors (e.g., smoking, caffeine consumption, alcohol use, illicit drug use) from estimated date of conception
- Current pregnancy information (e.g., LMP, method of conception, gestational age, estimated date of delivery [EDD], date and results of any prenatal tests, number of fetuses)
- Maternal weight and weight gain during pregnancy
- Maternal medical history:
    - Pregnancy history (e.g., parity, gravidity, previous preterm births, previous pregnancy complications, previous spontaneous abortions or elective or therapeutic terminations, reason for any elective or therapeutic termination, history of congenital malformations, significant disability or neurodevelopmental delay in previous children)
    - Surgical and medical history/significant maternal conditions (e.g., diabetes, high blood pressure)
    - COVID-19 history (positive test dates, antibody status, treatment(s) and hospitalization status)
    - Comorbid conditions

- Family reproductive history (e.g., multiple births, congenital malformations, spontaneous abortions, premature births, chromosomal anomalies, developmental delay)
- Moderna COVID-19 vaccine administration dates

- Current and prior medication use from 28 days prior to LMP (including date of last dose/administration for potentially teratogenic medications, folic acid, other vitamins and supplements, prenatal vitamins, vaccinations, medications to treat other chronic diseases)
- Serious adverse events (SAEs) related to pregnancy

Follow-Up During Pregnancy (During Each Trimester, Approximately at 14, 25, and 34 Weeks Gestation):

- Date of contact
- Reporter of information (patient, obstetrician)
- Changes in contact information (maternal, secondary contact, and HCP). This information is confidential and remains at the CC. It is not recorded in the electronic case report forms (eCRF)
- Changes in pregnancy status
  - Gestational age estimated based on the date of LMP, unless ultrasound results provide an updated estimate
  - Any prenatal testing performed and results (e.g., blood group and Rh factor, glucose screen, screening for teratogenic infectious diseases, genetic screening for inherited conditions, screening for chromosomal abnormalities, ultrasound scans)
  - Pregnancy outcome, if applicable (e.g., elective or therapeutic termination, spontaneous abortion, ectopic pregnancy, molar pregnancy)
    - Reason for elective or therapeutic termination (e.g., prenatal testing finding, risk to mother's health, undesired pregnancy), if applicable
    - Autopsy results and pathology reports, if available
- Changes in COVID-19 status, including test dates, results, and treatment
- Moderna COVID-19 vaccine administration updates [if applicable]
- Changes in comorbid conditions
- Current lifestyle factors (e.g., smoking, caffeine consumption, alcohol use, illicit drug use)
- Maternal weight
- Other medications (teratogenic medications or medication with potential fetal health implications, corticosteroids, folic acid, other vitamins, and supplements, prenatal vitamins, vaccinations, medications to treat other chronic diseases)
- Serious adverse events (SAEs) related to pregnancy (see protocol definition)

Birth Outcome Follow-up (Approximately 4 Weeks After Estimated Date of Delivery):

- Date of contact and date of pregnancy outcome or gestational age (in weeks)
- Changes in contact information; contact information for infant's HCP
- Reporter of information (patient, obstetrician, infant HCP)
- Pregnancy outcome (e.g., live birth, stillbirth, spontaneous abortion, elective or therapeutic termination):
  - Reason for elective or therapeutic termination (e.g., prenatal testing finding, risk to mother's health, undesired pregnancy), if applicable
  - Autopsy results and pathology reports, if available
  - Mode of birth (vaginal delivery, assisted delivery/cesarean section, type of anesthesia)
  - Presentation at delivery (i.e., vertex, non-vertex)
- Changes in COVID-19 status, including test dates, results, and treatment
- Moderna COVID-19 vaccine administration updates [if applicable]
- Changes in comorbid conditions

- Current lifestyle factors (e.g., smoking, caffeine consumption, alcohol use, illicit drug use)
- Maternal weight at end of pregnancy
- Other medications (teratogenic medications or medication with potential fetal health implications, corticosteroids, folic acid, other vitamins, and supplements, prenatal vitamins, vaccinations, medications to treat other chronic diseases)
- SAEs related to pregnancy (see protocol definition)
- Infant characteristics:
    - Gestational age at birth
    - Sex
    - Weight
    - Length
    - Head circumference
    - Birth order (for multiple births), and number of fetuses
    - Apgar scores (1, 5, and 10 minutes)
    - Congenital malformations noted (including description and attribution)
    - Infant COVID-19 test results, if applicable
    - Whether infant is breastfed
    - All infant SAEs including hospitalizations other than for the standard post-birth hospital stay

Pediatric Follow-up (Approximately at 12, 26, and 52 Weeks After Birth):

- Reporter of information (patient, obstetrician, infant HCP)
- Maternal current lifestyle risk factors (e.g., smoking, caffeine consumption, alcohol use, illicit drug use)
- Infant characteristics:
    - Feeding behavior (including breastfeeding)
    - Weight
    - Length
    - Head circumference
    - Developmental milestones (e.g., social/emotional, language/communication, cognitive, movement/physical development milestones, as defined by the Centers for Disease Control [CDC])
    - Evidence of any new congenital malformation since last follow-up
    - Infant COVID-19 test results and treatments, if available
    - All infant SAEs including hospitalizations other than for the standard post-birth hospital stay

Early Termination of Study Participation Contact, If Applicable:

- Reporter of information (patient, obstetrician, infant HCP)
- Assessments appropriate for the time of withdrawal
- Reason for program withdrawal
- Changes in COVID-19 status, including test dates and results
- Moderna COVID-19 vaccine administration updates [if applicable]
- Other medications (including teratogenic medications or medication with potential fetal health implications, corticosteroids, folic acid, other vitamins, and supplements, vaccinations, medications to treat other chronic diseases)
- Pregnancy status:

- Gestational age
- Any prenatal testing performed and results (e.g., rubella titer, toxoplasmosis, venereal disease research laboratory test, hepatitis screen, ultrasounds, amniocentesis, maternal serum alpha-fetoprotein screen, glucose screen)
- Pregnancy outcome, if applicable (elective or therapeutic termination, spontaneous abortion, ectopic pregnancy, molar pregnancy)
- Reason for elective or therapeutic termination (e.g., prenatal testing finding, risk to mother's health, undesired pregnancy), if applicable
- Autopsy results and pathology reports, if available
- SAEs related to pregnancy (see protocol definition)

- Infant characteristics (for live births):
  - Gestational age at birth
  - Sex
  - Weight
  - Length
  - Head circumference
  - Birth order (for multiple births), and number of fetuses
  - Apgar scores (1, 5, and 10 minutes)
  - Congenital malformations noted (including description and attribution)
  - Whether infant is breastfed, if applicable
  - All infant SAEs including hospitalizations other than for the standard post-birth hospital stay

Data Management and Quality Assurance:

Patients' data obtained via questionnaires administered to patients and/or their HCPs will be recorded on eCRFs by the CC. Electronic questionnaire responses obtained directly from patients may also be obtained, where possible. The degree of detail and completeness of data collected is dependent on local clinical practice. Patients' data will be recorded on eCRFs. All data elements for collection are specified *a priori* and data collection forms will be developed prior to patient enrollment.

Safety:

Only SAEs related to pregnancy and infant SAEs will be collected and reported throughout the study. The AE reporting period begins when the patient is enrolled in the study and continues through the study's follow-up period. SAEs will be recorded on the appropriate forms (e.g., eCRFs) as designated by Moderna and reported within the required time window.

Statistical Considerations:

Sample size

To adequately power a comparison of the proportion of major congenital malformation events in the Moderna COVID-19 vaccine exposed with an external comparator, and assuming a 15 drop-out rate and a live birth rate of 75%, and enrollment of approximately 1/3 of the cohort during first trimester, 1,000 Moderna COVID-19 vaccine exposed pregnant women would need to be enrolled. This sample size would provide >80 power to detect a risk ratio of 2.0 when compared to an external comparator at a significance level of =0.05. This sample size is also expected to generate estimates of prevalence with reasonable precision in terms of the expected 95% confidence interval. The sample size is also informed by the precision of the confidence intervals (CIs) for frequencies of study outcomes. The width of the expected CI based on a sample size of 1,000 patients suggests that meaningful data for the estimation of the prevalence of study outcomes, including major congenital malformations will be obtained.

Statistical Analyses:

The study will compare proportions of major congenital malformations in infants of women exposed to the Moderna COVID-19 vaccine at any point from 28 days prior to LMP through pregnancy with the prevalence of birth defects in the general population estimated in the external comparators. Variables identified for the subgroup analysis will be evaluated as potential confounders in the comparative analysis of the risk ratio for major congenital malformations in the Moderna COVID-19 vaccine exposed and external comparator (when possible).

Data analysis for major congenital malformations will be based on the first trimester exposure to the Moderna COVID-19 vaccine. Adjudicated major congenital malformations reported up to 1 year of age by the mother or by an HCP will be included in this analysis. Women who have received any first trimester prenatal testing after enrollment, with either negative or positive test result will be included in this analysis, ***except***:

- Women who have received first trimester prenatal screening, in which either aneuploid disorders or genetic disorders that cause major congenital malformations have been detected, because these disorders are unrelated to medication use
- Any prematurity-related disorders and transient conditions
- Women where the outcome is known, prior to enrollment in the registry, either positive or negative, for major congenital malformations that are unrelated to genetic or aneuploid disorders will be analyzed separately as a subgroup analysis

Descriptive analyses will be performed to gain an understanding of the qualitative and quantitative nature of the data collected and the characteristics of the sample studied. Continuous variables will be reported as mean (and standard deviation), median, minimum, maximum and range where appropriate. Categorical variables will be summarized as number and proportion of the total study population, and by subgroups where appropriate. Analyses will be conducted overall (ever exposed during pregnancy) as well as by earliest trimester of administration of the Moderna COVID-19 vaccine, as applicable. All analyses will be performed in aggregate for all participants and stratified by country or region of residence. If sufficient numbers are obtained, analyses will also be presented by the subgroups of maternal age, race/ethnicity, prior history of elective or therapeutic

pregnancy termination status, prenatal screening result (positive versus negative), prenatal testing status (performed vs not performed), exposure to medications of special interest, and other important risk factors.

The prevalence of major and minor congenital malformations will be calculated using MACDP and EUROCAT conventions. Major malformations will be analyzed separately from minor malformations, with the analysis including only adjudicated major congenital malformations. The total prevalence will be calculated by dividing the number of adjudicated cases of each event (observed in live births, fetal deaths, elective or therapeutic terminations, and at any gestational age) by the total number of pregnancies (excluding spontaneous terminations and ectopic or molar pregnancies). The prevalence at birth will be calculated as number of cases observed in live births and stillbirths divided by the total number of births (stillbirths + live births). Data analysis for major congenital malformations will be based on first trimester exposure to the Moderna COVID-19 vaccine.

Prevalence of all outcome measures will be presented with 95% CIs for binomial proportion.

Comparative Analysis

External Comparator Cohort Analysis

Outcome prevalence for major congenital malformations in the Moderna COVID-19 exposed cohort will be compared with available external comparator cohort(s) representing the background prevalence of birth defects in the general US population (MACDP) (8) and the European population (EUROCAT). EUROCAT and MACDP classification of congenital malformations will be implemented to ensure comparability with European and US pregnancy data sources, respectively.

The difference in prevalence of major congenital malformations in Moderna COVID-19 vaccine exposed cohort and the external comparator cohort will be compared using a risk ratio (95% CI) estimate. Categorical distributions available in the MACDP report will be summarized using the same categories among exposed pregnancies (9). Indirect standardization methods will be applied for categorical distributions of maternal age, gestational age, and race/ethnicity. Indirect standardization involves calculation of the observed number of events (i.e., major congenital malformations) and applying the maternal age, gestational age, and race ethnicity distributions from the reference population (i.e., MACDP) to calculate the expected number of major congenital malformations. The ratio of the observed number of major congenital malformations to the expected number of major congenital malformations is referred to as the standardized prevalence ratio (SPR). Adjusted prevalence can be calculated by multiplying the SPR by the crude congenital malformation rate.

Additional available published external comparator data in pregnant women and other COVID-19 pregnancy surveillance data will be evaluated to contextualize the registry findings for pregnancy complications and pregnancy/infant adverse outcomes.

Sensitivity Analysis

Sensitivity analyses will be performed on the Moderna COVID-19 vaccine exposed cohort if sufficient sample size allows, and include but are not limited to the following:

- A sensitivity analysis of major congenital malformations will include women who have received any prenatal screening, regardless of the findings.
- A sensitivity analysis of women who received the full administration schedule of the Moderna COVID-19 vaccine, a partial schedule (e.g., one dose) or a mixed administration of vaccines (e.g., one dose manufactured by Moderna and the second dose manufactured by another marketing authorization holder [MAH[).
- A sensitivity analysis of major congenital malformations will include women where the result is known, regardless of the findings, prior to enrollment in the registry. Subsequently, a sensitivity analysis of major

congenital malformations will include women who received any first trimester prenatal screening before enrollment where the result is known to be negative.

- A sensitivity analysis of major and minor congenital malformations will be performed that analyzes different cut points of exposure to the Moderna COVID-19 vaccine, accounting for each trimester of exposure. While the primary cut point will be the date of LMP to the end of the first trimester (14 weeks gestation), additional sensitivity cut points will include: 28 days prior to LMP through the end of the first trimester, LMP date to the end of pregnancy, 28 days prior to LMP to the end of pregnancy, second trimester exposure only, and third trimester exposure only.
- Spontaneous abortions defined as loss of a fetus due to natural causes occurring before 22 weeks gestation rather than 20 weeks gestation (per the main study definition) will also be examined in a sensitivity analysis to account for global variation in the definition for this outcome.
- For spontaneous abortion, a sensitivity analysis will be performed based on gestational age at enrollment.

Sensitivity analyses may rely on sufficient sample sizes in order to execute.

Subgroup Analysis

Additional subgroups of interest may be explored beyond what is outlined, below. If the difference in subgroups is meaningful, these covariates will be considered for adjustment of confounding in the analysis.

The Moderna COVID-19 vaccine exposed cohort will be summarized for pregnancy and infant outcomes both overall and by the subgroups of following parameters, if sufficient sample size allows:

- Maternal age category
- Country or region of residence
- Race/ethnicity, where local regulation permits
- Smoking status

Ethical and Regulatory Considerations:

This non-interventional study will be conducted in accordance with the protocol and all applicable laws and regulations including, but not limited to good pharmacoepidemiology practices (GPP), and the ethical principles that have their origins in the Declaration of Helsinki and applicable privacy laws. Data protection and privacy regulations will be strictly observed in capturing, forwarding, processing, and storing patient data. Every effort will be made to protect participant confidentiality according to the Directive 95/46/EC on the protection of individuals, and in compliance with Safe Harbor privacy principles. An IRB/IEC must review and approve the protocol and ICF before any patients are enrolled.

Documentation of Protocol Amendments

Not applicable (original protocol).

1. BACKGROUND

The severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) global pandemic emerged from China in December 2019 causing the widespread respiratory illness known as COVID-19. Evidence of the impact of COVID-19 infection among pregnant women is currently evolving. A recent meta-analysis reported severe COVID-19 infection was more common among women with pre-existing conditions such as diabetes or high blood pressure (1). COVID-19-infected pregnant women were more likely to require intensive care admission and invasive ventilation compared with non-pregnant women and were more likely to deliver preterm compared with uninfected pregnant women (1). Conversely, a large US cohort study among 3374 pregnant women reported no significant differences in adverse pregnancy outcomes between COVID-19 infected women compared with uninfected pregnant women (2).

mRNA-1273 is a lipid nanoparticle (LNP)-encapsulated messenger RNA (mRNA)-based vaccine that encodes for a full-length, prefusion stabilized spike (S) glycoprotein of the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) (3). The vaccine is one of several SARS-CoV-2 vaccine candidates developed in response to the global pandemic that targets the S glycoprotein, responsible for mediating host cell attachment and viral entry. The vaccine is administered as two separate doses (injections) into the deltoid muscle, occurring approximately 1 month apart.

In October 2020, Moderna completed enrollment of 30,000 participants into its Phase 3 randomized, placebo-controlled COVE trial (NCT00470427) for mRNA-1273. In the primary efficacy analysis, mRNA-1273 demonstrated 94.1% vaccine efficacy, which was based on a total of 196 COVID-19 cases (185 cases observed in the placebo arm versus 11 cases in the vaccinated arm). The COVE trial's secondary endpoint, severe COVID-19 case classification, there were 30 cases were observed, all in the placebo arm. mRNA-1273 was well-tolerated, and adverse events (AEs) were more commonly reported after the second injection. The most commonly reported AEs in COVE were fatigue, myalgia, arthralgia, headache, pain, and erythema as the site of injection. Pregnant women were excluded from COVE. Women of childbearing potential could enroll in the trial if they fulfilled all the following criteria:

- Had a negative pregnancy test at screening visit and on the day of the first dose
- Practiced adequate contraception or abstained from all activities that could result in pregnancy for at least 28 days prior to the first dose
- Agreed to continue adequate contraception through 3 months following the second dose
- Were not currently breastfeeding

On November 30, 2020, Moderna submitted for emergency use authorization (EUA) with the U.S. Food and Drug Administration (FDA) as well as for Conditional Marketing Authorization (CMA) with the European Medicines Agency (EMA). In December 2020, the FDA granted EUA for mRNA-1273. In January 2021, the European Commission granted a conditional marketing authorization.

This longitudinal, observational study aims to collect pregnancy and birth outcome information among women vaccinated with mRNA-1273 during pregnancy.

2. RATIONALE

Although the Moderna COVID-19 vaccine (mRNA-1273) clinical trials have demonstrated a favorable risk-benefit profile, there are no studies on the effects on pregnancy and offspring associated with the administration of the Moderna COVID-19 vaccine during pregnancy, during lactation, and/or before conception.

The Moderna COVID-19 Vaccine Pregnancy Registry will collect and analyze information on the potential impact of exposure to the Moderna COVID-19 vaccine on pregnancy complications and birth outcomes for exposed pregnancies; the proportion of major congenital malformations will be compared with the prevalence in the general population.

3. OBJECTIVES

To evaluate outcomes of pregnancy in females exposed to the Moderna COVID-19 vaccine (mRNA-1273) during pregnancy. Specifically:

- To estimate the proportion of major congenital malformations in offspring of women exposed to the Moderna COVID-19 vaccine (mRNA-1273) at any point from 28 days prior to their last menstrual period (LMP) through pregnancy

- To compare the proportion of major congenital malformations in infants of women exposed to the Moderna COVID-19 vaccine at any point from 28 days prior to LMP through pregnancy with the prevalence of birth defects in the general population in the EU and US (European Surveillance of Congenital Anomalies [EUROCAT] and Metropolitan Atlanta Congenital Defects Program [MACDP] external comparator)

- In women exposed to the Moderna COVID-19 vaccine during pregnancy

  - To estimate the proportion of pregnancy complications, including:

    - preeclampsia/eclampsia
    - pregnancy-induced hypertension
    - antenatal bleeding
    - preterm labor
    - gestational diabetes
    - dysfunctional labor
    - premature rupture of membranes

- placenta previa
- postpartum hemorrhage
- small-for-gestational-age fetus/intrauterine growth restriction
- non-reassuring fetal status
- COVID-19 diagnosis

- To estimate the proportion of spontaneous abortion, fetal death/stillbirth, elective termination, and preterm birth

- In infants of women exposed to the Moderna COVID-19 vaccine during pregnancy

- To estimate the proportion of minor congenital malformations
- To estimate the proportion of neonatal/infant adverse outcomes, including:
  - neonatal infections (including COVID-19)
  - neonatal encephalopathy
  - respiratory distress in the newborn
  - neonatal/infant death
- To estimate the proportion of small-for-gestational age at birth and low birth weight, and describe postnatal growth (height and weight) and development milestones through the first year of life

4. STUDY DESIGN

4.1 Study Description

The design of this prospective, observational pregnancy exposure registry is consistent with relevant guidelines and recommendations (4-7). The registry will collect primary data from pregnant women who have received the Moderna COVID-19 vaccine and their healthcare providers (HCPs) (e.g., primary care physician [PCP], obstetrician [OB], nurse midwife or pediatrician) from North America (US and Canada) and several EU countries (including Germany, Italy, and Finland pending vaccine availability for pregnant women).
E-consent and patient-reported data will be obtained via app and web-based technology, and the coordinating center (CC) will be responsible for ensuring completion of informed consent, patient-reported data and all HCP contacts during the study. Patients' data obtained via questionnaires administered to patients or their HCPs will be recorded on electronic case

report forms (eCRFs) by the CC; electronic questionnaire responses directly from patients may also be obtained, where possible.

Study outcomes include major congenital malformations and other pregnancy, maternal, fetal, and infant outcomes. Data on risk factors, exposures, other therapeutic or environmental exposures, and adverse maternal, fetal, and infant outcomes will be collected from patients and their HCPs during pregnancy and through 1 year after birth (infant's HCP and/or the patient). Major and minor congenital malformations will be classified according to the MACDP and EUROCAT classification systems and evaluated by a committee of at least two qualified, independent teratologists using all available medical records.

The study is voluntary, and exposure to the Moderna COVID-19 vaccine or any other COVID-19 vaccines during the study period will be according to national public health recommendations and local standard of care. Follow-up will cease if the patient is lost to follow-up, consent is withdrawn, death (mother and/or infant), study termination, or the study ends (whichever comes first). The total duration of per patient participation is up to 21 months (9 months of pregnancy + 12 months of infant follow-up) and the total expected duration of the study is approximately 3 years.

4.2 Study Population

The study will aim to enroll approximately 600 pregnant women exposed to the Moderna COVID-19 vaccine from North America (US and Canada) and several countries in the EU (including Germany, Italy, and Finland).

Women who have been exposed the Moderna COVID-19 vaccine during the 28 days prior to their LMP or at any time during pregnancy are eligible for this exposed cohort. Administration of the Moderna COVID-19 vaccine as part of this observational study is at the discretion of the HCP in accordance with local clinical practice and national public health recommendations.

To reduce bias that may occur if outcome information is known prior to enrollment, women should be enrolled in the study as soon as their pregnancy is known, preferably prior to any informative prenatal testing (where the knowledge of the study outcome of the pregnancy would be known – either normal or abnormal), and preferably in the first trimester or before 20 weeks' gestation.

4.2.1 Inclusion Criteria

The following criteria must be met in order to be enrolled in the study:

- Patient consent obtained prior to enrollment (written or verbal per local regulations or Ethics Committee requirements)
- Aged 18 years or older
- Currently pregnant

- The outcome of pregnancy (i.e., pregnancy loss or live birth) must not be known at entry

- Agrees to electronically sign the release of medical information form permitting the study to contact her HCPs (e.g., PCP, obstetrician, nurse midwife) and the infant's HCP (e.g., pediatrician) for medical information

- Received the Moderna COVID-19 vaccine at any point from 28 days prior to LMP throughout pregnancy

4.2.2 Exclusion Criteria

Patients meeting ANY of the following criteria are not eligible for participation:

- Has received any other COVID-19 vaccines at any point from 28 days prior to LMP throughout pregnancy

- Women currently participating in another investigational device or drug study, currently taking an investigational medicinal product, or having taken an investigational product within 28 days prior to LMP or during pregnancy

4.2.3 Patient Withdrawal

Patients may withdraw consent and discontinue participation in the study at any time, with no effect on their medical care or access to treatment. If a patient is withdrawn prior to completing the study follow-up period, any known reason for withdrawal should be documented in the database. All information already collected as part of the study will be retained for analysis; however, no further efforts will be made to obtain or record additional information regarding the patient.

4.2.4 Coordinating Center

The registry CCs will be responsible for reviewing the informed consent form (ICF) with the patient. After the patient has reviewed, they will provide "verbal consent," (if allowed by local regulations) which will be indicated in the electronic data capture (EDC), or e-consent if completed electronically by the patient. The CC will then deliver the medical records release (and assent for the child), or the patient will complete the release electronically.

The virtual study site will comprise the Principal Investigator (PI) and a remote study team. Patient guides are nurses who work with patients on all direct study-related issues. They will be the primary point of contact for the patients from screening through study completion.

Patients' data obtained via questionnaires administered to patients or their HCPs will be recorded on eCRFs by the CC; electronic questionnaire responses obtained directly from patients may also be obtained, where possible.

4.2.5 Recruitment and Retention

Keys to ensuring successful enrollment, engagement and retention in the Moderna COVID-19 Vaccine Pregnancy Registry include a Registry Hub website together with a targeted awareness campaign. In addition, IQVIA will use existing data assets to identify high prescribers of Moderna COVID-19 vaccine to target for the awareness campaign.

4.2.5.1 Pharmacovigilance Bridging

As the registry is being built, Moderna will collect enrollment information relevant for the pregnancy registry as part of existing pharmacovigilance work. If a patient consents to be contacted for the registry, the CC will follow-up as soon as the registry is live.

4.2.5.2 Registry Hub

In support of the registry, a branded website will be developed to support and inform both patients and HCPs. The patient section of the website will include content about the Moderna COVID-19 Vaccine Pregnancy Registry, what to expect, CC contact information, and pre-screening. If the patient decides they are interested in joining the registry, they will have the option to enter their contact information for the CC to follow-up or to complete follow-up electronically. Once the patient is contacted, the CC will enroll the patient by reviewing informed consent and opt them in for retention messaging. Once enrolled, patients will receive a digital welcome communication and registry brochure. There is also the option to provide ongoing communications, such as supportive emails and newsletters, to the patient to keep patients engaged in the registry and minimize the number of patients lost to follow-up.

4.2.5.3 Awareness Campaign

To support referrals, HCPs on the ‘top prescriber list’ generated using the Moderna COVID-19 vaccine-specific Current Procedural Terminology (CPT) code will receive a physician awareness email that will help drive physician and patient awareness of the registry with graphics and key messages. The email will also provide a link to the Registry Hub for further information.

Registry flyers and briefing notes will be created to be used in routine interaction with HCPs or other locations where the Moderna COVID-19 vaccine is administered. For example, we will use existing relationships with pharmacy chains (e.g., Walgreens) as the vaccine is FDA approved and distributed more widely through other channels.

As the landscape for COVID-19 vaccines continues to evolve, awareness campaigns will be adapted to ensure that enrollment is optimized for eligible pregnant women.

4.2.6 External Comparator Cohorts

An internal comparator was considered. However, significant limitations to the recruitment of an internal comparator group were noted. Specifically, women who enroll in an internal comparator may have different risks for pregnancy outcomes compared to those who do not

enroll, women who enroll in an unvaccinated internal comparator may have different risks for pregnancy outcomes compared with those who enroll in the vaccinated cohort, the number of unvaccinated women who elect to enroll in an internal comparator may be small given that vaccination coverage is expected to be high, and the urgent need to provide informative safety data in pregnancy among vaccinated women in a timely manner may be slowed by recruitment in an internal comparator. Therefore, an internal comparator was deemed infeasible, methodologically inappropriate, and will not be included in this study. External population-based comparators (including MACDP and EUROCAT for the comparison of major congenital malformations and additional available published external comparator data in pregnant women and other COVID-19 pregnancy surveillance data for the comparison of pregnancy/infant adverse outcomes) will instead be used to contextualize study outcomes and aid in the interpretation of the risk of study outcomes estimated in the study population. Comparisons will be adjusted (standardized or stratified) for relevant covariates (when possible) to assure comparability of estimates.

External comparators will be used to descriptively characterize study results, representing the estimated underlying prevalence of major structural or genetic birth defects in the general US and EU populations. Only aggregate, population-level data or published reports would be used for comparison. EUROCAT classification of congenital malformations will be implemented to ensure comparability with any European data sources available for descriptive comparison with this registry.

4.2.6.1 Metropolitan Atlanta Congenital Defects Program (MACDP)

The MACDP, a population-based tracking system for birth defects, was established in 1967 as the first population-based system for the active collection of information about birth defects in the US (8). Currently, the MACDP tracking system captures approximately 35,000 births per year from three large metropolitan counties in the Atlanta area (five counties were captured in earlier years). MACDP has monitored trends in birth defects rates and has served as a case registry for descriptive, risk factor, and prognostic studies of birth defects. Since 1998, MACDP surveillance has required that any signs or symptoms of a defect in the child be reported before their sixth birthday. In a 2007 report, the MACDP presented data on the prevalence and descriptive characteristics of birth defects, including 67 individual defects, in metropolitan Atlanta, Georgia, from 1968 to 2003.

The frequency of birth defects is measured as prevalence at birth, expressed as the number of affected infants per 1,000 live births. Major structural or genetic birth defects affected approximately 3% of births in the US (9). The prevalence estimates of stillbirth in 2006 and 2008 using MACDP data were 8.0 and 7.6 per 1000 live births plus stillbirths (95% CIs: 7.3, 8.7, and 6.9, 8.4), respectively (10).

4.2.6.2 European Surveillance of Congenital Anomalies (EUROCAT)

EUROCAT is a European network of population-based registries for the epidemiologic surveillance of congenital anomalies. Started in 1979, the registry includes over 1.7 million births surveyed annually in Europe from 43 registries in 23 countries. Approximately 29% of the European birth population is covered by this network. These population-based registries

facilitate the early warning of new teratogenic exposures, evaluate the effectiveness of primary prevention measures, and assess the impact of developments in prenatal screening.

Using 13 registries from the EUROCAT network from 01 January 1998 through 31 December 2011, Groen et al. reported an overall prevalence of congenital anomaly of 27.3 per 1000 births (range, 19.1–39.3 per 1000 births) (11). Of the 84,387 pregnancies with a known outcome (99.4%), 2.33% pregnancies were stillbirths, the proportion of early neonatal mortality (within 7 days of birth) was 2.37% and the proportion of late neonatal mortality (between 7 days to 27 days of life) was 0.84%.

4.3 Data Sources and Collection

4.3.1 Collection of Data on the eCRF

Patients' data obtained via questionnaires administered to patients and/or their HCPs will be recorded on eCRFs by the CC; electronic questionnaire responses obtained directly from patients may also be obtained, where possible. The degree of detail and completeness of data collected is dependent on local clinical practice. Patients' data will be recorded on eCRFs. All data elements for collection are specified *a priori* and data collection forms will be developed prior to patient enrollment.

4.3.2 Data Collected During the Observation Period

After a patient provides consent, the CC will obtain demographic and contact information in addition to baseline information at the time of enrollment. Alternatively, this data may be reported to the CC electronically by the patient. All patient and HCP contact information will be confidential and will remain at the CC. The CC will then contact the patient each trimester to update contact information and ascertain the occurrence of pregnancy outcomes or other events (Figure 1).

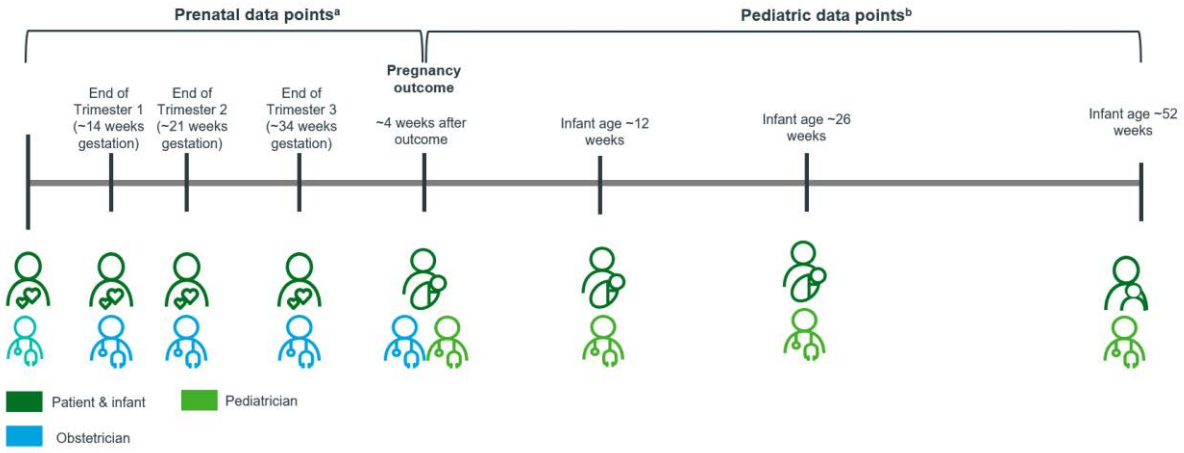

Figure 1 Expected time points of contact with registry participants

After a patient is enrolled, there will be at least three attempts made to contact the patient and/or the HCP via phone, email, fax, and mail, as appropriate, approximately ten business days apart. If data are obtained after a follow-up interval is passed, the CC will accept and enter the data and continue follow-up of the patient. If an HCP is not responsive at the time points described above (Figure 1), the patient will be asked to provide the information contained on the HCP worksheets. If the HCP then responds to contact, their information will supersede the patient-reported information. At all-time points, the type of reporter (patient, obstetrician, or infant HCP) will be recorded.

In the routine care setting, patients are seen regularly by their treating physicians either for treatment or for regular assessment after treatment. Thus, no study-specific visits or evaluations are required by this protocol.

If the patient experiences an adverse pregnancy outcome or has an elective or therapeutic termination or a termination of unknown cause, the HCP and patient will be encouraged to report the outcome to the CC as soon as possible. In the event of an elective or therapeutic termination, spontaneous abortion, fetal death or stillbirth, communications with the patients will cease after pregnancy outcome information has been obtained.

See Appendix 1- Data Collection Overview.

4.3.3 Loss to Follow-up

For study purposes, patients will be considered lost to follow-up if any time-based assessment is missed and the corresponding data have not been received by the CC after making additional follow-up attempts using all contact methods available (e.g., phone, fax, registered letter). At least three attempts will be made up to 4 months after the expected date of the missed assessment. The patient will be re-opened if additional information is later obtained. All HCPs and secondary contacts will also be contacted prior to considering a patient lost to follow-up. All data collected prior to the patient being lost to follow-up will be used for analyses, if possible. For analysis purposes, the date of study discontinuation will be recorded as the date of last contact.

4.4 Variables

4.4.1 Exposure Definition and Measures

This is an observational pregnancy exposure registry. No medication or vaccinations are provided as part of participation. Documentation of exposure to the Moderna COVID-19 vaccine from 28 days prior to LMP or at any point during the patient's pregnancy will be used to confirm exposure. Exposure information recorded will include administration dates for both doses of the vaccine.

4.4.2 Outcome Definitions and Measures

All outcomes defined in this section will be assessed in the Moderna COVID-19 vaccine-exposed women. Patient-level data will be collected prospectively, however it is possible that known results of imaging or genetic testing prior to enrollment in the study could allow a woman to enroll with an outcome already known. As such, we will identify outcomes known at the time of enrollment (i.e., retrospectively identified outcomes) as well as outcomes not known at the time of enrollment (i.e., prospectively identified outcomes). All outcomes will be included in primary analyses. Sensitivity analyses will restrict to women for whom outcomes were prospectively identified.

The outcome of major congenital malformations will be compared with the prevalence reported for the external comparator population that provides aggregate data, only (MACDP and EUROCAT).

Major Congenital Malformations

Congenital malformations will be classified according to the MACDP and EUROCAT classification systems. Suspected major and minor congenital malformations will be evaluated by at least two qualified, independent teratologists using all available medical records. The classification of malformations according to EUROCAT and MACDP conventions will be based on the teratologists' adjudication, who will be blinded to patient exposure status. In the event of discordances between the teratologists, a third expert will be consulted to provide the final classification.

Major malformations are those that have significant medical, social or cosmetic consequences, and typically require surgical intervention or are life-threatening (e.g., cleft lip, spina bifida). Minor malformations pose no significant health problem in the neonatal period and tend to have limited social or cosmetic consequences, rarely requiring surgical intervention (e.g., single palmar crease, clinodactyly). Both major and minor congenital malformations identified up to 1 year of age by the mother or by the infant's pediatrician via the dysmorphological examination conducted as part of the standard of care will be included in the analysis. Any defects identified after 1 year of age will be included if available, and descriptive analysis on these defects will be provided. More details will be provided in the SAP.

Pregnancy Complications

- Preeclampsia

  Primary preeclampsia will be based on HCP reported diagnosis. It is often defined as the presence of hypertension on two occasions at least 4 hours apart after 20 weeks gestation (in a woman with a previously normal blood pressure) and proteinuria; or in the absence of proteinuria, a new-onset hypertension accompanied by one of the following conditions: thrombocytopenia, renal insufficiency, impaired liver function, pulmonary edema, or cerebral or visual symptoms.

- Eclampsia

  Eclampsia will be based on HCP reported diagnosis. It is defined as new-onset grand mal seizures in a patient with preeclampsia, without other provoking factors.

- Pregnancy-Induced Hypertension

  High blood pressure (elevated: systolic between 120-129 and diastolic less than 80 mg Hg; Stage 1 hypertension: systolic between 130–139 or diastolic between 80–89 mm Hg; Stage 2 hypertension: systolic at least 140 or diastolic at least 90 mm Hg) associated with pregnancy, as diagnosed by the treating HCP.

- Antenatal bleeding

  Bleeding from or in to the genital tract, occurring from 24+0 weeks of pregnancy and prior to the birth of the baby (in the majority of cases the bleeding is vaginal and obvious, but the syndrome includes bleeding contained within the uterine cavity, the intraperitoneal space, or the retroperitoneal space).

- Preterm Labor

  Preterm labor will be based on HCP reported diagnosis. It is often as regular contractions of the uterus resulting in changes in the cervix hat starting before 37 weeks of pregnancy. Any interventions or treatments provided to the patient as a result of preterm labor will be collected.

- Gestational Diabetes

  Gestational diabetes will be based on HCP reported diagnosis. It is often characterized by the development of carbohydrate intolerance with first onset or first recognition during pregnancy; a record of an oral glucose tolerance test during pregnancy will also be accepted for data collection, where available.

- Dysfunctional labor (12)

  First stage of labor: woman in labor defined by regular contractions and cervical dilation of at least 4cm AND progress of <0.5cm cervical dilation per hour for at least 4 hours and with confirmed membrane rupture

  Second stage of labor:

  Nulliparous women: full cervical dilation AND onset of the active stage AND greater than 2 hours of pushing OR use of instrument delivery for the indication of dystocia OR Cesarean delivery for the indication of dystocia

Multiparous women: full dilation of the cervix AND onset of the active stage AND greater than 1 hour of pushing OR use of instrument delivery for the indication of dystocia OR Cesarean delivery for the indication of dystocia

- Premature rupture of membranes (PROM)

  Clinically confirmed rupture of amniotic sac prior to 37 weeks gestation

- Placenta Previa

  Physician-diagnosed placenta previa: when the baby's placenta fully or partially covers the mother's cervix.

- Postpartum hemorrhage

  Total blood loss of >500 mL after vaginal delivery or of >1000 mL after cesarean section

- Small–for–gestational-age (SGA) fetus and intrauterine growth restriction (IUGR)

  SGA is defined as fetal abdominal circumference or estimated fetal weight <10th centile; IUGR implies a pathological restriction of the genetic growth potential, with growth-restricted fetuses manifesting evidence of fetal compromise

- Non-reassuring fetal status (13)

  Category III fetal heart rate tracings detected via continuous cardiotocography (as defined by the National Institute of Child Health and Human Development [NICHD]) absent baseline fetal heart rate variability AND any of the following: recurrent late decelerations, recurrent variable deceleration, bradycardia (<110 bpm) OR sinusoidal pattern AND umbilical cord blood analysis consistent with metabolic acidosis (pH <7.0 and Base deficit >12mmol/L)

Pregnancy Outcomes

- Spontaneous Abortions

  A spontaneous abortion is defined as loss of a fetus due to natural causes at <20 weeks of gestation. If available, information from gross or pathologic examination of the abortus or fetus will be evaluated for structural and chromosomal defects.

- Fetal Death or Stillbirth

  Fetal death or stillbirth refers to the death of a fetus at ≥20 weeks of gestation. In the event of a stillbirth or fetal death, full pathology details will be requested and examined for structural or chromosomal defects. The final classification between fetal death/stillbirth and spontaneous abortion will be based on gestational age.

- Live Birth

  A live birth refers to a complete expulsion or extraction from its mother of a surviving neonate.

- Elective or Therapeutic Pregnancy Terminations

  Elective or therapeutic pregnancy terminations are defined as any induced or voluntary fetal loss during pregnancy. If available, data from pathologic examination of the abortus or fetus will be evaluated for structural and chromosomal defects. The reason for elective or therapeutic termination will be collected.

- Preterm Birth

  A live birth will be classified as preterm prior to 37 weeks of gestation. Early preterm (<34 weeks), late preterm (34–36 weeks), early term (37–38 weeks) are additional stratifications that may be considered during the analysis and will be outlined in the Statistical Analysis Plan (SAP).

- Ectopic Pregnancies

  Any reported ectopic pregnancy will be sub-classified in the respective pregnancy outcome, including induced termination, maternal death, or spontaneous pregnancy loss.

- Molar Pregnancies

  Any reported molar pregnancy will be sub-classified in the respective pregnancy outcome, including induced termination, maternal death, or spontaneous pregnancy loss.

- Maternal Death

  Maternal death is defined as the death of a pregnant woman during pregnancy, labor, or delivery. Maternal deaths for up to 12 weeks after delivery will also be reported and full pathology details will be requested.

- COVID-19 diagnosis

  COVID-19 diagnosis is defined as a laboratory confirmed infection diagnosed by a HCP at any time during pregnancy. Severity will also be considered.

Infant Outcomes

- Minor Congenital Malformations

Minor malformations pose no significant health problems in the neonatal period and tend to have limited social or cosmetic consequences, rarely requiring surgical intervention (e.g., single palmar crease, clinodactyly). Minor congenital malformations identified up to 1 year of age by the mother or by the infant's pediatrician via the dysmorphological examination conducted as part of the standard of care will be included in the analysis. Any defects identified after 1 year of age will be included if available, and descriptive analysis on these defects will be provided. All potential minor congenital malformations will be evaluated by at least two qualified, independent teratologists using all available medical records. The classification of potential minor congenital malformations will be based upon the teratologists' adjudication, who will be blinded to patient exposure status. Adjudicated minor congenital malformations will not be included in the analysis of the study objective.

- Size for Gestational Age (height and weight)

  All live births will be classified as small, appropriate, or large for gestational age using the Centers for Disease Control (CDC) definition of birth weight and height below the 10^{th} percentile, between the 10^{th} and 90^{th}, and above the 90^{th} percentile for age, respectively.

- Low Birth Weight

  An infant with low birth weight will be classified as weighing under 2500 g. Very low birth weight are infants who weigh less than 1500 g and moderate birth weight ranges between 1500 g and 2499 g; these are additional stratifications that may be considered during the analysis and will be outlined in the SAP.

- Size for Age (height and weight)

  All live infants will be classified, during follow-up, as below the 10^{th} percentile, between the 10^{th} and 90^{th}, and above the 90^{th} percentile of weight and height for age using the World Health Organization Child Growth Standards.

- Failure to Thrive

  An infant may be diagnosed as failing to thrive by his/her treating physician for criteria such as a significant weight or weight-for-height deceleration. Any reported instances of failure to thrive will be captured.

- Hospitalization of Infants

  Any infant hospitalization, other than for a standard post-birth hospital stay, will also be captured.

- Neonatal Death

A neonatal death is defined as a death occurring in a neonate prior to 28 days of life. In the event of a neonatal death, full pathological details will be requested, and any structural or congenital defects detected will be evaluated.

- Perinatal Death

  Perinatal death is defined as the death of an infant between 28 days of life and 12 weeks of life. In the event of a perinatal death, full pathological details will be requested, and any structural or congenital defects will be evaluated.

- Neonatal encephalopathy (14)

  Abnormal level of alertness or seizures AND difficulty with initiating and maintaining respiration AND depression of tone, among newborns (1-28 days) born at or beyond 35 weeks

- Respiratory distress in the newborn (15)

  Abnormal respiratory rate among newborns (0-28 days), defined as tachypnea (respiratory rate of 60 or more breaths per minute), bradypnea (respiratory rate of less than 30 breaths per minute), OR apnea (cessation of respiratory effort (no breaths) for at least 20 seconds AND clinical observation of nasal flaring (dilatation of alae nasi); noisy respirations in the form of expiratory grunting, stridor, or wheeze; retractions or increased chest indrawings on respiration; central cyanosis on room air; or low Apgar score (<7 points) at 10 minutes with respiration score <2 Low Apgar Score (<7 points) at 10 min, with respiration score <2

- Neonatal/infant infection

  Clinically or laboratory-confirmed infection in infant up to 12 months of age, including COVID-19 infection

- Infant Death

  Infant death is defined as the death of an infant occurring between 12 and 52 weeks of life. In the event of an infant death, full pathological details will be requested, and any structural or congenital defects will be evaluated.

- Infant Developmental Milestones

  Infant developmental milestones will be assessed based on data available in medical records.

Additional available published external comparator data in pregnant women and other COVID-19 pregnancy surveillance data will be evaluated to contextualize the registry findings for pregnancy complications and pregnancy/infant adverse outcomes.

4.4.3 Information Collected from Study Participants

4.4.3.1 Study Entry:

- Documentation of informed consent when needed
- Reporter of information (patient, obstetrician)
- Patient demographics and characteristics (e.g., age of mother and father, education level, occupation/employment status, race/ethnicity, height, weight, body mass index [BMI]) where local regulations permit
- Patient, secondary contact, and HCP contact information. This information is confidential and remains at the CC, it is not recorded in the eCRF.
- Lifestyle risk factors (e.g., smoking, caffeine consumption, alcohol use, illicit drug use) from estimated date of conception
- Current pregnancy information (e.g., LMP, method of conception, gestational age, estimated date of delivery [EDD], date and results of any prenatal tests, number of fetuses)
- Maternal weight and weight gain during pregnancy
- Maternal medical history:
    - Pregnancy history (e.g., parity, gravidity, previous preterm births, previous pregnancy complications, previous spontaneous abortions or elective or therapeutic terminations, reason for any elective or therapeutic termination, history of congenital malformations, significant disability or neurodevelopmental delay in previous children)
    - Surgical and medical history/significant maternal conditions (e.g., diabetes, high blood pressure)
    - COVID-19 history (positive test dates, antibody status, treatment(s) and hospitalization status)
    - Comorbid conditions
    - Family reproductive history (e.g., multiple births, congenital malformations, spontaneous abortions, premature births, chromosomal anomalies, developmental delay)
    - Moderna COVID-19 vaccine administration dates
- Current and prior medication use from 28 days prior to LMP (including date of last dose/administration for potentially teratogenic medications [see Appendix 2], folic acid, other vitamins and supplements, prenatal vitamins, vaccinations, medications to treat other chronic diseases)
- Serious adverse events (SAEs) related to pregnancy

4.4.3.2 Follow-Up During Pregnancy (During Each Trimester, Approximately at 14, 25, and 34 Weeks Gestation):

- Date of contact
- Reporter of information (patient, obstetrician)
- Changes in contact information (maternal, secondary contact, and HCP). This information is confidential and remains at the CC. It is not recorded in the eCRF
- Changes in pregnancy status
    - Gestational age estimated based on the date of LMP, unless ultrasound results provide an updated estimate
    - Any prenatal testing performed and results (e.g., blood group and Rh factor, glucose screen, screening for teratogenic infectious diseases, genetic screening for inherited conditions, screening for chromosomal abnormalities, ultrasound scans)
    - Pregnancy outcome, if applicable (e.g., elective or therapeutic termination, spontaneous abortion, ectopic pregnancy, molar pregnancy)
        - Reason for elective or therapeutic termination (e.g., prenatal testing finding, risk to mother's health, undesired pregnancy), if applicable
        - Autopsy results and pathology reports, if available
- Changes in COVID-19 status, including test dates, results, and treatment
- Moderna COVID-19 vaccine administration updates [if applicable]
- Changes in comorbid conditions
- Current lifestyle factors (e.g., smoking, caffeine consumption, alcohol use, illicit drug use)
- Maternal weight
- Other medications (teratogenic medications or medication with potential fetal health implications [see Appendix 2], corticosteroids, folic acid, other vitamins, and supplements, prenatal vitamins, vaccinations, medications to treat other chronic diseases)
- SAEs related to pregnancy

4.4.3.3 Birth Outcome Follow-up (Approximately 4 Weeks After Estimated Date of Delivery):

- Date of contact and date of pregnancy outcome or gestational age (in weeks)

- Changes in contact information; contact information for infant's HCP
- Reporter of information (patient, obstetrician, infant HCP)
- Pregnancy outcome (e.g., live birth, stillbirth, spontaneous abortion, elective or therapeutic termination):
    - Reason for elective or therapeutic termination (e.g., prenatal testing finding, risk to mother's health, undesired pregnancy), if applicable
    - Autopsy results and pathology reports, if available
    - Mode of birth (vaginal delivery, assisted delivery/cesarean section, type of anesthesia)
    - Presentation at delivery (i.e., vertex, non-vertex)
- Changes in COVID-19 status, including test dates, results, and treatment
- Moderna COVID-19 vaccine administration updates [if applicable]
- Changes in comorbid conditions
- Current lifestyle factors (e.g., smoking, caffeine consumption, alcohol use, illicit drug use)
- Maternal weight at the end of pregnancy
- Other medications (teratogenic medications or medication with potential fetal health implications [see Appendix 2], corticosteroids, folic acid, other vitamins, and supplements, prenatal vitamins, vaccinations, medications to treat other chronic diseases)
- SAEs related to pregnancy
- Infant characteristics:
    - Gestational age at birth
    - Sex
    - Weight
    - Length
    - Head circumference
    - Birth order (for multiple births), and number of fetuses
    - Apgar scores (1, 5, and 10 minutes)
    - Congenital malformations noted (including description and attribution)
    - Infant COVID-19 test results, if applicable
    - Whether infant is breastfed
    - All infant SAEs including hospitalizations other than for the standard post-birth hospital stay

4.4.3.4 Pediatric Follow-up (Approximately at 12, 26, and 52 Weeks After Birth):

- Reporter of information (patient, obstetrician, infant HCP)
- Maternal current lifestyle risk factors (e.g., smoking, caffeine consumption, alcohol use, illicit drug use)
- Infant characteristics:
    - Feeding behavior (including breastfeeding)
    - Weight
    - Length
    - Head circumference
    - Developmental milestones (e.g., social/emotional, language/communication, cognitive, movement/physical development milestones, as defined by the Centers for Disease Control [CDC])
    - Evidence of any new congenital malformation since last follow-up
    - Infant COVID-19 test results and treatments, if available
    - All infant SAEs including hospitalizations other than for the standard post-birth hospital stay

4.4.3.5 Early Termination of Study Participation Contact, If Applicable:

- Reporter of information (patient, obstetrician, infant HCP)
- Assessments appropriate for the time of withdrawal
- Reason for program withdrawal
- Changes in COVID-19 status, including test dates and results
- Moderna COVID-19 vaccine administration updates [if applicable]
- Other medications (including teratogenic medications or medication with potential fetal health implications (see Appendix 2), corticosteroids, folic acid, other vitamins, and supplements, vaccinations, medications to treat other chronic diseases)
- Pregnancy status:
    - Gestational age
    - Any prenatal testing performed and results (e.g., rubella titer, toxoplasmosis, venereal disease research laboratory test, hepatitis screen, ultrasounds, amniocentesis, maternal serum alpha-fetoprotein screen, glucose screen)
    - Pregnancy outcome, if applicable (elective or therapeutic termination, spontaneous abortion, ectopic pregnancy, molar pregnancy)

- Reason for elective or therapeutic termination (e.g., prenatal testing finding, risk to mother's health, undesired pregnancy), if applicable
- Autopsy results and pathology reports, if available
- SAEs related to pregnancy (see protocol definition)

- Infant characteristics (for live births):

  - Gestational age at birth
  - Sex
  - Weight
  - Length
  - Head circumference
  - Birth order (for multiple births), and number of fetuses
  - Apgar scores (1, 5, and 10 minutes)
  - Congenital malformations noted (including description and attribution)
  - Whether infant is breastfed, if applicable
  - All infant SAEs including hospitalizations other than for the standard post-birth hospital stay

5. STATISTICAL METHODS

5.1 Sample Size

To adequately power a comparison of the proportion of major congenital malformation events in the Moderna COVID-19 vaccine exposed, and assuming a 15% drop-out rate and a live birth rate of 75%, and enrollment of approximately 1/3 of the cohort during first trimester, 1,000 Moderna COVID-19 vaccine exposed pregnant women would provide >80% power to detect a risk ratio of 2.0 when compared to an external comparator at a significance level of α=0.05 (Figure 2).

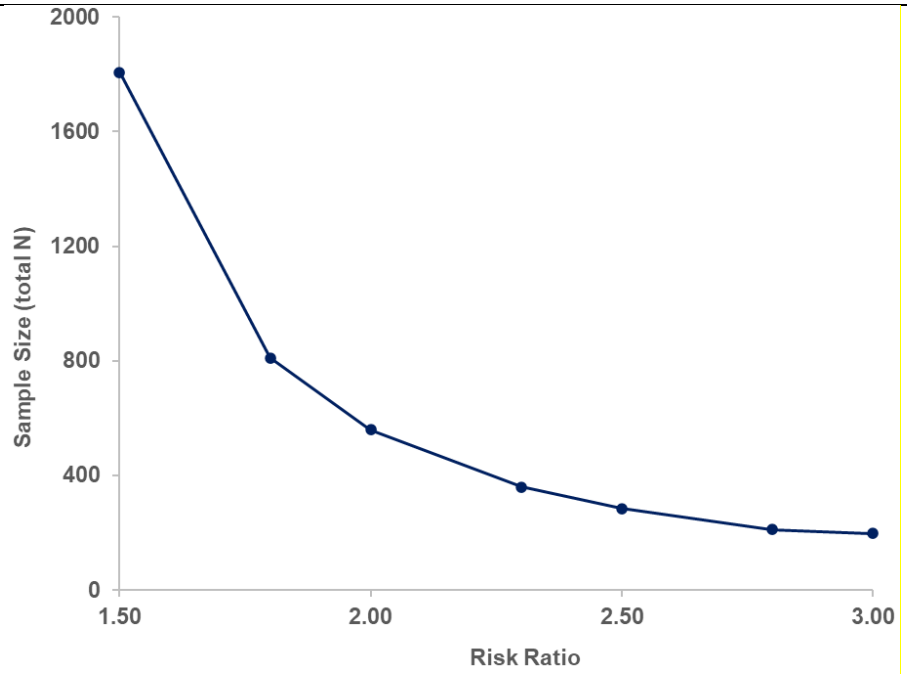

Figure 2. Sample size calculations assuming 15% drop-out rate, 75% live birth rate, and enrollment of approximately 1/3 of the cohort during the first trimester with an external comparator for 80% power

To ensure that the study obtains meaningful data for the estimation of the prevalence of all study outcomes, including major congenital malformations, anticipated precision of the confidence intervals (CIs) for observed frequencies was also considered.

The sample size (n) was calculated based on the normal approximation using the following formula:

$$n = p\ x\ (1-p)\ x\ \left(\frac{1.96}{e}\right)^2$$

where p is the frequency and e is the precision (i.e., half of the total width of the 95% CI).

Table 1 presents the precision and the corresponding 2-sided 95% CI for the frequency of a given outcome varying from 1.0% to 15.0% and a sample size varying from 50 to 1000 patients.

Table 1. Precision and 95% CI obtained for a sample size between 50 to 1000 patients and proportions between 1.0% and 15.0%.

N	N1	N2	P1	P2	P3	P4	P5	P6	P7	P8	P9
			1%	2%	3%	4%	5%	8%	10%	12%	15%
50	59	79	0.00, 4.76	0.00, 6.88	0.00, 8.73	0.00, 10.43	0.00, 12.04	0.00, 16.52	0.69, 19.32	1.99, 22.01	4.10, 25.90
100	118	158	0.00, 3.45	0.00, 5.24	0.00, 6.84	0.00, 8.34	0.23, 9.77	2.18, 13.82	3.62, 16.38	5.13, 18.87	7.50, 22.50
150	177	236	0.00, 2.93	0.00, 4.57	0.00, 6.06	0.53, 7.47	1.18, 8.82	3.33, 12.68	4.87, 15.13	6.47, 17.53	8.95, 21.05

200	236	315	0.00, 2.63	0.00, 4.19	0.39, 5.61	1.03, 6.97	1.73, 8.27	3.99, 12.01	5.59, 14.41	7.25, 16.75	9.80, 20.20
250	295	394	0.00, 2.43	0.07, 3.94	0.69, 5.32	1.37, 6.63	2.10, 7.90	4.44, 11.56	6.08, 13.92	7.77, 16.23	10.37, 19.63
300	353	471	0.00, 2.29	0.25, 3.75	0.90, 5.10	1.62, 6.38	2.37, 7.63	4.76, 11.24	6.44, 13.56	8.16, 15.84	10.79, 19.21
350	412	550	0.00, 2.19	0.39, 3.61	1.07, 4.93	1.80, 6.20	2.57, 7.43	5.02, 10.99	6.71, 13.29	8.45, 15.55	11.12, 18.88
400	471	628	0.00, 2.10	0.50, 3.50	1.20, 4.80	1.96, 6.05	2.74, 7.26	5.22, 10.78	6.94, 13.07	8.69, 15.31	11.38, 18.62
450	530	707	0.00, 2.03	0.60, 3.41	1.31, 4.69	2.08, 5.92	2.88, 7.13	5.38, 10.62	7.12, 12.88	8.89, 15.11	11.59, 18.41
500	589	786	0.03, 1.97	0.67, 3.33	1.41, 4.60	2.18, 5.82	2.99, 7.01	5.52, 10.48	7.27, 12.73	9.05, 14.95	11.77, 18.23
600	706	942	0.12, 1.88	0.80, 3.20	1.55, 4.45	2.35, 5.65	3.17, 6.83	5.75, 10.25	7.52, 12.48	9.32, 14.68	12.06, 17.94
700	824	1099	0.19, 1.81	0.89, 3.11	1.67, 4.34	2.48, 5.52	3.31, 6.69	5.92, 10.08	7.71, 12.29	9.52, 14.48	12.28, 17.72
800	942	1256	0.25, 1.75	0.97, 3.03	1.76, 4.25	2.58, 5.42	3.43, 6.57	6.06, 9.94	7.86, 12.14	9.69, 14.31	12.46, 17.54
900	1059	1412	0.29, 1.71	1.03, 2.97	1.83, 4.17	2.66, 5.34	3.52, 6.48	6.17, 9.83	7.98, 12.02	9.82, 14.18	12.61, 17.39
1000	1177	1570	0.33, 1.67	1.08, 2.92	1.89, 4.11	2.74, 5.27	3.60, 6.40	6.27, 9.73	8.09, 11.91	9.94, 14.06	12.74, 17.26

Two-sided confidence interval for one proportion (assuming confidence level 95%, dropout rate of 15% and live birth rate of 75%. Values reported as 0.00% correspond to <0.01%. P=proportion. N= sample size; N1=N adjusted for dropout rate; N2 = N adjusted for dropout and live birth rates.

Based on the estimates presented in Table 1, a planned sample size of 1,000 is considered sufficient to address the objectives of this observational study, with a reasonable precision.

5.2 Data Analyses

5.2.1 General Considerations

All computations and generation of tables, listings and data for figures will be performed using SAS® version 9.2 or higher (SAS Institute, Cary, NC, USA).

The analysis plan will be fully described in a written and approved SAP. Descriptive analyses will be performed to gain an understanding of the qualitative and quantitative nature of the data collected and the characteristics of the sample studied. Continuous variables will be reported as mean (and standard deviation) or median and range where appropriate. Categorical variables will be summarized as number and proportion of the total study population, and by subgroups where appropriate.

The study will evaluate the proportion of major congenital malformations in infants of women exposed to the Moderna COVID-19 vaccine at any point from 28 days prior to LMP through pregnancy as well other maternal, fetal, and infant outcomes variables identified for the subgroup analysis will be evaluated as potential confounders in the comparative analysis of the risk ratio for major congenital malformations in the Moderna COVID-19 vaccine exposed and external comparator (when possible).

Data analysis for major congenital malformations will be based on the first trimester exposure to the Moderna COVID-19 vaccine. Adjudicated major congenital malformations reported up to 1 year of age by the mother or by an HCP will be included in the analysis. Women who have received any first trimester prenatal testing after enrollment, with either negative or positive test result will be included in the analysis, except:

- Women who have received first trimester prenatal screening, in which either aneuploid disorders or genetic disorders that cause major congenital malformations have been detected, because these disorders are unrelated to medication use

- Any prematurity-related disorders and transient conditions

- Women where the outcome is known, prior to enrollment in the registry, either positive or negative, for major congenital malformations that are unrelated to genetic or aneuploid disorders will be analyzed separately as a subgroup analysis

Descriptive analyses will be performed to gain an understanding of the qualitative and quantitative nature of the data collected and the characteristics of the sample studied. Continuous variables will be reported as mean (and standard deviation), median, minimum, maximum and range where appropriate. Categorical variables will be summarized as number and proportion of the total study population, and by subgroups where appropriate. Analyses will be conducted overall (ever exposed during pregnancy) for the Moderna COVID-19 vaccine-exposed cohort as well as by earliest trimester of administration of the Moderna COVID-19 vaccine, as applicable. All analyses will be performed in aggregate for all participants and stratified by country or region of residence. If sufficient numbers are obtained, analyses will also be presented by the subgroups of maternal age, race/ethnicity, prior history of elective or therapeutic pregnancy termination status, prenatal screening result (positive versus negative), prenatal testing status (performed vs not performed), exposure to medications of special interest, and other important risk factors.

The prevalence of major and minor congenital malformations will be calculated using MACDP and EUROCAT convention. Major malformations will be analyzed separately from minor malformations, with the analysis including only adjudicated major congenital malformations. The total prevalence will be calculated by dividing the number of adjudicated cases of each event (observed in live births, fetal deaths, elective or therapeutic terminations, and at any gestational age) by the total number of pregnancies (excluding spontaneous terminations and ectopic or molar pregnancies). The prevalence at birth will be calculated as number of cases observed in live births and stillbirths divided by the total number of births (stillbirths + live births). Data analysis for major congenital malformations will be based on first trimester exposure to the Moderna COVID-19 vaccine.

Prevalence of outcome measures will be presented with 95% CIs for binomial proportion.

5.2.2 Comparative Analyses

5.2.2.1 External Comparator

Outcome prevalence for major congenital malformations in the Moderna COVID-19 exposed cohort will be compared with available external comparator cohort(s) representing the background prevalence of birth defects in the general US population and the European population. MACDP (8) and EUROCAT classifications of congenital malformations will be implemented to ensure comparability with US and European data sources, respectively.

The difference in prevalence of major congenital malformations in Moderna COVID-19 vaccine exposed cohort and the external comparator cohort will be compared using a risk ratio (95% CIs) estimates. Categorical distributions available in the MACDP and EUROCAT reports will be summarized using the same categories among exposed pregnancies (9). Indirect standardization methods will be applied for categorical distributions of maternal age, gestational age, and race/ethnicity. Indirect standardization involves calculation of the observed number of events (i.e., major congenital malformations) and applying the maternal age, gestational age, and race ethnicity distributions from the reference population to calculate the expected number of major congenital malformations. The ratio of the observed number of major congenital malformations to the expected number of major congenital malformations is referred to as the standardized prevalence ratio (SPR). Adjusted prevalence can be calculated by multiplying the SPR by the crude congenital malformation rate.

Additional available published external comparator data in pregnant women and other COVID-19 pregnancy surveillance data will be evaluated to contextualize the registry findings for pregnancy complications and pregnancy/infant adverse outcomes.

5.2.3 Sensitivity Analyses

Sensitivity analyses will be performed on the Moderna COVID-19 vaccine exposed cohort if sufficient sample size allows, and include but are not limited to the following:

- A sensitivity analysis of major congenital malformations will include women who have received any prenatal screening, regardless of the findings.

- A sensitivity analysis of women who received the full administration schedule of the Moderna COVID-19 vaccine, a partial schedule (e.g., one dose) or a mixed administration of vaccines (e.g., one dose manufactured by Moderna and the second dose manufactured by another marketing authorization holder [MAH]).

- A sensitivity analysis of major congenital malformations will include women where the result is known, regardless of the findings, prior to enrollment in the registry. Subsequently, a sensitivity analysis of major congenital malformations will include women who received any first trimester prenatal screening before enrollment where the result is known to be negative.

- A sensitivity analysis of major and minor congenital malformations will be performed that analyzes different cut points of exposure to the Moderna COVID-19 vaccine, accounting for each trimester of exposure. While the primary cut point will be the date of LMP to the end of the first trimester (14 weeks gestation), additional sensitivity cut points will include: 28 days prior to LMP through the end of the first trimester, LMP date to the end of pregnancy, 28 days prior to LMP to the end of pregnancy, second trimester exposure only, and third trimester exposure only.

- Spontaneous abortions defined as loss of a fetus due to natural causes occurring before 22 weeks gestation rather than 20 weeks (per the main study definition) will also be examined in a sensitivity analysis to account for global variation in the definition for this outcome.

- For spontaneous abortion, a sensitivity analysis will be performed based on gestational age at enrollment.

Sensitivity analyses may rely on sufficient sample sizes in order to execute.

5.2.4 Subgroup Analyses

The Moderna COVID-19 vaccine exposed cohort will be summarized for study outcomes both overall and by the subgroups of following parameters, if sufficient sample size allows:

- Maternal age category
- Country or region of residence
- Race/ethnicity, where local regulation permits
- Smoking status

5.2.5 Handling of Missing Data

It is optimal to prevent missing data, to the extent possible, through strategies set forth in the design and conduct of a study. For the current study, we will aim to minimize missing information by the following:

- Ensuring that primary variables of interest are those that are routinely collected as part of real-world clinical care and are available via medical charts, HCP and/or patient reporting, as appropriate

- Collecting only critical data elements (i.e., variables aligned with the study objectives) to minimize patient burden

- Including "not applicable", "not done" on the questionnaires that are being completed by patients/HCPs to differentiate these from values that are truly unknown

- Training of CC staff regarding data collection
- Planning interim analyses to characterize enrollment and loss to follow-up
- Checking for patterns of missingness and addressing any issues with targeted operational strategies
- Implementing direct to patient strategies to facilitate capture of patient-reported information

Should missing data occur, the data will be analyzed as they are recorded in the study eCRFs. However, the amount of missing values for data elements will be reported and will be assessed for the likely impact of missing data on the analysis and the pattern of the missing information. Full details on handling of missing data will be described in detail in the SAP.

5.2.6 Limitations of Research Methods

Although all possible measures will be taken to ensure the quality and robustness of the data, there are several limitations inherent to the program design that should be acknowledged.

Spontaneous abortions most frequently occur in early pregnancy and may occur before the pregnancy is recognized. There is no reason to believe that this registry will be differentially impacted by this bias even though the spontaneous early losses may be underestimated, the relative rate compared with the other registries or data sources should not be affected.

This study plans to enroll both women with informative prenatal testing before enrollment which may provide knowledge of a study outcome prior to enrollment (i.e., retrospective outcomes), and women without prior informative prenatal testing who do not have knowledge of a specific pregnancy outcome (i.e., prospective outcomes. Patients who have been informed about a potential adverse pregnancy outcome prior to enrollment in the program may differentially recall their exposures during early pregnancy and may also have changed their exposures after learning of the outcome. Patients may also change their willingness to take part in the study after learning the outcome. These differences may lead to recall or selection bias, which we will attempt to address with the stratification analyses by retrospective and prospective case status. Additionally, the analyses will exclude women who have received first trimester prenatal screening in which either aneuploid disorders or genetic disorders that are known to cause major congenital malformations have been detected.

Finally, we will compare high level characteristics of enrollees with non-enrollees (in the US and EU separately), to assess any potential differences that may impact validity of external comparisons and generalizability of the results.

5.3 Data Reporting

5.3.1 Annual/Interim Analyses and Reporting

Interim reports are planned to occur every 6 months after the first patient is enrolled in the study through the end of the study period.

5.3.2 Final Analyses and Reporting

A final study report will be generated after all data collection is complete, including up to 1 year of infant follow-up for live births. The final report will encompass all planned analyses, including a description of the complete study population, as described above and in the SAP.

6. STUDY MANAGEMENT

This study will be performed by IQVIA with guidance, input, review and approval of Moderna including development of materials, recruitment, training and management of sites, EDC and data management and analysis.

6.1 Data Entry/Electronic Data Capture

All data will be collected and entered directly into the EDC system. All participating CCs will have access to the data entered regarding the individual site its own enrolled patients. All CCs will be fully trained on using the on-line data capture system, including eCRF completion guidelines and help files. CCs will be responsible for entering patient data into a secure internet-based EDC registry database via the eCRF; electronic questionnaire responses by participants using electronic patient-reported outcome software may also be used. Investigators and site personnel will be able to access their account with a username and password. All eCRFs should be completed by designated, trained personnel or the study coordinator, as appropriate. In most cases, the eCRF should be reviewed, electronically signed, and dated by the Principal investigator. All changes or corrections to eCRFs are documented in an audit trail and an adequate explanation is required.

6.2 Source Documents

Moderna or designee representatives may conduct remote source data verification (SDV) visits as defined in the Study Monitoring Plan at the study facilities for the purpose of monitoring various aspects of the study. Moderna or designee representatives may confirm that critical protocol data (i.e., source data) entered in the eCRF by authorized CC personnel into the EDC are accurate, complete, and verifiable from source documents (e.g., questionnaires).

Source documents (paper or electronic) are those in which patient data are recorded and documented for the first time.

Before study initiation, the types of source documents that contain study-relevant information will be clearly defined in the Study Monitoring Plan. The Study Monitoring Plan defines

which kind of source data – if available from clinical routine – can be used for documentation into an eCRF.

Source documents that are required to verify the validity and completeness of data entered in the eCRF must not be obliterated or destroyed and must be retained per the policy for retention of records described in Section 6.3.

To facilitate SDV, the CC Investigator must provide direct access to applicable source documents and reports for study-related monitoring, Moderna audits, and Institutional Review Board (IRB) review. The participating CC must also allow inspection by applicable health authorities.

6.3 File Retention and Archiving

To enable evaluations and/or audits from regulatory authorities or Moderna, the investigator agrees to keep records, including the identity of all participating patients, copies of all CRFs, SAE forms, source documents and adequate documentation of relevant correspondence (e.g., letters, meeting minutes, telephone calls reports). The records should be retained by the investigator according to local regulations, or as specified in the study contract, whichever is longer.

Each CC will receive a study site file at study initiation which contains all documents necessary for the conduct of the registry and is updated throughout the study. This file must be available for review in the event the site is selected for monitoring, audits, or inspections and must be safely archived for at least 5 years after the completing participation in the study. Documents to be archived include the patient enrollment log and the signed informed consent forms (ICF). In the event that archiving of the file is no longer possible at the site, the site will be instructed to notify Moderna.

6.4 Quality Assurance and Monitoring

A Study Monitoring Plan, including for-cause monitoring, that is appropriate for the study design will be developed and implemented.

During the site initiation visit, the monitor will provide training on the conduct of the study to the investigator, co-investigator(s), and all site staff involved in the study. In order to ensure the integrity of the data, sites will be monitored. Remote site monitoring will be performed by IQVIA CRAs to examine compliance with the protocol and adherence to the data collection procedures, to assess the accuracy and completeness of submitted clinical data, and to verify that records and documents are being properly maintained for the duration of the study. The monitor will perform SDV by review of original patient records.

The monitor will close out each site remotely after the last patient's final follow-up assessment is completed, all data have been entered and all outstanding monitoring issues have been resolved or addressed. All monitoring procedures and frequency of monitoring visits will be described in a monitoring plan. Monitor contact details for each participating site will be maintained in the Investigator Site File.

Representatives of Moderna's quality assurance unit/monitoring team and competent regulatory authorities must be permitted to inspect all study-related documents and other materials at the site, including the Investigator Site File, the completed eCRFs and the patients' original medical records. Audits may be conducted at any time during or after the study to ensure the validity and integrity of the study data.

6.5 Data Management

A data management plan will be created before data collection begins and will describe all functions, processes, and specifications for data collection, cleaning and validation. The eCRFs will include programmable edits to obtain immediate feedback if data are missing, out of range, illogical or potentially erroneous. Concurrent manual data review will be performed based on parameters dictated by the plan. Ad hoc queries will be generated within the EDC system and followed up for resolution.

High data quality standards will be maintained, and processes and procedures utilized to repeatedly ensure that the data are as clean and accurate as possible when presented for analysis. Data quality will be enhanced through a series of programmed data quality checks that automatically detect out of range or anomalous data.

6.6 Changes to the Protocol

Changes to the protocol will be documented in written protocol amendments. Major (i.e., substantial, significant) amendments will usually require submission to the relevant IRB/ IECs for approval or favorable opinion and to health authorities, as applicable. In such cases, the amendment will be implemented only after approval or favorable opinion has been obtained.

Minor (non-substantial) protocol amendments, including administrative changes, will be filed by at each participating site and will be submitted to the relevant IRB/IEC or regulatory authorities where required by pertinent regulations. Any amendment that could have an impact on the patient's agreement to participate in the study requires the patient's informed consent prior to continued participation in the study.

6.7 Publication Policy

Any publication of the results from this study must be consistent with Moderna's publication policy and guided by the Uniform Requirements for Manuscripts Submitted to Biomedical Journals: Writing and Editing for Biomedical Publication of the International Committee of Medical Journal Editors (ICMJE), updated April 2010. The rights of the investigator and of the Client with regard to publication of the results of this study/registry are described in the investigator contract.

7. SAFETY REPORTING

Only SAEs related to pregnancy and infant SAEs will be collected and reported throughout the study. The AE reporting period begins when the patient is enrolled in the study and

continues through the study's follow-up period. SAEs will be recorded on the appropriate forms (e.g., CRFs, eCRFs) as designated by Moderna and reported within the required time window.

7.1 Definitions

Adverse events (AEs)

An AE is any untoward medical occurrence in a patient or clinical study subject administered a pharmaceutical product and which does not necessarily have to have a causal relationship with the product. An AE can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding, for example), symptom, or disease temporally associated with the use of a product, whether or not considered related to the product.

Serious adverse events (SAEs)

An SAE is any experience that suggests a significant hazard, contraindication, side effect or precaution. An SAE must fulfill at least one of the following criteria at any dose level:

- *Results in death*
- *Is life-threatening as it occurred*
  Patient was at risk of death at the time of the event. This does not refer to an event which hypothetically might have caused death if it were more severe
- *Requires inpatient hospitalization or prolongation of existing hospitalization*
- *Results in persistent or significant disability/incapacity*
  Defined as a substantial disruption of a patient's ability to conduct normal life functions
- *Results in a congenital anomaly or birth defect*
- *Constitutes an important medical event*
  Based upon appropriate medical judgment, event may jeopardize the patient and may require medical or surgical intervention to prevent one of the outcomes listed above

Obstetric complications that fall into the above categories are defined as pregnancy-related SAEs in this study and should be reported to the CC.

A pregnancy outcome is as outlined in Section 4.4.2 and covers:

- Spontaneous abortion
- Fetal loss including stillbirth
- Ectopic pregnancy

- Molar pregnancy
- Congenital malformation
- Elective or therapeutic pregnancy terminations
- Premature birth

7.2 Methods and Timing for Capturing and Assessing Safety Parameters

The CC is accountable for ensuring that all SAEs collected as per protocol are recorded in the SAE section of the eCRF and reported to Moderna in accordance with instructions provided in this section and in Section 4.4.2.

7.2.1 Serious Adverse Event Reporting Period

The CC will seek information on pregnancy-related SAEs at each patient and HCP contact. All SAEs related to pregnancy, pregnancy outcomes, and infants, whether reported by the patient or by HCPs, will be recorded in the SAE section of the eCRF.

Once the patient is enrolled in the study, SAEs related to pregnancy will be collected until the end of their observation period, i.e. until a pregnancy outcome is reported, unless the patient withdraws from the study prematurely. SAEs and the selected non-serious AEs described above experienced by the infant will be reported until the first year of life.

7.2.2 Procedures for Recording Serious Adverse Events

HCPs should use correct medical terminology/concepts when reporting SAEs related to pregnancy and pregnancy outcomes to the CC. Colloquialisms and abbreviations should be avoided.

Only one SAE term should be recorded in the event field of the eCRF.

7.3 Reporting Requirements from Healthcare Professional to Marketing Authorization Holder

7.3.1 Immediate Reporting Requirements from Healthcare Professional to Marketing Authorization Holder

SAEs require immediate reporting to allow Moderna and the regulatory authorities to take appropriate measures to address potential new risks associated with the use of the medicine. The HCP must report such events to Moderna immediately; under no circumstances should reporting take place more than 24 hours after the HCP learns of the event.

If an HCP or a patient reports any non-pregnancy-related SAEs, these SAEs must be forwarded to Moderna to process as a spontaneous report. (Refer to local product label for relevant contact details).

In the event that the EDC system is temporarily unavailable, please refer to Section 7.3.3.

HCPs must also comply with local requirements for reporting SAEs to the local health authority and IRB/EC.

7.3.2 Reporting Requirements for Non-Serious Adverse Events

If an HCP or a patient reports any non-pregnancy-related AEs, these AEs must be forwarded to Moderna to process as a spontaneous report for COVID-19 vaccine events.

In the event that the EDC system is temporarily unavailable, please refer to Section 7.3.3.

7.3.3 If EDC System is Temporarily Unavailable

In the event that the EDC system is temporarily unavailable, a completed paper reporting form and fax coversheet should be faxed/scanned to Moderna Drug Safety or its designee immediately (i.e., no more than 24 hours after learning of the SAE), using the fax number or email address provided to physicians.

Once the system is available again, all information should additionally be entered and submitted via the EDC system.

7.3.4 Follow-Up of Patients After Serious Adverse Events

7.3.4.1 HCP Follow-Up

The HCP should follow each SAE until the event has resolved to baseline grade or better, the event is assessed as stable by the HCP, the patient is lost to follow-up, or the patient withdraws consent. Every effort should be made to follow all SAEs considered to be related to the Moderna COVID-19 until a final outcome can be reported.

During the study period, resolution of SAEs related to pregnancy (with dates) should be documented in the SAE section of the eCRF.

7.3.4.2 Moderna Follow-Up

For all SAEs related to pregnancy, Moderna or a designee may follow-up by telephone, fax, electronic mail, and/or a monitoring visit to obtain additional case details and outcome information (e.g., from hospital discharge summaries, consultant reports, autopsy reports) in order to perform an independent medical assessment of the reported case.

7.4 Safety Reporting Requirements for Non-Studied Products

Although adverse event information is not being actively solicited for non-studied products, the physician/consumers are reminded to report any adverse reactions (for which they suspect a causal role of a product) that come to their attention to Moderna of the suspected product, or to the concerned competent authorities via the national spontaneous reporting system.

In addition, the following should also be reported if occurring during exposure to a marketed product, even in the absence of AEs:

- Pregnancy
- Breastfeeding
- Abnormal laboratory findings
- Overdose, abuse, misuse, off-label use, medication error or occupational exposure
- Reports of lack of efficacy
- Product quality defects and falsified medicinal products
- Data related to a suspected transmission of an infectious agent via a medicinal product
- Drug interactions (including drug/drug, drug/food, drug/device and drug/alcohol)

When a patient is not exposed to a marketed medicinal product, but the HCP/consumer becomes aware of the potential for a medication error, or an intercepted medication error, this should also be reported.

8. ETHICAL AND REGULATORY CONSIDERATIONS

8.1 Guiding Principles

To ensure the quality and integrity of research, this study will be conducted under the guidelines good pharmacoepidemiology practices (GPPs) issued by the International Society for Pharmacoepidemiology (ISPE), the Declaration of Helsinki and its amendments, and any applicable national guidelines.

The study will be conducted in compliance with the U.S. FDA Title 21 CFR Part 50 – Protection of Human Patients and/or Part 56 – Institutional Review Boards; the International Conference on Harmonisation (ICH) GCP E6(R2) guidelines (15 December 2016) as they apply to non-interventional studies; the Declaration of Helsinki and its amendments; and the Health Insurance Portability and Accountability Act of 1996 (HIPAA).

8.2 Patient Confidentiality

In order to maintain patient confidentiality, each patient will be assigned a unique patient identifier upon study enrolment. This patient identifier will be used in place of patient name for the purpose of data analysis and reporting. Medical record number or other local reference identifiers are not collected as part of the database. All parties will ensure protection of patient personal data and will not include patient names on any study forms, reports, publications, or in any other disclosures, except where required by law. In accordance with local regulations in each of the registry countries, patients will be informed about data handling procedures and

asked for their consent. Data protection and privacy regulations will be observed in capturing, forwarding, processing, and storing patient data. Every effort will be made to protect participant confidentiality according to the Directive 95/46/EC on the protection of individuals, and in compliance with Safe Harbor privacy principles.

8.3 Independent Ethics Committee (IEC)/Institutional Review Board (IRB)

Consistent with local regulations and prior to enrollment of patients at a given site, the study protocol will be submitted together with its associated documents (e.g., ICF) to the responsible IRB/IEC for its review. Patient enrolment will not start at any site before the Client has obtained written confirmation of a favorable opinion/approval from the relevant central or local IRB/IEC. The IRB/IEC will be asked to provide documentation of the date of the meeting at which the favorable opinion/approval was given that clearly identifies the study, the protocol version, and the ICF version reviewed.

Before implementation of any substantial changes to the protocol, protocol amendments will also be submitted to the relevant IRB/IEC in a manner consistent with local regulations. Pertinent safety information will be submitted to the relevant IECs during the course of the study in accordance with local regulations and requirements. It is the responsibility of the investigator to have prospective approval of the study protocol, protocol amendments, and ICF, and other relevant documents, if applicable, from their local IRB/IEC and provide documentation of approval to IQVIA. All correspondence with the IRB/IEC should be retained in the investigator file.

Should the study be terminated early for any unanticipated reason, the investigator will be responsible for informing the IRB/IEC of the early termination.

9. REFERENCES

1. Allotey J, Stallings E, Bonet M, Yap M, Chatterjee S, Kew T, et al. Clinical manifestations, risk factors, and maternal and perinatal outcomes of coronavirus disease 2019 in pregnancy: living systematic review and meta-analysis. BMJ. 2020;370:m3320.
2. Adhikari EH, Moreno W, Zofkie AC, MacDonald L, McIntire DD, Collins RRJ, et al. Pregnancy Outcomes Among Women With and Without Severe Acute Respiratory Syndrome Coronavirus 2 Infection. JAMA Netw Open. 2020;3(11):e2029256.
3. Jackson LA, Anderson EJ, Rouphael NG, Roberts PC, Makhene M, Coler RN, et al. An mRNA Vaccine against SARS-CoV-2 - Preliminary Report. N Engl J Med. 2020;383(20):1920-31.
4. Guideline on the exposure to medicinal products during pregnancy: need for post-authorisation data2005.
5. Registries for evaluating patient outcomes: a users guide. http://www.effectivehealthcare.ahrq.gov/registries-guide-3.cfm: Agency for Healthcare Research and Quality; 2014.
6. Public Policy Committee ISoP. Guidelines for good pharmacoepidemiology practice (GPP). Pharmacoepidemiol Drug Saf. 2016;25(1):2-10.
7. Postapproval Pregnancy Safety Studies Guidance for Industry 2019.
8. Metropolitan Atlanta Congenital Defects Program (MACDP): Centers for Disease Control and Prevention; 2016 [Available from: https://www.cdc.gov/ncbddd/birthdefects/macdp.html.
9. Prevention CfDCa. Update on overall prevalence of major birth defects-- Atlanta, Georgia, 1978-2005. MMWR Morb Mortal Wkly Rep. 2008;57(1):1-5.
10. Duke W, Gilboa SM. Using an existing birth defects surveillance program to enhance surveillance data on stillbirths. J Registry Manag. 2014;41(1):13-8.
11. Groen H, Bouman K, Pierini A, Rankin J, Rissmann A, Haeusler M, et al. Stillbirth and neonatal mortality in pregnancies complicated by major congenital anomalies: Findings from a large European cohort. Prenat Diagn. 2017;37(11):1100-11.
12. Boatin AA, Eckert LO, Boulvain M, et al. Dysfunctional labor: Case definition & guidelines for data collection, analysis, and presentation of immunization safety data. Vaccine. 2017;35(48 Pt A):6538-6545. doi:10.1016/j.vaccine.2017.01.050
13. Gravett C, Eckert LO, Gravett MG, et al. Non-reassuring fetal status: Case definition & guidelines for data collection, analysis, and presentation of immunization safety data. Vaccine. 2016;34(49):6084-6092. doi:10.1016/j.vaccine.2016.03.043
14. Sell E, Munoz FM, Soe A, et al. Neonatal encephalopathy: Case definition & guidelines for data collection, analysis, and presentation of maternal immunisation safety data. Vaccine. 2017;35(48 Pt A):6501-6505. doi:10.1016/j.vaccine.2017.01.045

15. Sweet LR, Keech C, Klein NP, et al. Respiratory distress in the neonate: Case definition & guidelines for data collection, analysis, and presentation of maternal immunization safety data. Vaccine. 2017;35(48 Pt A):6506-6517. doi:10.1016/j.vaccine.2017.01.046

10. APPENDIX 1- DATA COLLECTION OVERVIEW

Data Collection [a]	Enrollment	Prenatal Follow-Up			Pregnancy Outcome	Pediatric Follow-Up	Early Termination of Study Participation
		End 1st Trimester (~14 weeks)	Mid 2nd Trimester (~25 weeks)	Mid 3rd Trimester (~34 weeks)	~4 weeks after EDD	Infant Age 12, 26, and 52 Weeks	End of Patient Participation in Study
Informed consent [b]	x						
Inclusion/exclusion criteria	x						
Patient demographics and characteristics	x						
Medical history	x						
Pregnancy history, and current pregnancy information [c]	x						
Lifestyle factors [d]	x	x	x	x	x	x	
COVID-19 information [e]	x	x	x	x	x	x	x
COVID-19 vaccine information [f]	x	x	x	x	x	x	x
Prior and concomitant medications [g,h]	x	x	x	x	x		
Comorbid conditions	x	x	x	x	x		
Current pregnancy status		x	x	x			x [i]
Gestational age (weeks)		x	x	x	x		x [i]
Pregnancy outcome [j]					x		x [i]
Infant characteristics					x [k]	x [l]	x [i]
Infant abnormalities [m]					x	x	x [i]
SAEs related to pregnancy, pregnancy outcome, or infant SAEs [n]	x	x	x	x	x	x	x [i]
Reason for early termination of study participation							x

EDD = expected date of delivery; LMP = last menstrual period; SAE = serious adverse event

[a] Available data will be collected; no additional diagnostic or monitoring procedures shall be applied to the patients outside of routine clinical practice.

[b] Written or verbal informed consent must be obtained before any data collection (per local regulations or ethics committee requirements).

[c] Including previous pregnancy outcomes, detailed family history including pregnancy complications, adverse pregnancy outcomes and developmental abnormalities, and information about baseline risks.

[d] Including smoking, use of caffeine, use of alcohol, and use of recreational drugs.

[e] Including testing dates (diagnostic and antibody), results, and severity.

[f] Including type of vaccine, manufacturer, and dates of administration starting 28 days prior to LMP.

[g] Prior and concomitant medications up to 28 days prior to LMP.

[h] Start and stop dates, dose, dosing frequency, reason for discontinuation (if applicable)

[i] If applicable

[j] Including live births, spontaneous abortions, stillbirths, elective or therapeutic terminations, reason for elective or therapeutic termination (e.g., prenatal testing finding, risk to mother's health, undesired pregnancy), and autopsy results and pathology reports, if available

[k] Gestational age, sex, weight, length, birth order (for multiple births), Apgar scores, breastfeeding status, and any congenital malformation noted, including description and attribution.

[l] Including postnatal growth and development: feeding behavior, weight, length, developmental milestones, breastfeeding status, evidence of any abnormality collected through 52 weeks.

[m] Detailed information on any infant abnormalities identified after infant birth.

[n] Reported throughout the study or until study discontinuation as applicable

11. APPENDIX 2- LIST OF TERATOGENIC MEDICATIONS

Medications were selected on the basis of published data on teratogenicity, approval in the US with a Risk Evaluation and Mitigation Strategy (REMS) including Elements to Assure Safe Use (ETASU) related to the prevention of pregnancy exposure, or designation by the US FDA as pregnancy category X prior to the 2015 Pregnancy and Lactation Labelling Rule. The list will be reviewed at the time of final analysis to ensure that it is comprehensive.

- ACE inhibitors
- Acitretin
- Aliskiren
- Ambrisetan
- Aminopterin
- Bosentan
- Carbamazepine
- Danazol
- Diethylsilbesterol
- Griseofulvin
- Isotretinoin
- Lamotrigine
- Leflunomide
- Lenaliomide
- Lithium
- Macitentan
- Methimazole
- Methotrexate
- Methylene blue
- Misoprostol
- Mycophenolate mofetil
- Paramethadione
- Penicillamine
- Phenobarbital
- Phenytoin, Fosphenytoin
- Pomalidomide
- Ribavirin
- Riociguat
- Thalidomide
- Topiramate
- Triazolam
- Trimethadione
- Valproate/valproic acid/divalproex
- Warfarin