
Study Synopsis

Full Study Title: Moderna COVID-19 Vaccine Pregnancy Registry			
Phase:	Post marketing	Type:	Observational
Number of Patients: 1200 total patients, 600 per exposure group		Duration of Patient Participation: up to 21 months (9 months of pregnancy and 12 months of infant follow-up)	
Number of Sites: one coordinating site per country in the US and EU		Duration of study: approximately 3 years	
Milestones: <u>Study start:</u> Authorization of the EUA <u>Interim reports:</u> every three months from the initiation of recruitment after FDA approval of the protocol through the end of the study period (December 2023). <u>Final report:</u> end of June 2024.			
Rationale: 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. Emerging information suggests that pregnant women with symptomatic COVID-19 were more likely to give birth prematurely (1). Although the Moderna COVID-19 vaccine (mRNA-1273) clinical trials have demonstrated a favorable risk-benefit profile, there are no adequate or well-controlled 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 compared with unvaccinated pregnancies.			

Objectives:

Primary objective:

- 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 with infants of women unvaccinated with any COVID-19 vaccine (internal comparator).

Secondary objectives:

- In women exposed to the Moderna COVID-19 vaccine during pregnancy,
 - To estimate the proportion of pregnancy complications
 - To estimate the proportion of spontaneous abortion, stillbirth, elective termination, and preterm birth
- In infants of women exposed to the Moderna COVID-19 vaccine during pregnancy,
 - To estimate the proportion of small-for-gestational age
 - To estimate the proportion of minor congenital malformations
 - To estimate the proportion of postnatal growth and development deficiency through the first year of life
- 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 (EUROCAT and MACDP external comparator)
- To compare the proportion of maternal, fetal, and infant outcomes of women exposed to the Moderna COVID-19 vaccine at any point from 28 days prior to LMP through pregnancy with women who have not been exposed to any COVID-19 vaccine from 28 days prior to LMP or during pregnancy (internal comparator)

Study design:

The design of this prospective pregnancy exposure registry is consistent with relevant guidelines and recommendations (2-5). This prospective observational 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 the US and several EU countries [final country list to be determined based on approval of the Moderna COVID-19 vaccine]. The nurse-staffed coordinating center (CC) is responsible for obtaining informed consent and all patient and 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.

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 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 local labeling.

The internal comparator cohort (unvaccinated) will consist of currently pregnant women who were not exposed to any COVID-19 vaccine in the 28 days prior to their LMP or at any time during pregnancy. Internal comparator cohort patients will be enrolled and follow the same study procedures for follow-up and data collection as the exposed cohort.

An external unvaccinated population (e.g., MACDP and EUROCAT) will also be used to contextualize study outcomes.

Major congenital malformations are the primary outcomes of interest for this study, and other pregnancy, maternal, fetal, and infant outcomes are classified as secondary. 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 Metropolitan Atlanta Congenital Defects Program (MACDP) classification system and evaluated by a committee of at least 3 qualified, independent teratologists using all available medical records.

The outcomes will be presented in comparison with both existing databases and the internal comparator cohort. The primary 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 internal unvaccinated cohort.

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 labeling 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). In particular, for eligible patients under 18 years old, consent must be obtained from the patient's legally authorized representative.
- 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
- *Exposed group only:* received the Moderna COVID-19 vaccine at any point from 28 days prior to LMP through pregnancy

Exclusion criteria

- Receipt of any other COVID-19 vaccines at any point from 28 days prior to LMP through pregnancy
- Current participation in another investigational device or drug study, currently taking an investigational medicinal product, or having taken an investigational product within 12 weeks prior to MP 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 is 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.

Within the coordinating study site model, the IQVIA Registry CC will review ICF with the patient over the phone (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, they will provide “verbal consent,” (if allowed by local regulations) which will be indicated in the EDC. The CC will use the IQVIA eConsent platform to deliver medical records release (and assent for the child) and require an eSignature.

IQVIA will operate as the study site under the direction of (b) (6), who will serve as the study’s PI. The virtual study site will comprise the PI and a remote study team of nurses from our Registry CC who serve as patient guides. 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. A call center environment enables us to quickly add more resources should the need arise, while keeping the number small facilitates a relationship with patients and HCPs

Patients’ data obtained via questionnaires administered to patients or their HCPs will be recorded on electronic case report forms (eCRFs) by the CC.

Suspected major and minor congenital malformations will be evaluated by at least 2 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 brought in 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 coordinating center (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 12 weeks 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, 21, 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 coordinating center (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)
- 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

Sample Size

To adequately power an internal 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 85%, 600 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 2.5 or greater in major congenital malformations relative to an assumed prevalence of 3% in the internal comparator cohort (6) at a significance level of $\alpha=0.05$.

This sample size will also offer >80% power to detect risk ratios of as low as 2.0 when compared with an external comparator.

Statistical Analysis

The primary outcome for this study is the comparison between 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 unvaccinated internal comparator. All other outcomes will be classified as secondary.

Variables identified for the subgroup analysis will be evaluated as potential confounders in the primary comparative analysis of the risk ratio for major congenital malformations in the Moderna COVID-19 vaccine exposed and unvaccinated internal comparator.

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 primary analysis. Women who have received any first trimester prenatal testing after enrollment, with either negative or positive test result will be included in the primary 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

In addition to the comparison to an unvaccinated internal comparator cohort, results will be descriptively compared to existing data sources or published reports representing the general population prevalence of birth defects in the general population.

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 Moderna COVID-19 vaccine-exposed and internal comparator cohorts 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 at baseline, and other important risk factors.

The prevalence of major and minor congenital malformations will be calculated using MACDP convention. Major malformations will be analyzed separately from minor malformations, with the primary 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 primary and secondary outcome measures will be presented with 95% CIs for binomial proportion. The analyses summarized in this section will be performed on the Moderna COVID-19 vaccine exposed cohort and the internal comparator cohort consisting of pregnant women who were not exposed to any COVID-19 vaccine; Characteristics can be matched or stratified in relation to the exposed cohort to control for important covariates such as maternal age.

Comparative Analysis

Internal Comparator Analysis

Primary and secondary outcome proportions in the Moderna COVID-19 vaccine exposed cohort will be compared with the internal comparator cohort using the risk ratio (95% CIs). Also, comparisons may be explored using ORs adjusted to relevant covariates as applicable, if a sufficient number of outcomes are available in the subgroups. The covariates of interest may include the maternal age, prior history of elective or therapeutic pregnancy termination status, and baseline alcohol status.

Additionally, to assess the impact of exposure on the primary outcomes the propensity score matching may be explored. Baseline characteristics such as age and parameters of obstetric history will be explored to match between the Moderna COVID-19 vaccine exposed and internal comparator cohorts.

If a woman in the internal comparator group chooses to receive a COVID-19 vaccine (Moderna or other manufacturer) during pregnancy they will be excluded from the primary 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 and the European population. The MACDP will be the main external comparator cohort (7). EUROCAT classification of congenital malformations will be implemented to ensure comparability with any European data sources available for descriptive comparison with this registry.

The difference in prevalence of major congenital malformations in Moderna COVID-19 vaccine exposed cohort and the external comparator cohort will be compared similarly as to the internal comparator, with the estimate of risk ratio (95% CIs). Categorical distributions available in the MACDP report will be summarized using the same categories among exposed pregnancies (6). 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 (ie, 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.

Sensitivity Analysis

Sensitivity analyses will be performed on both the Moderna COVID-19 vaccine exposed and internal comparator cohorts 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 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 occurring before 22 weeks gestation will also be examined in a sensitivity analysis to account for global variation in the definition for this outcome.
- A sensitivity analysis will be performed to examine the impact of time-varying exposure on primary and secondary outcomes. A time-varying exposure cox regression model will adjust for fixed covariates such as maternal age, presence of comorbidities, previous history of obstetric complications, and gestational age at exposure as time-varying covariate. Details will be provided in the SAP.
- 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 primary analysis.

Both the Moderna COVID-19 vaccine exposed and internal comparator cohorts will be summarized for primary and secondary 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

Patient Enrollment, Engagement, 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.

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.

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, contact center 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 call center to follow up. Once the patient is contacted, the representative 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.

Awareness Campaign

To support referrals, HCPs on the 'top prescriber list' generated using the Moderna COVID-19 vaccine-specific 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 our 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.

Potential Considerations and Mitigations	
Scientific Bias	Sources and Mitigation Strategies
Selection Bias	<ul style="list-style-type: none"> Survivor bias - women typically enroll after recognition of pregnancy; thus, the study will include a select group of pregnancies that survive to that point of gestation Guidelines recommend enrollment of women as early as possible during pregnancy, ideally prior to informative prenatal testing Loss to follow-up due to missing pregnancy outcomes (unknown outcome status) and shortened follow-up due to preterm delivery to be mitigated by low burden for participants and active follow-up Decreasing availability of internal comparator patients as the vaccine becomes more available and developing systematic differences between vaccine recipients and vaccine decliners—to be mitigated by contextualizing using an external comparator of pregnant women in the general population
Information Bias	<ul style="list-style-type: none"> Maximize accuracy of recall of exposure by pregnant women by using structured questionnaires, detailed questions, and calendars to help establish gestational timing and recall of dates Cross-validate self-reported maternal exposure and medical history with reports from HCPs, when possible Avoid diagnostic bias (outcome misclassification) by using blinded validation and adjudication of outcomes by a team of independent teratologists.
Confounding	<ul style="list-style-type: none"> Concerns with confounding factors (socioeconomic status, maternal age, tobacco and alcohol use, illicit drug use, maternal body mass index [BMI], vitamin use, over the counter [OTC] medicine use, etc.),
Operational Challenge	Preventive Action
Enrollment	<ul style="list-style-type: none"> Targeted awareness and education plan with strong messaging to ensure all stakeholders potential patients and HCPs are aware and understand how and why to participate in the registry Leverage existing systems, to the extent possible, to identify potential patients (i.e., Vaccine information sheets, Moderna Therapeutics pharmacovigilance, patient support networks, medical science liaison [MSL]/KOL relationships) Responsive process for optimizing enrollment to include pharmacies and other vaccine delivery modalities Implement streamlined informed consent process
Patient Retention and Follow-up	<ul style="list-style-type: none"> Promote retention through relationship building with the patient (rapport established by the registry staff at the call center)
Stakeholder Burden	<ul style="list-style-type: none"> Minimize burden through streamlined CRFs Website includes background information and decreases burden through ease of use
Timely and Complete Data Collection	<ul style="list-style-type: none"> Implementing verbal informed consent and electronic medical release forms to reduce burden on patients and increase the likelihood of timely and thorough data collection Use a nurse-staffed call center trained to maximize results Engage in regular contact between the site and IQVIA site manager for data required from the treating physicians

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