

Title	Menveo® pregnancy registry: an observational study on the safety of Menveo exposure in pregnant women and their offspring
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BB-BLA No	Not applicable.
Active substance	Oligosaccharides derived from capsular polysaccharides of <i>Neisseria meningitidis</i> serogroups A, C, W and Y, each conjugated to the CRM ₁₉₇ carrier protein.
Medicinal product	Meningococcal quadrivalent CRM-197 conjugate vaccine (Menveo®)
Product reference	Not applicable.
Procedure number	Not applicable.
Marketing authorisation holder(s)	Novartis Vaccines and Diagnostics
Joint PASS study	No
Research question and objectives	The objective of the Menveo Pregnancy Registry is to evaluate pregnancy outcomes among women immunized with the Menveo vaccine within 28 days prior to conception or at any time during pregnancy. The primary outcomes of interest include major congenital malformation, preterm birth, and low birth weight.

Country(ies) of study	United States
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2.0 LIST OF ABBREVIATIONS

ACIP	Advisory Committee on Immunization Practices
AEs	Adverse Events
BRFSS	Behavioral Risk Factor Surveillance System
CBER	Center for Biologics Evaluation, Research and Review
CEDD	Corrected estimated date of delivery
CDC	Centers for Disease Control and Prevention
CFR	Code of Federal Regulations
CRF	Case report form
DSUR	Development Safety Update Report
EDC	Electronic data capture
EDD	Estimated date of delivery
ELISA	Enzyme-linked immunosorbent assay
FDA	Food and Drug Administration
GLP	Good Laboratory Practice
GPP	Good Pharmacoepidemiological Practice
HCP	Health care provider
HIPAA	Health Insurance Portability and Accountability Act
HMO	Health maintenance organization
IAB	Induced abortion
ICSR	Individual Case Safety Reports
IM	Intramuscular
IRB	Institutional review board
LMP	Last menstrual period
LBW	Low birth weight
MACDP	Metropolitan Atlanta Congenital Defects Program
MCM	Major congenital malformation
MSL	Medical science liaison
NVD	Novartis Vaccines and Diagnostics
NVSS	National Vital Statistics System
PMC	Post marketing commitment
PRAMS	Pregnancy Risk Assessment Monitoring System
PSUR	Periodic Safety Update Report
RCC	Registry Coordination Center
SAB	Spontaneous abortion
SAC	Scientific Advisory Committee
SAEs	Serious Adverse Events
SAP	Statistical analysis plan
SOP	Standard operating procedure
STROBE	STrengthening the Reporting of OBservational studies in Epidemiology
US	United States

3.0 RESPONSIBLE PARTIES

3.1 Main Author(s) of the Protocol

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3.2 Principal Investigator

PPD [REDACTED] MD, PPD

3.3 Coordinating Investigator(s)

Not applicable.

3.4 CRO or Other Service Provider

PPD
PPD [REDACTED]

3.5 Advisory Committee

The Scientific Advisory Committee (SAC) will provide an independent review of registry data and will include specialists from appropriate fields such as obstetrics, pediatrics, clinical research, genetics, epidemiology, and teratology from academic institutions, private practice, and/or government agencies.

4.0 ABSTRACT

Name of Sponsor	Protocol number:	Health authority study registration number(s):	Date of Protocol Abstract:
Novartis Vaccines and Diagnostics	V59_72OB	N/A	16 AUG 13
Title of Study: Menveo® pregnancy registry: an observational study on the safety of Menveo exposure in pregnant women and their offspring			
Study Period: The pregnancy registry will be implemented after approval by applicable regulatory authority and central institutional review board (IRB) with the goal of enrolling 100 exposed pregnancies over a 3-year period. The data collection process for each participant will begin at enrollment (during pregnancy), and follow-up will occur at the end of the second trimester (approximately 24 weeks' gestation) and at pregnancy outcome (delivery or early termination).		Study Type: This study is established to meet a post marketing commitment (PMC) agreed upon with CBER to establish a pregnancy registry to prospectively collect data on pregnancy exposures to Menveo.	
Rationale and Background: The Menveo® Pregnancy Registry is established to meet a CBER PMC and is designed to collect prospective data on pregnancy outcomes among pregnant women vaccinated with Menveo within 28 days prior to conception or at any time during pregnancy. The 28-day window prior to conception corresponds with the time to immunologic response as indicated in the Menveo product label (Menveo package insert, 2012). The Advisory Committee on Immunization Practices (ACIP) recommends routine administration of a MenACWY vaccine for all persons aged 11 through 18 years. Thus, the registry population will primarily consist of adolescents. Menveo is not indicated in pregnancy. However, inadvertent pregnancy exposures are anticipated because the targeted age group for the vaccine includes young women of reproductive potential. The registry will add to the current clinical experience with Menveo by supplementing data from animal toxicology studies and human exposure data. Pregnancy data will be collected at registry enrollment, at the end of the second trimester of pregnancy, and at pregnancy outcome for both mother and infant. Novartis Vaccines and Diagnostics (NVD) sponsors the registry in consultation with specialists from appropriate fields such as obstetrics, pediatrics, clinical research, genetics, epidemiology, and teratology from academic institutions, private practice, and/or government agencies. These individuals constitute the Scientific Advisory Committee			

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<p>(SAC) and will provide an independent review of registry data.</p>			
<p>Research Question and Objectives: The objective of the Menveo Pregnancy Registry is to evaluate pregnancy outcomes among women immunized with the Menveo vaccine within 28 days prior to conception or at any time during pregnancy. The primary outcomes of interest include major congenital malformation (MCM), preterm birth, and low birth weight (LBW). Other pregnancy outcomes will be collected, including spontaneous abortions (SABs) and stillbirths.</p>			
<p>This registry is primarily descriptive and designed to detect potential safety signals rather than test hypotheses.</p>			
<p>Study Design: The Menveo Pregnancy Registry is a prospective, observational study of women inadvertently immunized with the Menveo vaccine within 28 days prior to conception or at any time during pregnancy as part of routine care. It is strictly observational; the schedule of office visits and all treatment regimens will be determined by the treating health care provider (HCP). This phase 4 pregnancy registry follows current Food and Drug Administration (FDA) guidance for designing and implementing pregnancy exposure registries (FDA, 2002).</p>			
<p>Population: The study population will include pregnant women within the United States (US) who were immunized with the Menveo vaccine within 28 days prior to conception or at any time during pregnancy. Because the vaccine is not indicated in pregnancy, the majority of exposures will be inadvertently administered in the first trimester of pregnancy. Enrollment and data collection will be coordinated through a registry coordination center (RCC). The registry will allow eligible pregnant women to self-enroll and also allow HCPs and/or health maintenance organizations (HMOs) to report de-identified data on pregnancy exposures and outcomes. An evaluable subject is a pregnant woman with data submitted or confirmed by an HCP that contains at least the minimum criteria for a report and is not lost to follow-up. The minimum criteria required for enrollment into the registry are as follows:</p> <ul style="list-style-type: none">▫ Sufficient evidence to confirm that Menveo exposure occurred within 28 days prior to conception or at any time during pregnancy▫ Sufficient information to determine whether the pregnancy is prospectively or retrospectively registered (ie, whether the outcome of pregnancy was known at the time of first contact with the registry)			

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<ul style="list-style-type: none">▫ Date the pregnancy exposure is registered▫ Full reporter (ie, HCP) contact information to allow for follow-up (name, address, etc.)			
<p>Because registry enrollment is open to all eligible pregnant women, an active recruitment campaign will reach out to immunization providers and their patients in a broad variety of settings. The recruitment strategy will target HCPs who are known to immunize patients specifically with the Menveo vaccine. These providers will be identified through NVD Menveo distribution data and medical science liaisons (MSLs), as well as HCP provider networks and HMOs.</p>			
<p>The primary population for analysis will include prospectively enrolled pregnant women exposed to Menveo who are not lost to follow-up (ie, with outcome information that meet the minimum criteria for evaluation). Retrospective reports will also include exposed pregnant women for which the pregnancy outcome is known (ie, an abnormality has been identified on a diagnostic prenatal test prior to enrollment). Retrospective reports can be biased toward the reporting of more unusual and severe cases and are less likely to be representative of the general population experience than cases reported prior to knowledge of outcome. Therefore, retrospective reports will not be included in the primary analysis and statistical calculation of risk. Retrospective reports with reported MCMs will be captured in the registry and reviewed to aid in detection of early signals and will be listed in registry reports.</p>			
<p>Data from HCP provider networks and HMOs that provide de-identified data on all exposed pregnancies in their networks will fall into the category of prospective registry reports, as these networks/HMOs provide objective data on every pregnancy exposure in the network/HMO, both positive and negative outcomes. Thus, they avoid the reporting bias inherent in retrospective reporting only after a negative outcome has been noted.</p>			
<p>Background rates from external surveillance sources and rates from published literature will be the primary comparators. Background rates in the general population on pregnancy outcomes, such as preterm birth and LBW, are readily available from national vital statistics (Martin, 2012). Published rates of MCMs are available from the Centers for Disease Control and Prevention (CDC)'s Metropolitan Atlanta Congenital Defects Program (MACDP), which is an ongoing population-based birth defects surveillance program (Correa, 2007). To the extent possible, comparator rates will be</p>			

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age-adjusted to reflect the age distribution of the Menveo Pregnancy Registry population.			
Variables:			
Exposure(s) of interest			
<p>This pregnancy registry is strictly observational. Menveo vaccination is not indicated in pregnancy. Therefore, Menveo vaccination exposure in pregnancy is expected to be inadvertent and to occur in early pregnancy. When a pregnant woman self-enrolls in the registry, she will be asked when and where she was immunized with the Menveo vaccine. She will then be asked to provide a medical release that allows the registry to confirm Menveo vaccination with the appropriate source. The registry will contact the Menveo vaccination provider to confirm the vaccination date, brand, and lot number. If HCPs provide de-identified data to the registry, they must be able to verify the Menveo vaccination and date of vaccination.</p>			
Outcome(s) of Interest			
<p>MCM: The registry defines an MCM as any major structural or chromosomal defect or combination of 2 or more conditional defects in live-born infants, stillbirths, or fetal losses of any gestational age (including outcomes prior to 20 weeks' gestation or weighing <500 g). This definition is consistent with, but not restricted to, the CDC MACDP definition.</p>			
<p>Preterm birth: An infant born at gestational age <37 weeks.</p>			
<p>LBW: An infant whose birth weight is <2500 g.</p>			
<p>Outcome variables will be provided by the obstetric HCP and/or pediatrician attending the birth. The HCP will be asked to describe any congenital malformations observed in the infant or fetus and will also be asked to report the gestational age and birth weight. These 2 variables will be used to calculate preterm birth (gestational age <37 weeks at birth) and LBW (birth weight <2500 g).</p>			
<p>A teratologist/geneticist will review all reported congenital anomalies and classify them using the CDC's MACDP system. Additionally, the teratologist/geneticist will provide an opinion regarding the possible temporal association of the Menveo exposure to the</p>			

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development of observed defects. The SAC will meet periodically to review the data and reach consensus on the coding and classification of MCMs and other outcomes of interest.			
<u>Other Variables</u>			
Maternal characteristics: Age, ethnicity, race			
Prenatal data: Last menstrual period (LMP), estimated date of delivery (EDD), corrected estimated date of delivery (CEDD)			
Obstetrical history: Previous pregnancies, live births, stillbirths, SABs, induced abortions (IABs), births with congenital malformations, family history of congenital malformations			
Concomitant medical conditions			
Concomitant medications and vaccines			
Alcohol, tobacco, and illicit drug use			
Pregnancy outcomes			
Each pregnancy outcome will be classified in 1 of the following mutually exclusive categories:			
<ul style="list-style-type: none">▫ Live birth: an infant born alive▫ Stillbirth: a fetal death occurring at 20 weeks' gestation or greater, or if gestational age is unknown, a fetus weighing 500 g or more▫ SAB: fetal death or expulsion of products of conception prior to 20 weeks' gestation. Terminology may include missed abortion, incomplete abortion, and inevitable abortion.▫ IAB: voluntary interruption of pregnancy, including pregnancy termination that occurs electively, to preserve maternal health, or due to fetal abnormalities▫ Ectopic pregnancy: implantation of a conception outside of the uterus▫ Molar pregnancy: a conception that results in a gestational trophoblastic tumor			

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<p>Data Sources: The pregnant woman and/or appropriate members of her health care team will serve as data reporters to the registry. The registry is strictly observational; the schedule of office visits and all treatment regimens will be determined by the treating HCP. There are no additional laboratory tests or assessments required as part of this registry. Only data noted as part of routine care will be collected.</p>			
<p>Study Size: The registry seeks to enroll 100 exposed pregnancies. Approximately 58% of these pregnancies can be expected to result in a live birth (Ventura, 2012). Given the patient population will primarily be adolescents, a high percentage of these pregnancies can be expected to be unintended, unwanted, and likely to result in IAB. It is expected that the vast majority (99%) of prenatal exposures will occur during the first trimester (before pregnancy status is known).</p> <p>According to the CDC MACDP, the prevalence rate of MCMs for mothers <25 years of age in the US is 2.54% (Correa, 2007). With a sample size of 58 first-trimester exposed pregnancies resulting in a live birth, the study will have 80% power to detect a 4.46-fold increase in the prevalence rate of MCMs as compared with the CDC MACDP rate. According to the CDC National Vital Statistics System (NVSS), the prevalence rates of preterm birth and LBW for mothers <25 years of age are 12.37% and 8.70%, respectively (Martin, 2012). With a sample size of approximately 58 exposed live births, the study will provide 80% power to detect a statistically significant 1.99-fold increase in the prevalence rate of preterm birth and 2.40-fold increase in the prevalence rate of LBW, as compared with the CDC NVSS rates.</p>			
<p>Data Analysis: This registry is primarily descriptive and designed to detect potential safety signals, rather than test hypotheses.</p> <p>Demographic and baseline characteristics will be summarized with simple descriptive statistics and data listings for the evaluable populations of pregnant women and live births. Demographic and baseline characteristics will also be summarized for the population that is lost to follow-up and compared with the evaluable populations to assess potential differences. These data will be reviewed for potential confounding factors that could affect the interpretation of comparisons of registry outcome rates with that of comparators.</p> <p>Overall and stratum-specific point estimates and 1-sided 95% confidence intervals will be calculated using the exact binomial distribution for prevalence rates of MCMs,</p>			

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preterm birth, and LBW among pregnant women exposed to Menveo and their live births.			
<p>For MCM, the overall prevalence of MCM will be reported. Since most structural defects have their origins in the first trimester of pregnancy during the period of organogenesis, analyses of MCM will be stratified by trimester of exposure if applicable. It is expected that the vast majority (99%) of prenatal exposures will occur during the first trimester before the pregnancy is recognized. The prevalence rate of combined MCMs reported to the registry will be calculated as a proportion, with the number of MCMs as the numerator and the number of live births as the denominator. Pregnancy losses with reported MCMs occurring at or after 20 weeks' gestation will be included in the numerator of the estimate of risk for MCMs to increase sensitivity and to allow comparison with the CDC MACDP following the outcome, which calculates rates by this convention. A secondary analysis will be conducted including pregnancy losses with reported MCMs occurring at less than 20 weeks' gestation in the calculation of risk. The prevalence rate of combined MCMs in exposed subjects will be compared with that of the CDC MACDP (Correa, 2007). The prevalence rates of preterm births and LBW will be calculated as proportions, with the number of live births as the denominator. These prevalence rates in exposed subjects will be compared with those of the CDC NVSS (Martin, 2012).</p>			
<p>Informed Consent and Ethical Approval: As a post marketing safety reporting activity, this registry qualifies for exemption of US Health Insurance Portability and Accountability Act (HIPAA) authorization. It also qualifies for a waiver of documentation of informed consent (verbal consent) for adult women who self-enroll, and it qualifies for a waiver of informed consent for de-identified data reported to the registry. If a minor requests participation in the registry and all eligibility criteria are met, the registry will obtain assent from the minor and signed written consent from the parent or guardian. The protocol and informed consent waivers will be submitted to an IRB for approval prior to registry implementation.</p>			
<p>Milestones:</p> <p>Start of data collection: The registry will be implemented after approval by applicable regulatory authority and central IRB. Data collection will commence after a start-up period of approximately 4 months.</p>			

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<p>End of data collection: The registry seeks to enroll 100 participants, and enrollment is expected to take approximately 3 years. After all available follow-up data are collected on participants, the data will be cleaned. This follow-up and cleaning process may take approximately 10 months.</p> <p>Annual updates will be provided in the Annual CBER PMC updates and in the Periodic Safety Update Reports (PSURs) and Development Safety Update Reports (DSUR).</p> <p>Final report of study results: A final report will be produced approximately 6 months after all data have been collected and cleaned.</p>			

5.0 AMENDMENTS AND UPDATES

Number	Date	Section of the study protocol	Amendment or update	Reason
1	4 AUG 14	Title page, 2.0, synopsis, 9.5, 10.2, 11.0, 12.2, 13.0	Amendment	Main reasons: FDA's suggestion and align safety data collection and reporting activities with Novartis SOP and GVP module VI.

6.0 MILESTONES

Milestone	Planned date
Start of data collection	The registry will be implemented after approval by applicable regulatory authority and central IRB. Data collection will commence after a start-up period of approximately 4 months.
End of data collection	The registry seeks to enroll 100 participants, and enrollment is expected to take approximately 3 years. After all available follow-up data are collected on participants, the data will be cleaned. This follow-up and cleaning process may take approximately 10 months.
Annual updates	Annual updates will be provided in the Annual CBER PMC updates and in the PSURs and DSUR.
Final report of study results	A final report will be produced approximately 6 months after all data have been collected and cleaned.

7.0 RATIONALE AND BACKGROUND

Invasive meningococcal disease is a severe infection caused by the bacteria *Neisseria meningitidis*, and usually results in bacteremia and/or meningitis. The signs of meningococcal meningitis in adults include headache, stiff neck, fever, chills, malaise, and prostration. Asymptomatic colonization of the upper respiratory tract by encapsulated *N meningitidis* is common, yet only a small percentage of colonized persons develop disease.

The 5 major meningococcal serogroups associated with disease are A, B, C, Y, and W-135. Serogroup prevalence varies with geography, time of year, and age group. Currently, serogroup B and C strains are most prevalent in Europe, and serogroup B, C and Y strains are most prevalent in North America (ECDC, 2011; Stephens, 2007). *N meningitidis* serogroup A strains are responsible for large epidemics of bacteremia and meningitis in sub-Saharan Africa (Rosenstein, 2001). Outbreaks due to serogroup W have also recently been reported in the same geographic location and among Hajj pilgrims (Taha, 2002).

The case-fatality rate for meningococcal disease generally ranges from 9% to 12% but can be as high as 40% among patients with meningococcemia (Rosenstein, 2001). The overall incidence of meningococcal disease in the United States (US) during recent decades has been approximately 0.9 to 1.5 cases per 100,000 population, but attack rates in outbreaks in sub-Saharan Africa, mainly due to meningococcal serogroup A, have been more dramatic (approximately 500 to 1000 cases per 100,000) (Rosenstein, 2001). Risk factors for disease include overcrowded housing conditions, active and passive smoking, complement deficiency, and functional or anatomic asplenia (Goldschneider, 1969).

Novartis Vaccines and Diagnostics (NVD) has developed a quadrivalent conjugate vaccine (Menveo®) aimed at preventing disease in infants and older age groups due to *N meningitidis* serogroups A, C, W, and Y. The Advisory Committee on Immunization Practices (ACIP) recommends routine administration of a MenACWY vaccine for all persons aged 11 through 18 years. A single dose of vaccine should be administered at age 11 or 12 years, and a booster dose should be administered at age 16 years. As of May 2013, MenACWY is approved for adolescents and adults in more than 60 countries. More than 10 million persons worldwide have received doses of MenACWY that were distributed commercially.

The immunogenicity assessments of MenACWY were conducted in rabbits (single- and repeat-dose toxicity and reproductive and developmental toxicity studies). A pilot reproductive and developmental toxicity study (embryofetal development) was conducted to assess the maternal toxicity and teratogenic potential of 5 doses of AlPO4 adjuvanted and non-adjuvanted MenACWY. A definitive reproductive and developmental toxicity study, including postnatal evaluation, was also performed with non-adjuvanted MenACWY to evaluate any effect of 5 MenACWY doses on maternal toxicity, female

reproduction, embryofetal toxicity, and offspring development. The results of these studies are summarized below.

In the Good Laboratory Practice (GLP) range-finding (pilot) reproductive and developmental toxicity study, 40 female rabbits received a total of 5 intramuscular (IM) MenACWY doses, with or without alum. Three 25 µg/0.5 mL doses were injected prior to mating and two 25 or 50 µg/0.5 mL doses were injected during gestation. The vaccine was not maternally toxic or teratogenic, and no embryofetal alterations related to treatment with the test article or to the elicited antibodies were identified. Circulating antibodies were detected in maternal animals throughout the study and in fetuses at the end of gestation.

In the definitive reproductive and developmental toxicity study, 128 female rabbits received a total of 5 IM MenACWY doses; three 25 µg/0.5 mL doses were injected prior to mating and two 25 µg/0.5 mL doses during gestation. Two groups of animals underwent cesarean section, and embryos were subjected to external and visceral examination, while remaining rabbits delivered naturally and were observed for 4 weeks for effects on F1 offspring. The phases covered in this definitive study include effects on cohabitation through mating, tubal transport, implantation, gestation, early organogenesis and embryofetal development, parturition, lactation, maternal behavior, and development of offspring. The vaccine was not maternally toxic or teratogenic and had no effects on postnatal development at the clinical dose administered 5 times during the course of the study. Antibody titers (by enzyme-linked immunosorbent assay [ELISA]) and serum bactericidal activity (SBA) were maximal in the maternal animals after 2 and 3 doses. Antibodies (ELISA and SBA) were also detected in fetuses at the end of gestation and in kits 4 weeks after birth.

NVD did not study vaccination in pregnancy as one of the objectives of clinical studies before licensure. Pregnant women were excluded from enrollment, and the use of birth control, where appropriate, was an entry criterion. Despite this requirement, 43 women in studies V59P13, V59P17, and V59P18 were found to be pregnant during the 6-month follow-up period. Of these women, 37 were administered MenACWY. All 7 spontaneous abortions occurred among women vaccinated with MenACWY.

In addition to reports in clinical trials, NVD received reports of 10 additional instances of MenACWY exposure during pregnancy via passive post marketing safety surveillance. One pregnancy ended in spontaneous abortion (SAB) 52 days after vaccination with both MenACWY and a rabies vaccine. Two pregnancies ended in normal deliveries of healthy infants, and the outcomes of the remaining 7 pregnancies are unknown.

The Menveo Pregnancy Registry is established to meet a CBER post marketing commitment (PMC) and is designed to collect prospective data on pregnancy outcomes among women immunized with the Menveo vaccine within 28 days prior to conception or

at any time during pregnancy. The 28-day window prior to conception was established based on data from the Menveo product label (Menveo package insert, 2012). Effectiveness of the Menveo vaccine in subjects 11 through 55 years of age was evaluated in a randomized, controlled clinical study comparing the hSBA responses following 1 dose of Menveo, showing that 68%-75% subjects have seroresponse 28 days after vaccination with Menveo.

Menveo is not indicated in pregnancy. However, inadvertent pregnancy exposures are anticipated because the targeted age group for the vaccine includes young women of reproductive potential. The registry will add to the current clinical experience with Menveo by supplementing data from animal toxicology studies and human exposure data. Pregnancy data will be collected at registry enrollment, at the end of the second trimester of pregnancy, and at pregnancy outcome for both mother and infant. NVD sponsors the registry in consultation with specialists from appropriate fields such as obstetrics, pediatrics, clinical research, genetics, epidemiology, and teratology from academic institutions, private practice, and/or government agencies. These individuals constitute the Scientific Advisory Committee (SAC) and will provide an independent review of registry data.

8.0 RESEARCH QUESTION AND OBJECTIVES

The objective of the Menveo Pregnancy Registry is to evaluate pregnancy outcomes among women immunized with the Menveo vaccine within 28 days prior to conception or at any time during pregnancy. The primary outcomes of interest include major congenital malformations (MCM), preterm birth, and low birth weight (LBW).

Other pregnancy outcomes will be collected, including stillbirths and SABs. The probability of SAB varies greatly as a function of when the pregnancy is enrolled in the registry ([Savitz, 2002](#)). Because pregnancies will be reported to the registry at different and imprecise times during gestation, calculation of the prevalence rate of SAB from the registry is deemed inappropriate and could lead to erroneous conclusions. For example, if a woman enrolls in the registry at 16 weeks of pregnancy, only an SAB after this time could be detected and included in prospective reports. Similarly, SABs occurring earlier in gestation may not have been recognized and/or reported.

This registry is primarily descriptive and designed to detect potential safety signals rather than test hypotheses.

9.0 RESEARCH METHODS

9.1 Study Design

The Menveo Pregnancy Registry is a prospective, observational study of pregnant women immunized with the Menveo vaccine within 28 days prior to conception or at any time during pregnancy. It is strictly observational; the schedule of office visits and all treatment regimens will be determined by the treating health care provider (HCP). The registry will collect data that are routinely documented in the patient's medical record in the course of usual care.

The design of this pregnancy registry follows current Food and Drug Administration (FDA) guidance for designing and implementing pregnancy exposure registries ([FDA, 2002](#)).

9.2 Setting

9.2.1 Study Period

The pregnancy registry will be implemented after approval by applicable regulatory authority and central institutional review board (IRB). The target enrollment goal of the registry is 100 prospectively enrolled pregnant women. The data collection process for each participant will begin at enrollment (during pregnancy), and follow-up will occur at the end of the second trimester (approximately 24 weeks' gestation) and at pregnancy outcome (delivery or early termination).

9.2.2 Study Subjects

The study population will include pregnant women within the US who were immunized with the Menveo vaccine within 28 days prior to conception or at any time during pregnancy. Because the vaccine is not indicated in pregnancy, the majority of exposures will likely be inadvertently administered in the first trimester of pregnancy. Enrollment and data collection will be coordinated through a registry coordination center (RCC). Eligible pregnant women may self-enroll in this pregnancy registry, and HCPs may also report de-identified data on pregnancy exposures and outcomes.

9.2.3 Study Population Selection

The minimum criteria required for enrollment into the registry are as follows:

- Sufficient evidence to confirm that Menveo exposure occurred within 28 days prior to conception or at any time during pregnancy

- Sufficient information to determine whether the pregnancy is prospectively or retrospectively registered (ie, whether the outcome of pregnancy was known at the time of first contact with the registry)
- Date the pregnancy exposure is registered
- Full reporter (ie, HCP) contact information to allow for follow-up (name, address, etc.)

Because registry enrollment is open to all eligible pregnant women, an active recruitment campaign will reach out to immunization providers and their patients in a broad variety of settings. The recruitment strategy will target HCPs who are known to immunize patients specifically with the Menvo vaccine. These providers will be identified through NVD Menvo distribution data and medical science liaisons (MSLs), as well as HCP provider networks and health maintenance organizations (HMOs).

This targeted awareness will include the distribution of a comprehensive informational kit designed to solicit interest among pregnant women in registry participation. All messaging will be in line with product labeling.

The kit may include:

- Branded registry information sheet and/or brochure that will briefly describe the registry purpose and procedures
- Enrollment form and sample patient consent form
- Prescribing information
- Participant consent to contact card (this card enables the RCC to contact the potential patient and provide additional information about the registry)

Persistent awareness activities incorporating the above awareness materials as well as a variety of other approaches such as internet, product labeling, and messaging by MSLs may also be used, including the following:

- Internet:
 - FDA listing of pregnancy registries on www.fda.gov
 - www.clinicaltrials.gov
 - Society for Maternal-Fetal Medicine listing of registries
 - PPD website
 - NVD website
- Print:
 - Menvo prescribing information

- Menveo medication guide
- Medical journal advertising and/or direct to physician advertising
- Registry contact information in report(s)
- Education:
 - MSL outreach to treating HCPs
 - Scientific presentations and publications
 - Distribution of report(s) to HCPs

9.2.3.1 Reference Groups

Given the inherent difficulties in identifying a comparison group (Covington, 2009), several different methods may be used to review the data for safety signals. As described below, background rates from external surveillance sources and rates from published literature will be the primary comparators. To the extent possible, comparator rates will be age-adjusted to reflect the age distribution of the Menveo Pregnancy Registry population.

Background Rates on Pregnancy Outcomes

Background rates in the general population on pregnancy outcomes, such as premature birth and LBW, are readily available from national vital statistics or publications in the scientific literature (Martin, 2012).

Background Rates on Congenital Anomalies

Published rates of MCMs are available from the Centers for Disease Control and Prevention (CDC)'s Metropolitan Atlanta Congenital Defects Program (MACDP), which is an ongoing population-based birth defects surveillance program (Correa, 2007). The primary objectives of MACDP are to regularly and systematically monitor births of malformed infants for changes in incidence or other unusual patterns suggesting environmental influences, and to develop a case registry for use in epidemiological studies. MACDP actively searches for MCMs among the 50,000 annual births to residents of metropolitan Atlanta's 5 counties and abstracts medical records at all Atlanta obstetric hospitals, Atlanta pediatric referral hospitals, genetics labs, and vital records (Correa-Villasenor, 2003). While there are inherent problems with comparing data from women exposed to specific vaccines in pregnancy with background rates from the general population, this is not an unrealistic comparison (Honein, 1999), and background rates may be the only practical comparator. MACDP has been used as a comparator by over 60% of pregnancy registries identified in a recent survey (Covington, 2009). When an analysis includes data from an external comparator, it is important to thoroughly

understand the methodology of the external comparator, and to take this into consideration when designing the analysis plan ([Kennedy, 2004](#)).

Background Rates from Literature or Other Studies

The registry is committed to identifying other appropriate comparison groups, and research of the literature and other sources, such as other pregnancy registries or observational studies, will continue in order to obtain appropriate background rates.

9.3 Variables

The sections below describe the theoretical aspects of relevant variables. Data sources and operational definitions are discussed in [Section 9.4](#).

9.3.1 Exposure of Interest

This pregnancy registry is strictly observational, and prior Menveo vaccination is a condition of enrollment. Menveo vaccination is not indicated in pregnancy. Therefore, Menveo vaccination exposure in pregnancy is expected to be inadvertent and to occur within 28 days of conception or in early pregnancy. Data to be collected include the date of vaccination, facility (e.g., HCP office, clinic, or commercial facility such as a pharmacy or other retail outlet), dose, and lot number if available.

9.3.2 Outcome(s) of Interest

MCM: The registry defines and codes MCMs with criteria specified by CDC MACDP ([CDC, 2007](#)). The registry defines an MCM as any major structural or chromosomal defect or combination of 2 or more conditional defects in live-born infants, stillbirths, or fetal losses of any gestational age (including outcomes prior to 20 weeks' gestation or birth weight <500 g). This definition is consistent with, but not restricted to, the CDC MACDP definition. Clusters of conditional abnormalities (as defined by CDC MACDP) and data from aborted fetuses of less than 20 weeks' gestation, when available, will be included to increase sensitivity of monitoring. The MACDP includes conditional defects only if in the presence of a major defect. This registry will consider reports of 2 or more conditional defects as a defect case, to increase signal sensitivity and to capture instances where a combination of conditional events might constitute a major defect or syndrome.

The registry conforms to the CDC MACDP guidelines in disqualifying as defects those findings that are present in infants born at less than 36 weeks of gestation and are attributable to prematurity itself, such as patent ductus arteriosus, patent foramen ovale, or inguinal hernias. The CDC MACDP classification does include chromosomal defects. Though these defects are not likely to contribute to a risk for a vaccine exposure, the registry includes these defects to maintain this consistency with the CDC MACDP.

Live-born infants with only transient or infectious conditions or with biochemical abnormalities will be classified as being without reported MCMs unless there is a possibility that the condition reflects an unrecognized MCM. Detected and reported transient or infectious conditions or biochemical abnormalities in infants without reported MCMs and defects that are excluded by the CDC guidelines will be noted in an appendix in the registry reports.

Preterm birth: An infant born at gestational age <37 weeks

LBW: An infant whose birth weight is <2500 g

9.3.3 Other Variables

Maternal characteristics: Age, ethnicity, race

Prenatal data: Last menstrual period (LMP), estimated date of delivery (EDD), corrected estimated date of delivery (CEDD)

Prenatal tests: Name of test, date of test, result

Obstetrical history: Previous pregnancies, live births, stillbirths, SABs, induced abortions (IABs), births with congenital malformations, family history of congenital malformations

Concomitant medical conditions

Concomitant medications and vaccines

Alcohol, tobacco, and illicit drug use

Pregnancy outcomes

Each pregnancy outcome will be classified in 1 of the following mutually exclusive categories:

- Live birth: an infant born alive
- Stillbirth: a fetal death occurring at 20 weeks' gestation or greater, or if gestational age is unknown, a fetus weighing 500 g or more
- SAB: fetal death or expulsion of products of conception prior to 20 weeks' gestation. Terminology may include missed abortion, incomplete abortion, and inevitable abortion.
- IAB: voluntary interruption of pregnancy, including pregnancy termination that occurs electively, to preserve maternal health, or due to fetal abnormalities

- Ectopic pregnancy: implantation of a conception outside of the uterus
- Molar pregnancy: a conception that results in a gestational trophoblastic tumor

Infant Outcomes: Gestational age, birth weight, sex

9.4 Data Sources

The pregnant woman and appropriate members of her health care team will serve as data reporters to the registry. The registry is strictly observational; the schedule of office visits and all treatment regimens will be determined by the treating HCP. There will be no additional laboratory tests or assessments required as part of this registry. Only data noted as part of routine care will be collected. HCPs may also report de-identified data to the registry. The following table provides a summary of data that will be collected at specific time points and the source of data.

Table 9.4-1: Summary table of evaluations

Information Requested	Registration Provided by participant and/or Ob HCP	Interim Prenatal Follow-up (end of 2 nd trimester) Provided by Ob HCP	Pregnancy Outcome Provided by Ob HCP and/or Pediatrician attending birth	Targeted Follow-up Provided by relevant HCP
Maternal contact information, alternate contact information, HCP contact information	X	X ^a	X ^a	
Maternal characteristics (age, ethnicity, race, etc.)	X	X ^a		
Maternal prenatal information (LMP, EDD, CEDD, prenatal test results & timing)	X	X ^a	X ^a	
Obstetrical history	X	X ^a		X ^b
Family history of MCMs	X	X ^a		X ^b
Menveo exposure information	X	X ^a	X ^a	
Concurrent conditions, concomitant medications, alcohol & tobacco use during pregnancy	X	X ^a	X ^a	
Pregnancy status		X	X ^a	
Outcome information (live birth, still birth, SAB, gestational age, birth weight, infant/fetus sex)			X	
MCM noted & description			X	
Contributing factors			X	X ^b

^a Obtain updated information since the previous contact.^b Collect information not previously obtained, to facilitate characterization of the fetal loss and or MCMs.

Registration Process

Registry enrollment may be initiated by pregnant women or by their HCPs, who will act as data reporters to the registry. After applicable subject informed consent is obtained from eligible women, the reporter will complete the **Registration Form** and submit it to the registry. HCPs may also report de-identified pregnancy and outcome data to the registry. The registry will provide a variety of convenient means for reporters to communicate with and submit data to the registry.

Information Collected at Registration

Reporter Information

- Contact information for the patient (if the patient self-enrolls), as well as alternate contact information, such as a permanent address and/or next of kin
- HCP reporter contact information

Maternal Information

- Maternal demographics (age, ethnicity, race)
- LMP
- EDD determined from LMP
- CEDD (e.g., by ultrasound), if available
- Prenatal tests (diagnostic or screening) performed, date of test, and findings including the identification of congenital anomalies

Maternal Obstetrical History

- Number of previous pregnancies
- Outcome of previous pregnancies: live births, stillbirths, SABs, IABs, ectopic pregnancies, molar pregnancies
- History of offspring with congenital anomalies
- Maternal and paternal history of congenital anomalies

Maternal Menveo Exposure (may be provided initially by the pregnant woman at registry enrollment and confirmed by the vaccinating HCP)

- Menveo administration, including dose, timing, and lot number

Other Conditions and Exposures

- Concurrent maternal conditions
- Concomitant medications taken during pregnancy
- Tobacco, alcohol, and illicit drug use during pregnancy

Pregnancy Follow-up

Around the end of the second trimester and in the month of the EDD, the ***Interim Pregnancy Follow-up Form*** and ***Pregnancy Outcome Form*** (respectively) will be requested from the obstetric HCP.

Information Collected at Interim Pregnancy Follow-up and Pregnancy Outcome

Follow-up at End of Second Trimester

Pregnancy Status

- Updates to EDD (ie, CEDD)
- Subsequent prenatal tests (diagnostic or screening) performed and findings including the identification of congenital anomalies
- Pregnancy complications (preterm labor, eclampsia, placental abruption)
- Details of pregnancy outcome if pregnancy is not ongoing as described below

Other Exposures

- Concomitant medications
- Tobacco, alcohol, and illicit drug use during pregnancy

Additional Information Collected at Pregnancy Outcome

Fetal Outcome

- Pregnancy outcome (live birth, stillbirth, SAB, IAB, ectopic pregnancy, molar pregnancy)
- Date of outcome of pregnancy
- Gestational age at outcome
- Fetal/infant characteristics: sex, birth weight
 - MCM(s) and assessment of potential contributing factors
 - For a fetal loss (SAB, stillbirth), factors that may have had an impact on the fetal loss and attribution

Targeted Follow-up Process

If there is an MCM or other event of interest noted, in order to properly characterize the event, additional information may be requested from the reporting HCP on the ***Targeted Follow-up Form***:

- Details of the MCM/condition
- Etiology
- Outcome attribution
- Specific questions requested by NVD and/or the MCM evaluator

Attempts to Obtain the Follow-Up Information

In the month that the follow-up is due, the HCP will be contacted and asked to provide follow-up information. Three subsequent attempts, as necessary, will be made every 2 weeks via various modes of communication. If there is still no response from the provider, a final communication will be sent indicating the case is lost to follow-up. If this communication prompts a response from the HCP or the requested data is later received, the case will be re-opened and assessed for evaluability. If, at any point in the follow-up process, the reporter indicates that the patient is lost to follow-up, no further attempts will be made.

Follow-Up Process for Clarification of Information

For critical data points, if there are outstanding questions, discrepancies between forms, or missing data, the appropriate reporter will be contacted for clarification. Three subsequent attempts, as necessary, will be made every 2 weeks. If no further information is obtained on an otherwise evaluable case, the discrepant information in the data fields may be left blank, identified as “unspecified.” On a case-by-case basis, qualified registry staff or the principal investigator may make a determination on discrepant information (e.g., determination of partially illegible word or illogical year).

9.4.1 Operational Exposure Definition

Menveo administered 28 days prior to conception or at any time during pregnancy (from conception until pregnancy outcome) will constitute exposure. The 28-day window prior to conception corresponds with the time to immunologic response as indicated in the Menveo product label (Menveo package insert, 2012). Menveo exposure will be further categorized by earliest trimester of exposure. Menveo is not indicated in pregnancy and is typically given to adolescents and young adults. Thus, the vast majority of pregnancy exposures will be inadvertent first trimester exposures, most likely prior to recognition of the pregnancy. For this registry, gestational weeks will be estimated from the most

reliable EDD as reported by the HCP. If a CEDD is provided by the HCP, it will be used instead. The date of conception will be calculated as the most reliable EDD minus 38 weeks. If the EDD is not available or never estimated, the first day of the LMP may be used to estimate gestational age. The second trimester will be considered to begin at week 14 after the date of conception or LMP, and the third trimester, at week 28. If there is a discrepancy between gestational age calculated from LMP and reported gestational age, the HCP will be asked to verify the data.

When a pregnant woman enrolls in the registry, she will be asked when and where she was immunized with the Menveo vaccine. She will then be asked to provide a medical release that allows the registry to confirm Menveo vaccination with the appropriate source. The registry will contact the Menveo vaccination provider to confirm the vaccination date, brand, and lot number. If HCPs provide de-identified data to the registry, they must be able to verify the Menveo vaccination and date of vaccination.

9.4.2 Operational Outcome Definition and Identification Process

All outcome variables will be provided by the obstetric HCP and/or pediatrician attending the birth. The HCP will be asked to describe any MCMs observed in the infant or fetus and will also be asked to report the gestational age and birth weight. These 2 variables will be used to calculate preterm birth (gestational age <37 weeks at birth) and LBW (birth weight <2500 g). A teratologist/geneticist will review all reported congenital anomalies and classify them using the CDC's MACDP system as specified in [Section 9.3.2](#). Additionally, the teratologist/geneticist will provide an opinion regarding the possible temporal association of the Menveo exposure to the development of observed defects. If additional information is needed to aid in classification or temporality assessment, the teratologist will request additional information using the targeted follow-up process outlined in [Section 9.4](#).

The SAC will meet periodically to review the data, discuss the MCM cases and their classification and temporality with the teratologist, and reach consensus on the coding and classification of MCMs and other primary endpoints.

9.4.3 Operational Variable(s) Definition

As is indicated in [Section 9.4](#), for women who self-enroll in the registry, maternal characteristics will be provided by the pregnant woman at registry enrollment. After the woman provides consent and medical release for her HCP(s) to provide data, the obstetric HCP will provide prenatal data (LMP, EDD, and CEDD), prenatal test data (test, date of test, and result), obstetrical history (previous pregnancies, live births, stillbirths, SABs, IABs, births with congenital malformations, and family history of congenital malformations), concomitant medical conditions, concomitant medications and vaccines, and alcohol, tobacco, and illicit drug use. At pregnancy outcome, the obstetric HCP will

provide pregnancy outcomes data (live birth, stillbirth, SAB, IAB, or ectopic or molar pregnancy) and infant outcome (gestational age, birth weight, and sex).

If HCPs provide de-identified data to the registry, they will provide required data on maternal characteristics, prenatal data, obstetrical data, and pregnancy outcome data.

9.4.4 Advisory Committee(s)

An SAC will be established to oversee the scientific affairs of the registry, including its ongoing monitoring. The SAC will comprise recognized experts in the fields of teratology, epidemiology, maternal and fetal medicine, and therapeutic areas from government, academia, private practice, and NVD. The SAC will meet prior to each registry report to review the accumulated body of data from the registry, including review and classification of reported MCMs, and to carry out any actions required, including review and interpretation of interim data analyses and reports and publications of registry data. The SAC may meet on ad hoc occasions if indicated. In addition to the above activities, the SAC will design and implement strategies to heighten awareness of the registry.

9.5 Study Size

Currently the market share of Menveo is approximately 20%, with an annual absolute dose distribution of 1.8 million in 2012. It can be assumed that market shares will remain stable over the course of the 3-year duration of the study. The Advisory Committee on Immunization Practices (ACIP) recommends routine administration of a MenACWY vaccine for all persons aged 11 through 18 years. A single dose of vaccine should be administered at age 11 or 12 years, and a booster dose should be administered at age 16 years. It is roughly estimated that of all Menveo vaccinations, approximately 76% are provided to individuals less than 18 years of age ([Novartis Vaccines and Diagnostics, 2012](#)). Given the low rate of pregnancy in this age group, exposure during pregnancy at the recommended ages can be expected to occur infrequently. Likewise, vaccination among women of peak reproductive age (25-29 years) can also be expected to be rare ([Ventura, 2012](#)). In addition, willingness to participate and completion of follow-up in the pregnant adolescent population are expected to be very low. It is therefore anticipated that, per year, approximately 15 exposed women will be enrolled through the registry system and that approximately 60 supplemental identified exposures of Menveo in pregnancy can be expected from external sources.

The registry is expected to prospectively enroll approximately 100 women with exposure to Menveo 28 days prior to conception or during pregnancy over a 3-year period. Approximately 58% of these pregnancies can be expected to result in a live birth ([Ventura, 2012](#)). Given the patient population will be mainly adolescents, a high percentage of these pregnancies can be expected to be unintended, unwanted, and likely

to result in IAB. Therefore, it is anticipated that the registry will yield approximately 58 live births. It is expected that the vast majority (99%) of pregnancy exposures will occur within 28 days prior to conception or early in the first trimester (before pregnancy status is known). If exposures occur later in pregnancy, results will be stratified by trimester of exposure, acknowledging that the power of stratified analyses to detect statistically significant differences will be limited by the sample size of each subgroup.

The expected low frequency of Menveo exposure in pregnancy will limit the statistical power of this study. As noted below, there should be sufficient power to identify risks for relatively common outcomes such as preterm birth and LBW. However, there is less power to identify risks of rarer outcomes such as MCM.

According to the CDC MACDP, the prevalence rate of MCMs for mothers <25 years of age in the US is 2.54% ([Correa, 2007](#)). With a sample size of 58 first trimester exposed pregnancies resulting in a live birth, the study will have 80% power to detect a 4.46-fold increase in the prevalence rate of MCMs as compared with the CDC MACDP rate.

According to the CDC National Vital Statistics System (NVSS), the prevalence rate of preterm birth for mothers <25 years of age is 12.37% ([Martin, 2012](#)). With a sample size of approximately 58 exposed live births, the study will provide 80% power to detect a statistically significant 1.99-fold increase in the prevalence rate of preterm birth as compared with the CDC NVSS rate.

According to the CDC NVSS, the prevalence rate of LBW for mothers <25 years of age is 8.70% ([Martin, 2012](#)). With a sample size of 58 exposed live births, the study will provide 80% power to detect a statistically significant 2.40-fold increase in the prevalence rate of LBW as compared with the CDC NVSS rate.

The registry acknowledges the challenges of enrolling this number of exposed pregnancies and will carefully monitor enrollment trends and outcomes. This is an open registry with initiation of patient recruitment from the time of launch.

9.6 Data Management

9.6.1 Data Processing

Data for this prospective registry will be managed with an electronic data capture (EDC) platform, which is 21 CFR Part 11 compliant. Participants and their HCPs will provide data over the phone or by completing a paper case report form (CRF), which can be submitted to the registry via mail or fax. The data will be reviewed by a registry clinical research associate for correctness and completeness and entered into the database.

9.6.2 Software and Hardware

Power calculations presented in this protocol were conducted using SAS statistical software and a 1-sample binomial distribution with a 1-sided Type I error rate of 5%. Data analyses will be performed similarly using SAS (version 9.2 or higher; SAS Institute, Cary, NC).

9.7 Data Analysis

Registry Case Management and Disposition

Prospective Registry Reports

The registry will encourage prospective registration, which is defined as registration of a pregnancy exposure prior to knowledge or perceived knowledge of the pregnancy outcome (e.g., structural defect or genetic abnormality noted on a prenatal test). Those with no abnormalities identified on a prenatal test prior to enrollment will be considered prospective and included in the analysis. The rationale, potential bias, and analytic techniques to address any bias that may be introduced by this practice are addressed in [Section 9.7.4](#).

Data from HCP provider networks and HMOs that provide de-identified data on all exposed pregnancies in their network will fall into the category of prospective registry reports, as these networks/HMOs provide objective data on every pregnancy exposure in the network/HMO, both positive and negative outcomes. Thus, they avoid the reporting bias inherent in retrospective reporting only after a negative outcome has been noted.

Retrospective Registry Reports

Retrospective reports will also include subjects for whom the pregnancy outcome has already occurred or an abnormality has been identified on a diagnostic or screening prenatal test prior to enrollment. Retrospective reports can be biased toward the reporting of more unusual and severe cases and are less likely to be representative of the general population experience than reports reported prior to knowledge of outcome. Therefore, retrospective reports will not be included in the primary analysis and statistical calculation of risk. Retrospective reports with reported MCMs and/or spontaneous fetal losses will be reviewed to aid in detection of early signals and listed in registry reports. Retrospective reports will not be actively solicited by the registry and will not be captured in the registry database unless a congenital anomaly is reported.

Loss to Follow-Up

For a prospective report or pregnancy where follow-up information on the pregnancy outcome (live birth, fetal loss, etc.) is never obtained or is unavailable, the pregnancy will be considered lost to follow-up. Subjects lost prior to pregnancy outcome will be tallied in the registry reports but not included in the statistical analyses.

Duplicate Registry Reports

With registry reports coming from multiple health care providers, health care provider networks, and HMOs, it is important to ensure that each case is counted only once ([NBDPN, 2004](#)). Identification of duplicate reports may be problematic for the anonymously reported de-identified cases where there is no specific identifying information. Reports received by the registry will be reviewed for possible duplicate reporting. On receipt of a registration form, the report will be compared with other reports made by the same reporter or compared with other data (such as age, LMP, EDD, and exposure information) to determine if the same report was received previously. If no duplication is identified, the report will be entered into the database. If a duplicate report is later identified through recall or the systematic check for duplicates, the case reported earliest or the one with the most complete data will be maintained as the valid case and updated with any data from the other report not already captured. The duplicate report will be flagged and designated as “Invalid”, with the reason being “duplicate report”.

Evaluable Registry Reports

An evaluable report is a subject with data submitted or confirmed by an HCP that contains at least the minimum criteria for a report and is not lost to follow-up. Prospectively reported evaluable subjects with known outcomes will be included in the primary analysis for the registry report. Evaluable retrospective reports will be summarized separately in the report. Patient-reported data without HCP confirmation will be summarized separately in the report.

Invalid Registry Reports

An invalid registry report is a report for which the minimum data elements are never obtained despite requests for the missing data. If the minimum data are not provided initially, the report will be considered to be pending until all attempts to resolve queries for missing data and requests for follow-up information are complete. If, after all attempts at follow-up are made, the minimum criteria are still not met, the report will be considered invalid due to insufficient information. Invalid reports will not be included in the registry analyses.

Analysis Population

The primary population for analysis will include prospective evaluable subjects exposed to Menveo that are not lost to follow-up (ie, subjects with appropriate outcome information that meet the minimum criteria for evaluation).

Exclusions for Analysis Purposes

Invalid registry reports and pregnancies deemed lost to follow-up will be excluded from the primary analysis. Retrospective reports will not be included, although retrospective cases with MCMs will be reviewed and reported separately for signal detection purposes.

Sequential Pregnancies

The number and outcome of sequential pregnancies will be noted and presented. Sequential pregnancies will be included in the analytic dataset.

Multiple Gestation Pregnancies

The number, type (e.g., twin, triplet), and outcome of multiple gestation pregnancies will be noted and presented. Multiple gestation pregnancies will be included in the analytic dataset.

General Considerations for Data Analyses

This study is observational, and epidemiological methods will be employed for data collection and analyses.

Descriptive analysis will be performed for all prospective, evaluable data. The summary statistics for continuous and categorical variables to be used will be specified in the statistical analysis plan (SAP) but may include means, standard deviations, medians, minimums, maximums, percentiles, n's, and percentages. Adjustment for confounders of potential associations will be made with multivariate regression methods if appropriate and will be described in detail in the SAP.

The registry will identify the number of cases for the primary outcomes of MCM, preterm birth, LBW, and in addition for second trimester SABs; proportions of these outcomes will be calculated with 1-sided 95% confidence intervals from the total number of pregnant women or live births, or in the case of second trimester SABs, the subset of women exposed prior to the 20th week of gestation.

9.7.1 Statistical Hypotheses

This registry is primarily descriptive and designed to detect potential safety signals, rather than test hypotheses.

9.7.2 Analysis of Demographics and Baseline Characteristics

Demographic and baseline characteristics will be summarized with simple descriptive statistics and data listings for the evaluable populations of pregnant women and live births. Demographic and baseline characteristics will also be summarized for the population that is lost to follow-up and compared with the evaluable populations to assess potential differences. These data will be reviewed for potential confounding factors that could affect the interpretation of comparisons of registry outcome rates with that of comparators. Further details will be provided in the SAP.

9.7.3 Statistical Methods

Overall and stratum-specific point estimates and 1-sided 95% confidence intervals will be calculated using the exact binomial distribution for prevalence rates of MCMs, preterm birth, and LBW among pregnant women exposed to Menveo and their live births. Most structural defects have their origins in the first trimester of pregnancy, the period of organogenesis. In addition to overall prevalence of MCM, the analysis of MCMs will be stratified by trimester of exposure to Menveo. The prevalence rate of combined MCMs reported to the registry will be calculated as a proportion with the number of MCMs as the numerator and the number of live births as the denominator, among women with first trimester exposure. Pregnancy losses with reported MCMs occurring at or after 20 weeks' gestation will be included in the numerator of the estimate of risk for MCMs to increase sensitivity and to allow comparison of outcomes with the CDC MACDP, which calculates rates by this convention. A secondary analysis will be conducted including pregnancy losses with reported MCMs occurring at less than 20 weeks' gestation in the calculation of risk. The prevalence rate of combined MCMs in exposed cases will be compared with that of the CDC MACDP ([Correa, 2007](#)).

Only cases meeting the CDC MACDP criteria for a defect or with 2 or more conditional defects will be included in the primary analysis. Single minor defects do not constitute a MCM according to the CDC MACDP classification; therefore, they will be listed in the report, but not included in the primary analysis.

The prevalence rate of preterm births and LBW will be calculated as proportions, with the number of live births as the denominator. These prevalence rates in exposed cases will be compared with those of the CDC NVSS ([Martin, 2012](#)). Because MCMs are often associated with preterm birth and LBW, infants with MCMs will be excluded from

analyses of these outcomes and will not be counted in the numerator or denominator when prevalence rates are determined.

The outcome data will be stratified by the earliest trimester of exposure to Menveo. For this registry, gestational weeks are estimated from the most reliable EDD as reported by the HCP. If a CEDD is provided by the HCP, it will be used instead. The date of conception will be calculated as the most reliable EDD minus 38 weeks. If the EDD is not available or never estimated, the first day of the LMP may be used to estimate gestational age. The second trimester will be considered to begin at week 14, and the third trimester, at week 28. If there is a discrepancy between gestational age calculated from LMP and reported gestational age, the HCP will be asked to verify the data.

If it is feasible, comparisons between the registry and an appropriate internal and/or external comparison group will be examined (see [Section 9.2.3.1](#) for a description of potential comparators).

Methods to Control for Confounding and Effect Modification

For analyses of associations between pregnancy outcomes and Menveo exposure, confounding and effect modification will be evaluated. A detailed description of these analyses will be available in the SAP. Potential confounders/effect modifiers may include the following:

- Maternal characteristics (e.g., age, ethnicity, race)
- Previous pregnancy outcomes (e.g., MCMs, stillbirth)
- Pregnancy complications (e.g., preterm labor, eclampsia, placental abruption)
- Comorbidities (e.g., diabetes, hypertension)
- Concomitant exposures (e.g., medications, alcohol, tobacco)
- Infant/fetus sex

Subgroup Analyses

Analyses will be stratified by trimester of exposure and other potential subgroups of interest, potentially including gestational age at enrollment and maternal age. Additional details on subgroup analyses will be described in the SAP. Comparisons may be made to external cohorts, if appropriate.

9.7.4 Statistical Considerations

Because early prenatal testing is so prevalent, it may be difficult to achieve adequate numbers of prospectively identified pregnant women if all pregnancies with prior prenatal

testing are excluded from the analysis. Therefore, the primary analysis will include pregnancies enrolled prior to outcome but after prenatal test as long as the test does not indicate an abnormality. However, this practice could potentially bias the results by lowering the overall risk of MCMs (Honein, 1999). The analysis will attempt to address bias introduced by this practice.

While the registry analysis will be limited primarily to prospective reports, some pregnancy exposures will be reported only following pregnancy outcome (retrospective cases). Each retrospective report will be carefully reviewed. In general, retrospective reports of exposures to vaccines or medication following notification of outcome are biased toward reporting of the severe and unusual cases and are not reflective of the general experience with the vaccine or medication. Moreover, information about the total number of exposed persons is not known. Therefore, rates of outcomes cannot be calculated from these data. However, a series of reported MCMs can be analyzed to detect patterns of specific MCMs and can identify early signals of vaccine or medication risks.

Those pregnancies that have reached EDD, but for which outcome information was unobtainable after 4 attempts, will be considered lost to follow-up. It is possible that outcomes among pregnancies lost to follow-up could differ from those with documented outcomes. Because of differences in individual reporting patterns, it is currently not possible to assess with any certainty what impact the potential biases the losses to follow-up may have on the analysis. However, efforts at comparing some of the characteristics of each group may be conducted in an attempt to address this potential source of bias.

Following the MACDP convention, calculation of MCM risk will exclude fetal losses (SABs, IABs, stillbirths, etc.) for which no MCMs have been detected as they may introduce a classification bias. The percentage of these pregnancies consisting of potentially normal outcomes or MCMs is unknown. The data collection form attempts to obtain information on MCMs detected at the time of the outcome. However, the reporting physician may not know the condition of the aborted fetus.

9.8 Quality Control

9.8.1 Validation

Ensuring that the data obtained and delivered to NVD are of high quality will be an ongoing, multi-step process involving programming of edit checks for critical data variables in the EDC system and visual review for completeness, logic, consistency, and accuracy. As recommended in regulatory guidance documents, CRFs are carefully designed to ensure data quality and integrity. All subject-reported data will be verified by the appropriate HCP.

9.8.2 Record Retention

Investigators must retain all study records required by NVD and by the applicable regulations in a secure and safe facility. The investigator must consult a NVD representative before disposal of any study records, and must notify the sponsor of any change in the location, disposition, or custody of the study files. Documents that individually and collectively permit evaluation of the conduct of a study and the quality of the data produced will be retained for a period of 5 years in accordance with Good Pharmacoepidemiological Practice (GPP) guidelines. These documents should be retained for a longer period, however, if required by the applicable regulatory requirements or by an agreement with the sponsor. It is the responsibility of the sponsor to inform the investigator/institution as to when these documents no longer need to be retained.

These principles of record retention will also be applied to the storage of laboratory samples, if applicable and provided that the integrity of the stored sample permits testing.

For observational studies, study records or documents may include the analyses files, syntaxes (usually stored at the site of the database), but also questionnaires.

9.9 Limitations of the Research Methods

Since participation in the registry will be voluntary, the included subjects may not be representative of the overall US pregnant women population. Additionally, it is possible that even in prospectively reported cases, potential bias could exist. For example, high-risk pregnancies or low-risk pregnancies may be more likely to be reported. It is also possible, and entirely likely, that differences in the prevalence rates of pregnancy outcomes will be observed due to random variability ([NBDPN, 2004](#)). With the outcomes of interest occurring at relatively low prevalence rates, cases of a particular condition can be expected to be quite rare, and the coincidence of 2 or more cases in time may be just that: a coincidence. Confidence intervals will be carefully examined in order to assess the potential role of random variability.

Furthermore, it will be important to rule out other explanations for changing prevalence rates over time, including changes in medical diagnoses and technologies, changes in reporting and case ascertainment, and changes in the population at risk. In order to minimize the effect of these changes, the most current prevalence rates available at the time of reporting for the population of interest will be used for analyses.

9.10 Other Aspects

Not applicable.

10.0 PROTECTION OF HUMAN SUBJECTS

NVD respects the subjects' rights to privacy and will ensure the confidentiality of their medical information in accordance with applicable laws and regulations.

Each patient's identity will be known only to the third-party contractor (PPD), the central registry site (principal investigator and RCC), and the enrolling individual (i.e., patient or HCP). The registry will assign patient and infant identification numbers, which will be used to identify registry participants and their infant offspring. The dataset used in each analysis of data from the registry will contain coded registry subject identifiers only for both the pregnant mothers and infants.

Each full-time and temporary employee in the RCC is fully trained in the protection of human subjects and data privacy and follows established standard operating procedures (SOPs) that outline specifically how to maintain confidentiality and data protection of all registry participants. These SOPs also establish procedures to take should privacy be compromised in any way. The RCC staff must train and test on these privacy SOPs annually.

Exemption of HIPAA Authorization

As a post marketing safety reporting activity, this registry meets the criteria outlined below and is therefore exempt from the US HIPAA Authorization.

45 CFR 164.512 states:

“(iii) A person subject to the jurisdiction of the Food and Drug Administration (FDA) with respect to an FDA-regulated product or activity for which that person has responsibility, for the purpose of activities related to the quality, safety or effectiveness of such FDA-regulated product or activity. Such purposes include:

- a. To collect or report adverse events (or similar activities with respect to food or dietary supplements), product defects or problems (including problems with the use or labeling of a product), or biological product deviations;
- b. To track FDA-regulated products;
- c. To enable product recalls, repairs, or replacement, or lookback (including locating and notifying individuals who have received products that have been recalled, withdrawn, or are the subject of lookback); or
- d. To conduct post marketing surveillance;”

To further clarify this issue, an article published by the Pregnancy Labeling Task Force, US FDA, states:

- “the HIPPA Privacy Rule specifically permits the disclosure of protected health information by covered entities such as physicians or hospitals for public health purposes related to the quality, effectiveness and safety of FDA-regulated products to both the manufacturers and directly to the FDA. This includes collecting or reporting adverse events, tracking FDA-regulated products and conducting post-marketing surveillance to comply with requirements or at the direction of the FDA.” ([Kennedy et al, 2004](#)).

10.1 Regulatory and Ethical Compliance

This study was designed and shall be implemented and reported in accordance with GPP, with applicable local regulations and with the ethical principles laid down in the Declaration of Helsinki. The protocol will be submitted for approval to applicable regulatory authority and central IRB prior to registry implementation.

10.2 Informed Consent

Informed consent will be obtained for each registry participant who self-enrolls or is enrolled by her HCP. As is noted below, this registry qualifies for a waiver of documentation of informed consent. Adult participants will be given the option to provide verbal consent under the waiver of documentation of informed consent or signed informed consent if they prefer where consent is obtained in person.

Minors are defined as individuals who have not attained the legal age for consenting to treatments, procedures, or clinical investigations under applicable law in various states within the US. The definition of a minor and an emancipated minor varies by state within the US. Given the patient population for Mencevo vaccine, many of the potential registry participants may be minors. This registry will follow applicable laws for the state in which the participant resides. If a minor requests participation in the registry and all eligibility criteria are met, the registry will obtain assent from the minor and signed written consent from the parent or guardian. Written consent from both parents or guardians will be obtained in the US states in which this is required by local laws and regulations.

At the initial screening with potential participants, the registry associate will obtain consent to collect basic information about the individual, such as age and state of residence to determine whether the individual is a minor and to ensure that applicable local laws and regulations are followed.

Waiver of Documentation of Informed Consent

The following US regulations indicate that waiver of documentation of informed consent is appropriate for this registry.

As stated in the US Code of Federal Regulations (CFR) 21 CFR 56.109 (and additionally in 45 CFR 46.117(c)(2)):

- “(c) An IRB shall require documentation of informed consent in accordance with 50.27 of this chapter, except as follows:
 - The IRB may, for some or all subjects, waive the requirement that the subject, or the subjects legally authorized representative, sign a written consent form if it finds that the research presents no more than minimal risk of harm to subjects and involves no procedures for which written consent is normally required outside the research context.
 - (d) In cases where the documentation requirement is waived under paragraph (c)(1) of this section, the IRB may require the investigator to provide subjects with a written statement regarding the research.”

The research involves no more than minimal risk to the subjects. This is an observational study that involves no experimental intervention and poses no possibility of physical harm. The only potential risk is a breach of confidentiality, and the registry has well-established procedures in place to prevent any such breach of confidentiality. As described above, extensive safeguards are in place to ensure that patients' privacy is protected:

- a. An adequate plan is provided to protect the identifiers from improper use and disclosure (see [Section 10.0](#)).
- b. An adequate plan is provided to remove the identifiers at the earliest opportunity.
- c. Adequate assurances are provided that the protected health information will not be reused or disclosed to any other person or entity.

The research involves no procedures for which written consent is normally required outside the research context. Enrollment in this observational study will be strictly voluntary. The schedule of patient visits and all treatment regimens will be at the complete discretion of the treating HCP. Data submitted to the registry will be limited to data routinely collected and documented in the patient's medical record.

For HCPs who report de-identified pregnancy exposure and outcome data to the registry, a waiver of informed consent is applicable as specified under CFR 46.116 (d) waiver of informed consent requirement and CFR 45, part 164.512 waiver criteria for post-

marketing surveillance for the initial enrollment and follow-up through outcome of pregnancy.

The research will involve no more than minimal risk to the subjects. This will be an observational registry that is a PMC with CBER. It involves no experimental intervention and poses no possibility of physical harm. The pregnant patient's HCP, who is strictly obligated to maintain confidentiality, will submit routinely collected data to the registry. Patient confidentiality will be protected, as no identifying information will be sent to the registry. Only the HCP will know the identity of the patient. As described above, extensive safeguards will be in place to assure that patients' privacy is protected.

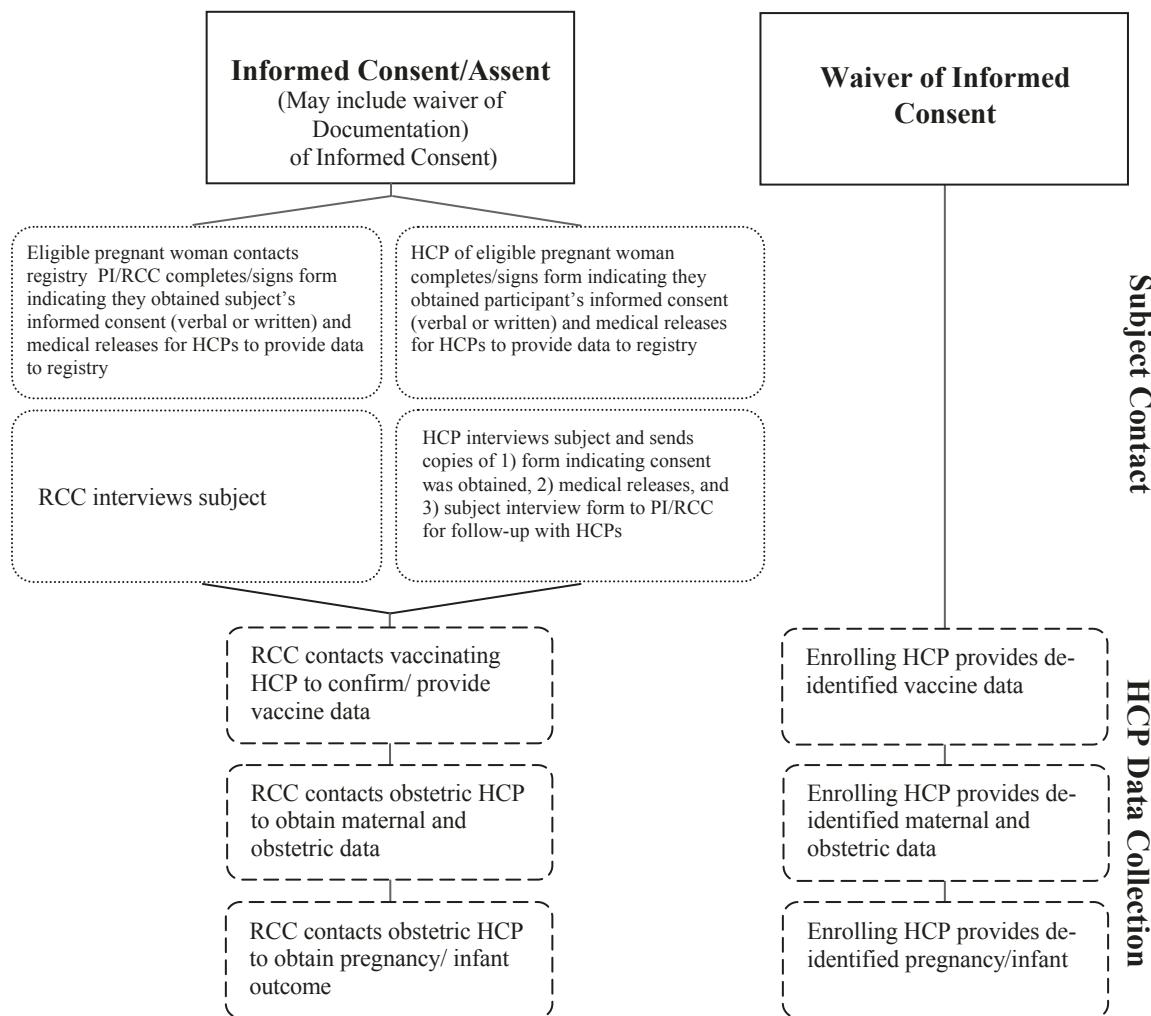
The waiver will not adversely affect the rights and welfare of the subjects. The privacy risks to individuals whose protected health information will be used or disclosed are reasonable in relation to the anticipated benefits to future patients, and the importance of the knowledge that may reasonably be expected to result from the research.

The research could not practicably be conducted without the waiver. A critical component of a registry such as this is the need to enroll a substantial number of subjects to have the statistical power necessary to assess risk. In order to enroll as many patients as possible, this registry seeks to accept self-enrollments from patients as well as de-identified data from HCPs under this waiver of informed consent.

[Figure 10.2-1](#) outlines the process flow for enrolling registry participants under the 3 models:

1. Self-enrollment with signed informed consent or verbal consent (waiver of documentation of informed consent)
2. HCP enrollment with signed informed consent or verbal consent (waiver of documentation of informed consent)
3. De-identified data provided by HCPs under the waiver of informed consent provision.

Figure 10.2-1: Consent and data collection process



10.3 Responsibilities of the Investigator and IRB

The protocol, waiver of documentation of informed consent, and waiver of informed consent will be reviewed and approved by an IRB before study implementation. A signed and dated statement that the protocol and waivers have been approved by the IRB will be given to NVD before study initiation. Prior to study start, the investigator will sign a protocol signature page confirming his/her agreement to conduct the study in accordance with these documents and all of the instructions and procedures found in this protocol. If

an inspection of the site is requested by a regulatory authority, the investigator must inform NVD immediately that this request has been made.

The principal investigator is responsible for providing oversight of the registry and all submissions (protocol, amendments) to the IRB. The principal investigator will be available to NVD and the SAC for ongoing consultations regarding the review, analysis, and conduct of the registry.

The RCC is responsible for assisting the PI in all aspects of patient recruitment, informed consent, data collection and management. As is noted in [Section 10.0](#), the RCC staff is fully trained and compliant in SOPs on the protection of human subjects and data privacy.

10.4 Protocol Adherence

The registry investigator will apply due diligence to protocol adherence. If a protocol amendment is necessary to improve the conduct of the study, such an amendment will be agreed upon by NVD and approved by the IRB before it can be implemented.

11.0 MANAGEMENT AND REPORTING OF ADVERSE EVENTS/ ADVERSE REACTIONS

The registry will follow industry guidance ([FDA, 2002](#)) for regulatory reporting of adverse events, as stated below:

“The Agency considers pregnancy exposure registry reports (both prospective and retrospective) as derived from active solicitation of patient information.

Accordingly, a sponsor holding marketing authorization for an approved drug or licensed biological product must submit to the Agency, within 15 calendar days, reports of adverse events from the registry that are both *serious* and *unexpected* by regulatory definition and where a reasonable possibility exists that the drug or biological product caused the adverse event (see 21 CFR 310.305(c)(1), 314.80(c)(2)(iii) and (e), and 600.80(c)(1), (c)(2)(iii) and (e)). Current reporting requirements in the regulations consider any congenital anomaly within the definition of a serious adverse event (21 CFR 314.80(a) and 600.80(a)).” ([FDA 2002](#))

In addition to the above, because the registry is a study specifically to follow-up in pregnant women, exposure in pregnancy to the vaccine of interest itself will not be reported individually but will be reported by PPD to the sponsor’s Safety Department on a monthly basis as line listings. The registry final report will summarize the data on these exposures in pregnancy reported to the registry. Additionally, annual CBER PMC updates, PSURs, and DSURs will provide data on exposure in pregnancy reported to the registry. For subjects enrolled in the registry, exposure in pregnancy to any other product (as well as the vaccine of interest) for which the sponsor is the marketing authorization holder (MAH) will be collected and reported on the monthly line listing. For subjects not enrolled in the registry exposure to any product for which the sponsor is the MAH will be reported within 1 business day to the sponsor’s safety department as an individual report.

The registry will limit active solicitation of adverse events to specific pregnancy outcomes and they will be classified as Serious Adverse Events. These actively solicited SAEs include: MCM, LBW, preterm birth, SAB, still birth, IAB, molar pregnancy, and ectopic pregnancy. In addition to actively solicited SAEs any maternal death will be reported as individual case safety reports (ICSRs) to the sponsor’s safety department.

For any product for which the sponsor is the MAH, all AEs and special scenarios, whether actively sought or not actively sought, which are reported to the study staff will be collected during the course of the registry and will be reported to the sponsor’s Safety Department within 1 business day of awareness by PPD. The sponsor’s Safety Department will be responsible for assessing the seriousness of these events.

The following reports are considered as special scenarios, irrespective if a clinical event has also occurred.

- Drug-drug or drug-food interaction
- Drug use during lactation or breast-feeding
- Lack of effectiveness
- Overdose
- Drug abuse and misuse
- Drug maladministration or accidental exposure
- Dispensing errors / Medication errors
- Withdrawal or rebound symptoms

All not actively sought AEs reported for the vaccine of interest will be summarized in the interim and final study reports as line listings in the appendix.

Reports of AEs for all products for which the sponsor is the MAH from subjects who are not enrolled in the registry will also be reported to the sponsor's Safety Department but will not be listed in the study report.

All AE reports will use the sponsor's report forms.

The sponsor's Safety Department will forward all applicable valid ICSRs of actively sought adverse events and vaccine exposure in pregnancy data to the appropriate regulatory authorities within the required timeframe, as required by regulations.

12.0 PLANS FOR DISSEMINATING AND COMMUNICATING RESULTS

12.1 Registration in Public Database(s)

Key design elements of this registry will be posted in publicly accessible databases including, but not limited to, the FDA pregnancy registry website and clinicaltrials.gov. Furthermore, key results of this registry will be posted in publicly accessible databases within the required time-frame from completion of the data collection where applicable and in compliance with current regulations.

12.2 Publications

Annual updates will be provided in the Annual FDA PMC updates and in the Periodic Safety Update Reports (PSURs) and Development Safety Update Reports (DSUR). These updates will include the following information, presented separately for prospective and retrospective reports.

1. Basic Information:

- number of pregnant women enrolled to date
- number of pregnancies with outcome known (stratified by live birth, spontaneous abortions, elective terminations, fetal deaths/stillbirths)
- number of pregnancies with outcome pending
- number of pregnancies lost to follow-up

2. For pregnancies with known outcome, line listings and summaries of:

- demographics, obstetrical, and medical history of mothers
- weeks of gestational age at exposure
- number of vaccine doses received
- weeks of gestational age at completion or termination of pregnancy
- for live births and deaths/stillbirths, whether multiple birth, small for gestational age, preterm delivery, and congenital anomalies or other fetal abnormalities
- for spontaneous abortions and elective terminations, abnormalities in products of conception if available.

Upon closure of the registry, a final report will be generated which will be submitted to the relevant regulatory authorities. The final report will also be available to HCPs.

The data may also be considered for reporting at scientific conferences or for publication in scientific journals. Preparation of such manuscripts will be prepared independently by the SAC and in accordance with the current guidelines of STrengthening the Reporting of OBservational studies in Epidemiology (STROBE). NVD will be entitled to view the results and interpretations included in the manuscript and provide comments prior to submission of the manuscript for publication.

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APPENDIX 1: LIST OF STAND-ALONE DOCUMENTS

Not applicable.

APPENDIX 2: ENCEPP CHECKLIST FOR STUDY PROTOCOLS

Not applicable.

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The individuals listed have approved this document for implementation using an electronic signature in the
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UserName: PPD

Title: Senior epidemiologist/Consultant

Date: Monday, 08 September 2014, 11:39 GMT

Meaning: As an approver, I agree with the content and format of this document.
