TITLE PAGE

Division: Worldwide Development

Information Type: Worldwide Epidemiology Study Protocol

Title:	The Mepolizumab Pregnancy Exposure Study: a VAMPSS post marketing surveillance study of Mepolizumab safety in pregnancy
Compound Number:	SB240563
Development Phase	IV
Effective Date:	09-NOV-2017
Subject:	Safety in pregnancy
Author(s):	PPD PPD

PASS information

Title	The Mepolizumab Pregnancy Exposure Study: a VAMPSS post marketing surveillance study of Mepolizumab safety in pregnancy
Protocol version identifier	2.0
Date of last version of protocol	12th May 2016
EU PAS (ENCEPP) register number	EUPAS13772
Active substance	Mepolizumab
Medicinal product	NUCALA TM
Product reference	Mepolizumab
Procedure number	Not applicable
Marketing authorisation holder(s)	GlaxoSmithKline
Joint PASS	No
Research question and objectives	To monitor planned and unplanned pregnancies exposed to mepolizumab and to evaluate the possible teratogenic effect of this medication relative to the pregnancy outcomes of major birth defects, preterm delivery, small for gestational age infants and
Countries of study	United States and Canada
Authors	PPD

MARKETING AUTHORISATION HOLDER(S)

Marketing authorisation holder(s)	GlaxoSmithKline Research & Development Limited 980 Great West Road Brentford
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WWEpi Project Identifier: PRJ2465

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Regulatory Agency Identifying Number(s): Not applicable

INVESTIGATOR PROTOCOL AGREEMENT PAGE

- I confirm agreement to conduct the study in compliance with the protocol.
- I acknowledge that I am responsible for overall study conduct. I agree to personally conduct or supervise the described clinical study.
- I agree to ensure that all associates, colleagues and employees assisting in the conduct of the study are informed about their obligations. Mechanisms are in place to ensure that site staff receives the appropriate information throughout the study.

Investigator Name:

Investigator Signature	Date

STUDY ADVISORY COMMITTEE

The Vaccines and Medications in Pregnancy Surveillance System (VAMPSS) has an independent scientific committee that consists of representation from the U.S. Centers for Disease Control and Prevention Center for Birth Defects and Developmental Disabilities, the Eunice Kennedy Shriver National Institute of Child Health and Development, a biostatistician, a consumer representative, and disease-specific specialty representatives. This standing committee meets annually and reviews all interim data, interim and final study reports as well as manuscripts that are produced from the study results. The committee comments on the study progress and poses questions that arise which are addressed by the investigators.

1. LIST OF ABBREVIATIONS

AE	Adverse Event
GA	Gestational Age
GSK	GlaxoSmithKline
LMP	Last Menstrual Period
MCM	Major Congential Malformation
PPD	PPD
PTB	Preterm Birth
SAE	Serious Adverse Event
SGA	Small for Gestational Age
DAP	Data Analysis Plan
VAMPSS	Vaccines and Medications in Pregnancy Surveillance System

Trademark Information

Trademarks of the GlaxoSmithKline group of companies
NUCALA

Trademarks not owned by the GlaxoSmithKline group of companies
SAS
Xolair

2. RESPONSIBLE PARTIES

Sponsor

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

Primary contact:

PPD

Global Regulatory Affairs Lead

Respiratory Therapeutic Group

Global Regulatory Affairs

GlaxoSmithKline Research & Development Ltd.

Study Coordination

The MAH has contracted with the PPD for the PPD to provide scientific leadership and to conduct the study. The PPD is the cohort arm of the Vaccines and Medications in Pregnancy Surveillance System (VAMPSS) in collaboration with the American Academy of Allergy, Asthma and Immunology (AAAAI). The PPD will conduct the study with review and input from the MAH.

The PPD will receive referrals from the North American PPD network of teratogen information counselling services. The North American PPD network is a network of university and health department based telephone information centers serving pregnant women and health care providers throughout the U.S. and Canada. The PPD network receives voluntary reports of pregnancy and exposures from women and health care providers.

The American Academy of Allergy, Asthma and Immunology (AAAAI) will assit the PPD in raising awareness of the study among healthcare providers who treat women with more severe asthma.

Principal Investigator:

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3. ABSTRACT

Rational and Background

Asthma in women of child bearing age and pregnant women is common. Although the majority of patients with asthma can be effectively treated with available controller medications, a subset of patients do not adequately respond to current standard therapy. Mepolizumab (NUCALA™) is an interleukin-5 antagonist monoclonal antibody (IgG1 kappa) indicated for add-on maintenance treatment of patients with severe asthma aged 12 years and older, and with an eosinophilic phenotype, and is given as 100mg by subcutaneous injection every four weeks. Package labelling in the US and Canada comments that the paucity of data concerning pregnancies is insufficient to inform on drug-associated risks to the fetus or mother. Nonetheless, mepolizmab will be knowigly utilized by pregnant women when they and their doctor believe the risk benefit favors its use. Also,given the the long half-life, inadvertent exposure in pregnancy is likely, even upon immediate cessation of treatment once pregnancy is suspected or confirmed. We therefore propose a pregnancy exposure cohort study to assess the safety of mepoluzimab in pregnancy. Information regarding the safety of mepolizumab in human pregnancy is essential from a public health perspective to help inform clinical practice.

Research Objectives and Study Design

The objectives of the study are to assess the risk or safety of mepolizumab exposure in pregnancy with respect to major birth defects, spontaneous abortion, stillbirth, preterm delivery, and small for gestational age infants. This is a prospective, observational, exposure cohort study of pregnancy outcomes in women exposed to mepolizumab during pregnancy compared to pregnancy outcomes in women with a diagnosis of asthma who have not used mepolizumab during pregnancy but have used other anti-asthmatic medications (treated disease comparison group), and pregnancy outcomes in women not diagnosed with asthma (non-disease comparison group).

Population

The study population consists of three cohorts: 1) a mepolizumab-exposed cohort with exposure to at least one dose of the drug from 8 weeks prior to the first day of the last menstrual period to the end of pregnancy; 2) a disease cohort with treated asthma who have not been exposed to mepolizumab within 8 weeks prior to the first day of the last menstrual period or throughout pregnancy; 3) a non-asthmatic cohort who have no current diagnosis of asthma and have not been exposed to any known human teratogen but may have potentially been exposed to non-teratogenic agents.

Variables

Exposure will be defined as mepolizumab treatment by maternal report and verified by medical record review. Outcome variables include major birth defects, spontaneous abortion, stillbirth, preterm delivery, and small for gestational age. These will be obtained by maternal report and verified by medical record review. Potential confounders or covariates to be collected include age, race/ethnicity, socioeconomic status, pregnancy and health history, lifestyle factors, comorbidities, medication, vaccine and vitamin/mineral exposures, prenatal tests, and measures of disease severity and symptom control.

Data Sources

Information will be obtained through standard maternal interviews conducted in each trimester and postpartum subsequent to study enrollment, and from medical records obtained from obstetric, hospital, pediatric and specialty providers.

Study Size and Timing

The target sample size for the study is 200 women in the mepolizumab-exposed cohort; 300 women in the treated disease cohort; and 300 women in the non-asthmatic cohort. Upon initiation of recruitment, the study is expected to continue for 6.5 years.

Data Analysis

Demographic and baseline characteristics will be compared between the cohorts. The primary analysis will be a comparison of the prevalence rate of major structural defects in live born infants between the mepolizumab-exposed cohort and the treated disease cohort. Where numbers permit, multivariable analyses will be conducted to determine the relationship of mepolizumab with the following primary outcomes: major birth defects, and secondary outcomes; small for gestational age, preterm delivery, spontaneous abortion and stillbirth as numbers permit.

4. AMENDMENTS AND UPDATES

GlaxoSmithKline Document Number	**Date**	**Version**
2016N282524_00	2016-MAY-12	Original
2016N282524_01	2017-NOV-09	Amendment No. 1
The purpose of the amendment is to include specific Adverse Event (AE) definition wording mandated by Health Canada, the Canadian regulatory authority. Text has been updated to state that the Final Report will include safety data related to any GSK product. Text to cover the referral of other ineligible mepolizumab-exposed pregnancies to the Sponsor has also been included. Data collection forms omitted in error from the original protocol have been included in Annex 2. Text has also been updated to reflect descriptive comparisons will be made to the Metropolitan Birth Defects Monitoting Program.		

Amendment or update no	**Date**	**Section of study protocol**	**Amendment or update**	**Reason**
1	09-NOV-17	9	The following wording has been added: • 'An AE can therefore be any unfavourable and unintended sign (including an abnormal laboratory finding) symptom or disease (new or exacerbated) temporally associated with the use of a Medicinal Product. For a marketed Medicinal	The primary purpose of the amendment is to include specific Adverse Event (AE) definition wording mandated by Health Canada, the Canadian regulatory authority.

Amendment or update no	Date	Section of study protocol	Amendment or update	Reason
			Product, this can also include failure to produce expected benefits (i.e. lack of efficacy, with or without an adverse event), and adverse events associated with circumstances of Overdose whether accidental or intentional, Medication Errors, Abuse or effects of drug withdrawal, or Misuse.'	
1	09-NOV-17	9	The following wording has been added: • Other ineligible mepolizumab-exposed pregnancies will also be referred to the Sponsor.'	The text was updated to cover the referral of other ineligible mepolizumab-exposed pregnancies to the Sponsor.
1	09-NOV-17	9	The following wording has been added: 'The final study report	The text was updated to state that the Final Report will include safety data related to

Amendment or update no	Date	Section of study protocol	Amendment or update	Reason
			will additionally include all adverse events that have been explicitly attributed to any known GSK product reported to the Sponsor	any GSK product.
1	09-NOV-17	7.7.1	The following wording has been added: A tertiary objective of the study is to descriptively compare the rate of major birth defects in the mepolizumab-exposed pregnancies, and control groups to external data from the Centers for Disease Control and Prevention (CDC) Metropolitan Atlanta Congenital Defects Program (MACDP), a population-based birth defects surveillance program (Centers for Disease Control and Prevention, 1998).	An additional analysis has been added to reflect PPD standard practice of comparisons to CDC MACDP.
1	09-NOV-17	Appendix 2	The following questionnaires have been added: • MTB Pregnancy Studies: Intake-Demographics & Medical Hx, Version 12, 27January 2015	Data collection forms omitted in error have been included in Annex 2.

Amendment or update no	Date	Section of study protocol	Amendment or update	Reason
			• MTB Pregnancy Studies: Exposure Interview Sheets, Version 12, 29January 2016 • Outcome – Delivery & Birth Information, revised 9/12/2011	

5. MILESTONES

Milestone	Planned date
Start of data collection	2016
End of data collection	2023
Interim Report 1	2017
Interim Report 2	2018
Interim Report 3	2019
Interim Report 4	2020
Interim Report 5	2021
Interim Report 6	2022
Registration in the EU PAS register	Jun-2016 – after Final Protocol is Approved
Final report of study results	2024

6. RATIONAL AND BACKGROUND

6.1. Background

Asthma is a common, life-long inflammatory disease of the airways that affects children and adults of all ages. It is one of the most common long-term diseases worldwide, and can be life-threatening. The prevalence of asthma in adults in the United States is estimated at 7% (National Health Interview Survey 2001-2003). Prevalence is higher in females than males and has considerably increased in recent years (National Health Interview Survey 2001-2003). Symptoms come and go and include shortness of breath, wheezing, chest tightness and cough. The cause of asthma is unknown; however, a family history of asthma, eczema or allergy makes it more likely that an individual will develop asthma.

Although the majority of patients with asthma can be effectively treated with available controller medications, a subset of patients do not adequately respond to current standard therapy. This subset of severe asthma is a heterogenous disease that affects approximately 5-10% of asthmatic patients but is responsible for a disproportionate percentage of the health care costs associated with asthma (Moore 2008; Godard 2002; Antonicelli 2004). About two-thirds of severe asthma patients are reported to have severe eosinophilic asthma in which their symptoms are associated with too many eosinophils (a type of white blood cells) in the blood and in phlegm in the airways.

Mepolizumab is an interleukin-5 antagonist monoclonal antibody (IgG1 kappa) indicated for add-on maintenance treatment of patients with severe asthma aged 12 years and older, and with an eosinophilic phenotype. It is administered as a 100mg subcutaneous injection given every 4 weeks. In randomized controlled trials mepolizumab has demonstrated about a 50% reduction in asthma exacerbations during the treatment period (Haldar 2009).

The prevalence of asthma and severe asthma in women of child bearing age, coupled with the chronic nature of treatment and the preset periodicity with which mepolizumab is given, makes inadvertent exposure in pregnancy likely. The fact that it is given by injection makes the ascertainment of exposed pregnancies early in gestation and documentation of gestational timing of exposure more feasible than in circumstances

where a drug is taken only as needed and not administered by a health care provider. We therefore propose a pregnancy exposure cohort study to assess the safety of mepoluzimab in pregnancy.

6.2. Rationale

Information regarding the safety of mepolizumab in human pregnancy is essential from a public health perspective as inadvertent pregnancy exposure to mepolizumab may take place, and safety information for women who may need this medication is necessary to inform clinical practice.

7. RESEARCH QUESTION AND OBJECTIVE(S)

The purpose of the Mepolizumab Pregnancy Exposure Study is to monitor planned and unplanned pregnancies exposed to mepolizumab and to evaluate the possible teratogenic effect of this medication relative to the primary pregnancy outcome of major birth defects and the secondary pregnancy outcomes of preterm delivery, small for gestational age infants and spontaneous abortion or stillbirth.

8. RESEARCH METHODS

8.1. Study Design

This is a prospective, observational, exposure cohort study of pregnancy outcomes in women exposed to mepolizumab during pregnancy compared to pregnancy outcomes in women with a diagnosis of asthma who have not used mepolizumab but have used other asthma medications during pregnancy (treated disease comparison group), and pregnancy outcomes in women not diagnosed with asthma who have not been exposed to any known teratogens but have potentially been exposed to non-teratogenic agents (see list of known teratogens in Annex 2); (non-disease comparison group). The study is conducted by the PPD located at the PPD The registry relies on voluntary reporting of pregnancy and exposures by women and health care providers

who contact the North American PPD network of teratogen information counselling services.

The study design is appropriate for the study objectives in that mothers are enrolled before the known outcome of the pregnancy, direct measures of relative and absolute risk can be computed, and a range of adverse pregnancy outcomes can be evaluated.

The study design includes the identification of women with mepolizumab exposure in pregnancy, and two appropriate comparison groups. The treated disease group assists with evaluation of the contribution of the underlying maternal disease to adverse pregnancy outcome, and also provides an appropriate comparison group for the mepolizumab-exposed cohort. This is essential, in that maternal asthma itself has been associated with a wide variety of adverse pregnancy outcomes (Rejnö et al, 2014; Namazy et al, 2013; Murphy et al, 2011). The non-asthmatic comparison group allows for comparison of asthmatic to non-asthmatic women, and if the distribution of underlying disease severity is similar in both the mepolizumab and the treated disease group as possible within the current clinical environment,, this could further illuminate the potential contribution of the disease (and disease-severity) to outcomes.

Women who agree to enroll will be consented orally over the telephone, and will then complete the initial telephone interview. Depending on the gestational timing of enrollment, a number of subsequent telephone interviews will be conducted during pregnancy and after birth. Medical records for both the women and infant will be obtained and abstracted for information to validate exposures and outcomes. Enrolled women will be followed until the completion of pregnancy and infants followed up to one year after birth to determine the outcome of pregnancy with respect to primary and secondary study outcomes (refer to Table 5, Section 8.7.1 for more information on the timing of study events)

8.2. Study Population and Setting

The study population consists of three cohorts of pregnant women (See Section 8.6 for sample size).

Participants will be recruited into the three cohorts on the basis of the following inclusion/exclusion criteria:

Cohort 1: Mepolizumab Exposed

Inclusion Criteria

- Eligible subjects will be currently pregnant women diagnosed with asthma who contact the PPD and who have been exposed to mepolizumab for any number of days, at any dose, and at anytime from 8 weeks before the first day of the last menstrual period up to and including the end of pregnancy.
- Eligible subjects will be currently pregnant women who agree to the conditions and requirements of the study including the interview schedule and release of medical records.

Exclusion Criteria

- Women will not be eligible for Cohort 1 if they first contact the PPD PPD after prenatal diagnosis of a major birth defect, although data will be collected on these retrospective reports and descriptive information will be included in annual and final study reports.
- Women will not be eligible for Cohort 1 if they have enrolled in the study with a previous pregnancy.

Cohort 2: Treated Disease Comparison

Inclusion Criteria

- Eligible subjects will be currently pregnant women diagnosed with asthma and who are exposed to asthma medications for any number of days, at

any dose, and at anytime from the first day of the last menstrual period up to the date of enrolment, who contact the PPD but who were not exposed to mepolizumab during pregnancy or within 8 weeks prior to the first day of the last menstrual period.

- Eligible subjects will be currently pregnant women who agree to the conditions and requirements of the study including the interview schedule and release of medical records.

Exclusion Criteria

- Women who have received treatment with mepolizumab but who are not eligble for Cohort 1 will not be eligble for Cohort 2.
- Women will not be eligible for Cohort 2 if they first come in contact with the PPD after prenatal diagnosis of a major birth defect.
- Women will not be eligible for Cohort 2 who have enrolled in the study with a previous pregnancy.

Cohort 3: Non-Asthmatic Comparison

Inclusion Criteria

- Eligible subjects will be currently pregnant women who contact the PPD PPD who were not exposed to any known teratogenic agents as determined by the PPD (list in Annex 2) for any number of days, at any dose, from the first day of the last menstrual period up to and including the end of pregnancy, and who do not have a current self-reported diagnosis of asthma. Eligible women may potentially have been exposed to non-teratogenic agents during this time period.
- Eligible subjects will be currently pregnant women who agree to the conditions and requirements of the study including the interview schedule and release of medical records.

Exclusion Criteria

- Women who have been exposed to any known teratogenic agents as determined by the PPD (list in Annex 2) for any number

of days, at any dose, from the first day of the last menstrual period up to and including the end of pregnancy will not be eligible for Cohort 3.

- Women will not be eligible for Cohort 3 if they have a current self-reported diagnosis of asthma.
- Women will not be eligible for Cohort 3 if they come in contact with the PPD after prenatal diagnosis of a major birth defect.
- Women will not be eligible for Cohort 3 if they have enrolled in the study with a previous pregnancy.

Other exclusions:

- Any pregnancy reported retrospectively, after the outcome is known, will not be eligible for enrollment but those that are reported, including those with adverse outcomes, will be referred to the Sponsor as indicated in Section 10.

The cohort study will be conducted by investigators at the PPD for the PPD as the cohort arm of the Vaccines and Medications in Pregnancy Surveillance System (VAMPSS) in collaboration with the American Academy of Allergy, Asthma and Immunology (AAAAI). The PPD organization is a network of university and health department based telephone information centers serving pregnant women and health care providers throughout the U.S. and Canada (Leen-Mitchell et al, 2000). These services receive spontaneous telephone inquiries from women who are pregnant or considering pregnancy as well as from health care providers about the safety or risk associated with environmental exposures in pregnancy, including medications. Trained Teratogen Information Specialists at each site provide appropriate risk assessment and referral for all patient and health care provider callers free of charge. These services also provide a basis for collaborative research such as this study. Thus, individual Teratogen Information Services located throughout the U.S. and Canada will serve as a primary source of referrals not only for mepolizumab-exposed pregnancies but also for similarly-ascertained pregnant women with a diagnosis of asthma but not treated with mepolizumab, and similarly-ascertained pregnant women not diagnosed with asthma who have not used mepolizumab nor any known human teratogen.

Other methods of raising awareness about the study are meeting exhibits at professional practice meetings nationally, regionally and locally, direct mail to health care providers, media, social media, and website. Because treatment with mepolizumb will require expertise in treating severe asthma for administration, these health care providers will be a particular focus of awareness activities. With the assistance of the American Academy of Allergy, Asthma and Immunology, providers who treat women with more severe asthma will be a priority target for awareness.

Women who are interested in hearing more about the study will be referred to or will self-refer themselves to the PPD for more information. Referrals may be by the woman's HCP or by the PPD service that the woman contacts directly. Those women who are interested and meet the study criteria as described in Section 8.1 will be invited to enroll. Women who agree to enroll will complete the oral consent process over the telephone, and will then complete the initial telephone interview. Depending on the gestational timing of enrollment, subsequent telephone interviews will be conducted according to the Schedule shown in Table 5 Section 8.7.3. Follow up interviews will be conducted by telephone, and medical records for both the women and infant will be obtained and abstracted for information to validate exposures and outcomes.

The study population by definition consists of volunteers; however, they are expected to represent a wide variety of maternal age, race/ethnic background, and health status (Chambers et al, 2013; Chambers et al, 2010; Bakhireva et al, 2008; Chambers et al, 1996). The participants will reside anywhere in the U.S. or Canada. By definition, the study paricipants are all female, as this is a pregnancy study. The age of participants is expected to be between 18 and 45; however, women under the age of 18 may enroll with parent/guardian consent, and women over the age of 45 may also enroll.

Upon initiation of recruitment, the study is expected to continue recruitment for five years. Infant follow-up will continue for one year after the last live birth following recruitment of the last subject.

Table 1 Recruitment Timetable

	Year 1	Year 2	Year 3	Year 4	Year 5
Cohort 1 Mepolizumab exposed group	20	40	55	55	30
Cohort 2 Asthmatic comparison group	30	60	83	83	44
Cohort 3 Non-asthmatic comparison group	30	60	83	83	44

8.3. Variables

8.3.1. Exposure definitions

Mepolizumab-exposed cohort: Exposure is defined as any dose of mepolizumab for any length of time from 8 weeks prior to the first day of the last menstrual period (LMP) through the end of pregnancy, as reported by the mother and validated through medical record review. The 8 week cut-off prior to LMP is based upon the terminal half life of mepolizumab of approximately 20 days (clearance of mepolizumab is based on five half-lives).

Exposure is defined as yes/no in the first trimester of pregnancy for major birth defects as the primary outcome. For this study, first trimester exposure is defined as any dose between eight weeks prior to 1st day of last menstrual period and 13 weeks after 1st day of last menstrual period. However, exposure to mepolizumab in the second (>13 weeks through 26 weeks after 1st day of last menstrual period) and third trimester (>26 weeks after 1st day of last menstrual period) will be considered for those selected major birth defects that are potentially biologically plausibly related to later pregnancy exposures, e.g., craniosynostosis. For spontaneous abortion, the exposure is defined as yes/no in the first 20 weeks' of gestation, and for the other secondary outcomes, exposure is defined as yes/no anytime in pregnancy.

Gestational age is determined by an algorithm using best available information. If the first day of last menstrual period and cycle length is known, and ultrasound measures of dating are not discrepant according to standard conventions depending on the timing of the ultrasound, the menstrual period dating will be used to calculate gestational age. If the menstrual period dating is uncertain or unknown, and an ultrasound is available, the earliest (and therefore more precise) available ultrasound dating will be used. In the event of absence of any information on dating, the delivery record best estimate of gestational age will be used.

In exploratory analyses, duration of mepolizumab use in pregnancy, specific gestational timing, and dose of mepolizumab will be explored. In the asthmatic comparison group, duration of other asthma medications duratio use in pregnancy, specific gestational timing, and doses will be explored.

8.3.2. Outcome definitions

Major Birth Defects: a major structural defect is defined and classified using the CDC coding manual (http://www.cdc.gov/ncbddd/birthdefects/documents/MACDPcode0807.pdf), reported by the mother and validated through the medical record. The CDC coding manual is utilized to classify defects reported through the ongoing population-based Metropolitan Atlanta Congenital Defects Program (MACDP) and is based on agreed-upon criteria by CDC investigators for major structural defects regardless of etiology. Infant medical records are abstracted and reviewed by the study research team leaders. Final validation of the classification of all major birth defects reported in the study will be conducted by a VAMPSS Investigator with expertise in the diagnosis of birth defects.

Preterm Delivery: preterm delivery is defined as a spontaneous or induced delivery at <37 gestational weeks, reported by the mother and validated through the medical record. Please refer to Section 8.3.1 for further description of the method for defining gestational age and therefore preterm birth.

Small for Gestational Age (SGA) Infants: Live born infants who are $\leq 10^{th}$ centile on birth weight for infant sex and gestational age will be considered small for gestational age.

The U.S. Centers for Disease Control and Prevention (NCHS) growth charts will be used for full term infants, and the Britton growth charts will be used for preterm infants (Britton et al, 1993). The outcome of birthweight is reported by the mother and validated through the medical record.

Spontanous Abortion: Spontanous abortion is defined as spontaneous pregnancy loss prior to 20 weeks' gestation. In this study, since women enrol after recognition of pregnancy, spontaneous abortions are only identified after enrollment in clinically recognized pregnancies. This outcome is reported by the mother and validated through the medical record.

Stillbith: Stillbirth is defined as a fetal death that occurs >20 weeks' gestation. This outcome is reported by the mother and validated through the medical record.

8.3.3. Confounders and effect modifiers (Abstraction forms in Annex 2)

The potential confounders/effect modifiers listed below will be considered in multivariable analyses, as well as others that are relevant to each of the study outcomes:

- Maternal and paternal age
- Previous pregnancy history: gravidity and parity, previous spontaneous abortions and elective terminations
- Maternal and paternal race/ethnicity, education, occupation, socioeconomic status
- Pre-pregnancy body mass index
- Previous preterm delivery
- Previous child with a birth defects
- Maternal conditions: e.g., depression, diabetes (see abstraction forms in Annex 2)
- Maternal exposures: gestational timing and dose of all over-the-counter and prescription medications, including all asthma medications used during pregnancy; vitamin and mineral supplements, herbal products; illnesses; fever; vaccinations
- Prenatal testing: ultrasound and other prenatal tests; timing in gestation and results
- Pregnancy complications: e.g., pregnancy induced hypertension, gestational diabetes
- Maternal lifestyle habits: cigarette smoking, alcohol consumption and illicit drug use

- Asthma related covariates: Asthma Control Test at each maternal interview, years since diagnosis of asthma, hospitalizations or unscheduled asthma visits for asthma exacerbations throughout pregnancy, use of systemic steroids for asthma exacerbations, and classification of asthma severity at enrollment based on women self-reported prescription classified by GINA (2016) guidelines.

Methods for identifying and controlling for these confounders and/or effect modifiers are described in Section 8.7.1. The Data Analysis Plan (DAP) will provide greater detail on the definitions of, the indentification of and the controlling for confounders and/or effect modifiers.

8.4. Data sources

Maternal Interviews: In all three study groups, data are collected by semi-structured maternal telephone interview on two to four occasions during and shortly after completion of pregnancy. The interviews include data on exposure timing, dose, and duration for all medications, including mepolizumab, taken anytime in pregnancy as well as data on a wide variety of confounders (See Section 8.3.3).

For women exposed to mepolizumab or other asthma medications, information on disease severity/symptom control from the Asthma Control Test is obtained directly from the mother at each maternal telephone interview. In addition, information on asthma-related hospitalizations and physician visits is collected at the enrollment interview and each of the subsequent maternal interviews. At the conclusion of pregnancy, regardless of the outcome, participants are interviewed about the outcome including presence or absence of birth defects, pregnancy and infant complications and infant size. At this time point the Asthma Symptom Control test questions are asked again to reflect the last four weeks of pregnancy. In addition, asthma treatment regimen at enrollment according to GINA guidelines will be used to classify disease severity.

Medical Records: Mothers are asked to release medical records to the study investigators from their obstetrician or other obstetric provider, specialty care provider such as allergist/pulmonologist, hospital of delivery, pediatrician, and any other health care provider involved in the pregnancy. These records are abstracted and used to validate pregnancy outcomes and when necessary to provide details regarding timing or dose of

mepolizumab and other asthma medications in the absence of clear information from maternal report. Self-reported prescriptions used for GINA classification will be validated with medical record information where available. Pre-defined definitions for each of the study outcomes are used for classification.

Validation of classification of major birth defects, the primary outcome, is conducted periodically and before each annual and final study reports by VAMPSS Investigators, who have the relevant expertise to review the outcomes.

Table 2 Variables collected per cohort

Variable	Cohort 1 Mepolizumab-exposed	Cohort 2 Asthmatic comparison	Cohort 3 Non-Asthmatic comparison
Maternal Interviews			
Exposure timing[1]	√	√	√
Dose[1]	√	√	√
Duration of medications[1]	√	√	√
Confounders/effect modifiers	√	√	√
Disease severity (ACT & asthma treatment regimen)	√	√	X
Asthma related hospitalizations and physician visits	√	√	X
Pregnancy outcome	√	√	√
Birth defects	√	√	√
Pregnancy complications	√	√	√
Infant complications	√	√	√
Infant size	√	√	√
Medical Record Abstraction[2]			
Pregnancy validation	√	√	√
Pregnancy outcome validation	√	√	√
Exposure timing validation[1]	√	√	√
Dose validation[1]	√	√	√
Self-reported	√	√	√

Variable	Cohort 1 Mepolizumab-exposed	Cohort 2 Asthmatic comparison	Cohort 3 Non-Asthmatic comparison
prescription validation[1]			
Major birth defects[3]	√	√	√

[1]For cohort 1& 2 primarily asthma medication will be assessed.
[2] Information will be dependent on the completeness of the medical record
[3]Performed periodically and before each annual and final study reports

8.5. Study size

The proposed sample sizes in each of the three study groups are as follows:

- 200 women exposed to mepolizumab at any time 8 weeks prior to 1st day of last menstrual period and throughout pregnancy
- 300 women with asthma, unexposed to mepolizumab, aiming to represent the full spectrum of asthma severity with emphasis on severe patients
- 300 non-asthmatic controls

Table 3 Risk and safety estimates for mepolizumab-exposed pregnancies relative to the primary comparison group for selected outcomes available from the cohort arm PPD after 4 years of enrollment and collection of outcomes at birth; all estimates use an α-level of 0.05.*

Outcome	**No. Exposed N = 200**	**No. Unexposed Asthmatic N = 300**	**Risk****	**Safety*****
All major birth defects	180	270	3.0	2.8
Preterm birth	180	270	2.2	2.0
SGA infant	180	270	1.9	1.8

*Sample size for all outcomes shown in the table based on 90% of enrolled pregnancies ending in live birth with completed outcome; sample size for all birth defects based on prevalence of 3% in the asthmatic comparison group; sample size for preterm birth based on prevalence of 7% in the asthmatic comparison group (Bakhireva et al, 2008); sample size for small for gestational age infants (SGA) based on prevalence of 10% in the asthmatic comparison group. Power calculations performed in OpenEpi software.
** Minimum RR detectable with 80% power.
***Upper 95 % confidence bound for RR=1.

The sample size is considered plausible based on the experience of the PPD research group with previous studies of asthma in pregnancy, but plausibility for the current study is unknown. Although it is unknown to what extent mepolizumab will be used by pregnant women, experience with recruitment in the omalizumab (Xolair) registry provides some support for the proposed sample size. In six years of recruitment, the EXPECT (omalizumab) registry recruited 191 exposed pregnancies (Namazy et al, 2015).

It is expected, based on experience with the EXPECT registry for omalizumab that virtually all mepolizumab-exposed participants will have exposure sometime in the first trimester and will typically enroll in the study upon recognition of pregnancy making the entire cohort analysable for the primary outcome and all secondary outcomes. It is possible that some participants in all three cohorts will enroll after 20 weeks' gestation and therefore will not be included in the analysis of spontaneous abortion.

8.6. Data management

Maternal interviews are conducted at enrolment and in each trimester thereafter, depending on the gestational age at which the mother enrolls. An additional outcome interview is conducted by telephone after the end of pregnancy, typically this occurs within 6 weeks but could be up to one year after . These interviews are conducted by telephone and typically take between 30 minutes and 1 hour to complete. The interviews are semistructured and follow interview data collection forms to ensure that all study questions are addressed. Data from each interview form is entered into the study database at the end of the interview by the same person who conducted the interview. Medical records are requested from the hospital of delivery (maternal and neonatal information), obstetric provider (maternal information), paediatrician (neonatal/infant) and any specialty physician (maternal and neonatal/infant information) . When records are

received and catalogued, data is abstracted by trained personnel from each record using a standard abstraction form and entered into the study database. Hard copies of all study forms and medical records are retained in the PPD at the PPD PPD Several logic checks are built into the study database. In addition, all data entry is validated for a series of predefined critical variables and a random subset are validated for non-critical variables. Access to the database is controlled by password with administrative level access required for certain operations. Hard copies of patient files and subject signed consent forms will be kept in locked file rooms and/or locked cabinets under the supervision of the study investigators.

8.6.1. Data handling conventions

Major birth defects are classified using the CDC coding manual (http://www.cdc.gov/ncbddd/birthdefects/documents/MACDPcode0807.pdf) by the Study Manager. All defect classifications are reviewed by co-Investigators. All prenatal exposures to medications and vaccines are coded using the Slone Drug Dictionary (http://sites.bu.edu/slone-drug-dictionary/).

Twins or higher order multiples are handled as one pregnancy outcome. For example, if the pregnancy ends in at least one live born infant, the outcome is considered a live born outcome. If either or both twins have a major birth defect, the outcome is considered one major birth defect outcome. Twins are excluded from analyses of preterm delivery and small for gestational age infants.

Lost-to-follow-up status is designated if a participant withdraws from the study, or if the study staff are unable to make contact with the study participant within 12 months of the estimated end of pregnancy in order to obtain outcome information.

Table 4 Denominators by Outcome

Outcome	Denominator
Major Birth Defects Among Live Births	Pregnancies ending in live birth; with exposure in 1st trimester for mepolizumab cohort, and other comparison groups at least one malformed infant in an individual pregnancy is considered one malformed outcome
Major Birth Defects Among All Pregnancies	Pregnancies with any outcome excluding those lost-to-follow-up; with exposure in 1st trimester for mepolizumab cohort, and other comparison groups; at least one malformed foetuses/infants in an individual pregnancy is considered one malformed outcome
Spontaneous Abortion	Pregnancies enrolled in the study prior to 20 weeks' gestation with at least 1 follow-up data collection point after enrollment date. Exposure can occur any time in pregnancy prior to event.
Preterm Delivery	Pregnancies enrolled prior to 37 weeks gestation and ending in at least one live born infant; excluding twins or higher order multiples due to inherent higher risk of preterm birth in multiples. Exposure can occur any time in pregnancy prior to event.
Small for Gestational Age Infants	Pregnancies ending in at least one live born infant; excluding twins or higher order multiples due to the inherent higher risk of reduced birth size in multiples. Exposure can occur any time in pregnancy prior to event.
Still Birth	All pregnancies, excluding lost-to-follow-up. Exposure can occur any time in pregnancy prior to event.

Coding of outcomes is performed by the study staff using the definitions provided in the protocol. The primary source of information on exposure and outcome is the participant. Validation of study outcomes is performed using medical records. In the case of discrepancies in the two sources of report, the participant is recontacted to determine if the discrepancy can be resolved, and an SOP for adjudicating these decisions has been developed.

Missing values for the critical data for PPD studies are typically very few and nearly always less than 10%. There is generally no need to include imputation strategies; however, depending on the prevalence of missingness, sensitivity analyses will be conducted. These will be documented in the DAP.

8.6.2. Resourcing needs

Not applicable.

8.6.3. Timings of Assessment during follow-up

Table 5 Timing of Cohort Enrollment, Interviews, Medical Records

	<20 weeks gestation	16-20 weeks gestation*	32-34 weeks gestation	0-6 weeks after delivery	0-12 months after delivery
Contact / Referral	√	√	√		
Enrollment and Consent	√	√	√		
Intake Interview	√	√	√		
Interim Interview I		√			
Interim Interview II			√		
Outcome Interview				√	
Medical Record Release Forms Sent for Signature				√	
Medical Record Review					√

8.7. Data analysis

8.7.1. Essential analysis

A detailed Data Analysis Plan will be prepared and finalised prior to the conduct of any study analysis or reporting.

Primary Endpoint: The primary endpoint will be major structural defects among live born infants. The primary comparison will be between the first-trimester mepolizumab-exposed group and the treated disease cohort.

Secondary comparisons for major birth defects will be conducted with the denominator including all pregnancies ending in live birth, spontaneous abortion, stillbirth or elective termination, excluding lost-to-follow-up, comparing first-trimester mepolizumab-exposed to the treated disease cohort.

Additional secondary comparisons will be made between the first-trimester mepolizumab-exposed group and the treated asthma and non-asthmatic cohort. A tertiary objective of the study is to descriptively compare the rate of major birth defects in the mepolizumab-exposed pregnancies, and control groups to external data from the Centers for Disease Control and Prevention (CDC) Metropolitan Atlanta Congenital Defects Program (MACDP), a population-based birth defects surveillance program (Centers for Disease Control and Prevention, 1998).

Secondary Endpoints:

Preterm Delivery: After exclusion of twins or higher order multiples, the rate of pregnancies ending in live birth <37 weeks' gestation will be compared between the mepolizumab group enrolled and exposed anytime in pregnancy prior to 37 weeks' gestation and the treated disease and non-asthmatic cohorts enrolled prior to 37 weeks' gestation.

Small for Gestational Age Infants: After exclusion of twins or higher order multiples, the proportion of pregnancies ending in a live born infant $\leq 10^{th}$ centile of birth

weight for gestational age and sex will be compared between the mepolizumab-exposed group and the treated disease and non-asthmatic cohorts.

Spontaneous Abortion: For those women in all three cohorts who enrolled in the study prior to 20 weeks' gestation, the rate of spontaneous abortion accounting for left truncation will be compared between those in the mepolizumab group enrolled and exposed any time in pregnancy prior to 20 weeks' gestation and the treated disease and non-asthmatic cohorts.

Stillbirth: The rate of pregnancies ending in stillbirth will be compared between those in the mepolizumab-exposed group and the treated disease and non-asthmatic cohorts.

Statistical methods: Descriptive tables will be prepared for characteristics of each of the cohorts in each interim and final report displaying means and standard deviations, or proportions and percentages.

For the primary endpoint of major structural defects and for the secondary endpoint of small for gestational age infants, crude comparisons will be made using exact methods to develop relative risk estimates and their 95% confidence intervals.

For the secondary endpoints of preterm delivery, spontaneous abortion, and stillbirth, survival methods will be used (Kaplan Meier) to estimate crude rates and confidence intervals accounting for gestational timing of enrollment in the study.

Adjusted analyses producing rates and 95% confidence intervals, where numbers permit, will be conducted for major birth defects and small for gestational age infants using logistic regression. Adjusted analyses producing rates and 95% confidence intervals, for preterm delivery, spontaneous abortion and stillbirth, where numbers permit, will be conducted using Cox Proportional Hazards. A minimum of 30 events in the overall analysis sample is required for adjusted analysis for those outcomes assessed with logistic

regression. A minimum of 20 events in the overall analysis sample is required for adjusted analysis for those outcomes assessed with Cox Proportional Hazards.

Confounders will be considered for each adjusted analysis separately, using the method of change in estimate of the effect of exposure to mepolizumab by 10% or more. If one confounder is identified, direct adjustment will be performed. However, given the expected low frequency of events in a study of this size, if two or more confounders are identified in any given analysis, a propensity score approach for adjustment will be considered.

Appropriateness of models will be assessed graphically and by standard statistical methods

8.7.2. Exploratory analysis

Exploratory analyses addressing potential effect modifiers such as Asthma Control Test measures of disease symptom control, and measures of asthma exacerbation will be addressed. In addition, subanalyses based on length and gestational timing as well as dose of exposure to mepolizumab will be performed. Additionally, stratified analyses based on prenatal diagnosis performed prior to enrollment in the study will be conducted for the primary endpoint. The purpose of this analysis is to address the inherent bias in excluding women at the time of enrollment in the cohort study who have already received prenatal diagnosis of a major birth defects, but including women who have already had a normal result or prenatal diagnosis for major birth defects prior to enrollment. Therefore, the planned stratified analysis will compare the birth prevalence of major birth defects among the subset of women enrolled in the cohorts *prior to* prenatal diagnostic testing for fetal structural anomalies, to the birth prevalence of major birth defects among the subset of women enrolled in the cohorts *after* prenatal diagnostic testing for fetal structural anomalies. Subanalyses excluding chromosomal or known genetic anomalies (based on specific defects categorized by expert based on know genetic etiology) will also be conducted.

8.7.3. General considerations for data analyses

The general approach to controlling for confounding is to evaluate each relevant confounder for the specific outcome to determine if inclusion of the confounder in a model containing exposure to mepolizumab changes the estimate of the effect of exposure by 10% or more. The confounders will be assessed univariately and those confounders that are identified are incorporated into multivariate analyses as described in the statistical analysis Section 8.7.1. Further details will be contained in the DAP. Control for confounding by indication is addressed by comparison to the treated disease group. However, as described in exploratory analyses in Section 8.7.2, attention to measures of disease symptom control and underlying severity will also be addressed by subgroup and stratified analysis.

8.8. Quality control and Quality Assurance

As noted in Section 8.7, quality control measures are in place throughout the entire period of data collection and data entry. Training and retraining of study staff is monitored per study SOP, and validation of data entry for critical study variables is conducted for 100% of study participant interactions. Data exported for interim and final analyses for this study are checked for logical errors, and range checks are performed. All major birth defect classifications are verified by the study investigators.

Data are reviewed on an interim basis by the VAMPSS external advisory committee. This committee consists of representation from the U.S. Centers for Disease Control and Prevention Center for Birth Defects and Developmental Disabilities, the Eunice Kennedy Shriver National Institute of Child Health and Development, a biostatistician, a consumer representative, and disease-specific specialty representatives. This standing committee meets annually and reviews all interim and final study reports as well as manuscripts that are produced from the study results. The committee comments on the study progress and poses questions that arise which are addressed by the investigators.

Final data sets are cleaned and utilized for preparation of the analyses and study reports. All analyses (coding and output) are reviewed by the lead study statistician and at least one other staff statistician. Study reports are reviewed by the Study Manager and the

Investigators. All data sets and analytic files are archived indefinitely at the PPD and analyses can be replicated as necessary.

8.9. Limitations of the research methods

Potential limitations of the research methods are as follows:

The study relies on a volunteer sample which may or may not be entirely representative of all women who take mepolizumab during pregnancy. However, for a new product used for a relatively rare condition this is likely one of the only methods of obtaining safety information for pregnancy exposures because of the ability to target key patient and provider groups, particularly physicians who treat patients with more severe asthma, to increase awareness about the study.

It is unknown what the distribution of timing of exposure will be in the mepolizumab-exposed cohort. In the EXPECT registry for omalizumab, pregnancy exposures were predominately limited to the first trimester (Namazy et al, 2015). Therefore, it is possible that the study will only be able to address the risks or safety of exposures that occur in the first four to six weeks of pregnancy before women typically recognize that they are pregnant.

The sample size that is achievable for a new product used for a relatively rare condition limits the power to detect differences, especially for rare outcomes such as major birth defects. The study will also be limited in ability to address increased risks for spontaneous abortion as the highest risk for spontaneous abortion occurs in the gestational weeks prior to when women would typically enroll in the study. However, based on expected gestational timing of enrolment, spontaneous abortion rates in late first trimester and early second trimester will be analyzable.

Strengths of the study design are the ability to build on the referral network of PPD member services across the U.S. and Canada to identify mepolizumab-exposed pregnancies as well as appropriate comparison group pregnancies, the PPD research groups' track record of excellent subject retention (<5% lost to follow-up). In addition,

the study design allows for appropriate comparison to a treated disease group, and for appropriate attention to confounding or effect modification.

8.9.1. Study closure/uninterpretability of results

In consultation with the Scientific Advisory Committee, discontinuation of the study will be considered at such time as:

- sufficient information has accumulated to meet the scientific objectives of the study
- other methods of gathering appropriate information become achievable or are deemed preferable
- the feasibility of collecting sufficient information diminishes to unacceptable levels because of low exposure rates, poor enrollment, or losses to follow up. Upon initiation of recruitment, the study is expected to continue to recruit for five years with recruitment ranging from 20-55 patients exposed to mepolizumab per year. Regular review of enrollment numbers will be performed and numbers compared to the sponsor's data and other external data on the uptake of mepolizumab to determine if uptake among women of reproductive age is consistent with enrollment rates in the cohort study. One of the sources of these data is the database arm of VAMPSS which represents a large population-based source of information on pregnancy exposures. Enrollment will also be reviewed with respect to key awareness activities.
- If the Sponsor discontinues manufacturing mepolizumab they may withdraw from the study upon written notification.

8.10. Other aspects

None

9. PROTECTION OF HUMAN SUBJECTS

9.1. Ethical approval and subject consent

The study is approved through the PPD (Institutional Review Board or IRB). All study participants must agree to the IRB-approved oral consent form at the time of enrollment and before completing the intake interview. Each participant must subsequently sign the IRB-

approved informed consent document in order to continue to participate in the Registry. Each participant is also asked to sign for release of medical information to allow the Registry to obtain information on the pregnancy and the pregnancy outcome from the participant's obstetrician, the hospital of delivery, and any other health care specialist, and for the infant from the infant's pediatrician.

The original oral and signed informed consent documents, and copies of the medical records release forms will be maintained at the Research Center.

Pregnant women under the age of 18 who are eligible for the study and who wish to participate will require written consent of their parent or guardian prior to the initial intake interview and written assent from themselves. Consent/assent forms and study participation materials are available in English or Spanish.

9.2. Subject confidentiality

The Registry makes every effort to assure participant confidentiality within the Registry. Personally identifiable information is maintained in secure files with restricted access limited to only authorized personnel.

Registry Investigators, data collection and management staff reside at the PPD located at the PPD PPD These personnel, under the supervision of the Investigators, have access to the physical files and electronic data, have documented completion of human subjects research training, and are listed individually as authorized to have access to the study data on the study IRB-approved research plan.

Sponsor representatives through the Registry Scientific Advisory Committee have access to de-identified summary data as part of the periodic annual review and the final study report. Final study data files for analysis are stripped of identifiers and archived without personal identifiers.

Care will be taken to ensure that no individual participant is identifiable in the data tables published in the Annual Reports, or other presentations or publications.

10. MANAGEMENT AND REPORTING OF ADVERSE EVENTS/ADVERSE REACTIONS

A Safety Management Plan (SMP) will be developed for the study and will provide detailed information on the study specific pharmacovigilance processes and procedures.

This study adopts the following ICH definitions:

Adverse event: *Any untoward medical occurrence in a patient or clinical investigation subject administered a pharmaceutical product and which does not necessarily have to have a causal relationship with this treatment.*

- An AE can therefore be any unfavourable and unintended sign (including an abnormal laboratory finding) symptom or disease (new or exacerbated) temporally associated with the use of a Medicinal Product. For a marketed Medicinal Product, this can also include failure to produce expected benefits (i.e. lack of efficacy, with or without an adverse event), and adverse events associated with circumstances of Overdose whether accidental or intentional, Medication Errors, Abuse or effects of drug withdrawal, or Misuse.

Serious adverse event: *any untoward medical occurrence that at any dose that 1) results in death, 2) is life threatening, 3) requires inpatient hospitalization or prolongs existing hospitalization, 4) results in persistent or significant disability/incapacity or 5) is a congenital anomaly.*

- Medical and scientific judgement should be exercised in deciding whether expedited reporting is appropriate in other situations, such as important medical events that may not be immediately life-threatening or result in death or hospitalisation but may jeopardise the patient or may require intervention to prevent one of the other outcomes listed in the definition above. These should also usually be considered serious. Examples of such events are intensive treatment in an emergency room or at

home for allergic bronchospasm; blood dyscrasias or convulsions that do not result in hospitalisation; or development of drug dependency or drug abuse.

The purpose of the Mepolizumab Pregnancy Exposure Study is to monitor planned and unplanned pregnancies exposed to mepolizumab and to evaluate the possible teratogenic effect of this medication. For mepolizumab exposed pregnancies pre-defined specific pregnancy outcomes that are classified as serious adverse events (SAE's) will be identified and reported. These selected SAEs include Major Congenital Malformation (MCM), spontaneous abortion, still birth and neonatal death. These events will be reported to the sponsor's safety department within 24 hours.

Additionally, for mepolizumab exposed pregnancies, all other adverse events, which are ascertained as part of the routine study data collection, will be abstracted from maternal interiews (and/or from available medical records) by dedicated and trained study staff. Each of the events will be assessed for causal relationship to mepolizumab exposure by a consulting physician with expertise in asthma and allergy treatment of women of reproductive age. This assessment of events will be performed on a monthly basis by the consulting physician. Only those adverse events attributed by the consulting physician to mepolizumab will be reported to the sponsor's safety department within 24 hours.

Any pregnancies in subjects exposed to mepolizumab reported to the PPD PPD retrospectively, after the outcome is known, will not be enrolled and will be referred to the Sponsor. Other ineligible mepolizumab-exposed pregnancies will also be referred to the Sponsor.

If during the study, the PPD investigators become aware of an adverse event explicitly attributed to any known GSK product, this will also be reported to the sponsor's safety department within 24 hours.

The interim and final study reports will include the serious adverse events that are the study endpoints as part of the hypotheses being tested, and a summary of all mepolizumab attributed adverse events. The final study report will additionally include

all adverse events that have been explicitly attributed to any known GSK product reported to the Sponsor.

11. PLANS FOR DISSEMINATING AND COMMUNICATING STUDY RESULTS

11.1. Target Audience

Healthcare providers treating women with asthma and regulatory authorities.

11.2. Study reporting and publications

Key design elements of this study will be posted in publicly accessible databases. Furthermore, key results of this study will be posted in publicly accessible databases within the required time-frame from completion of the data collection where applicable.

Interim reports will be prepared on study progress annually. Upon closure of the study, a final report will be generated by the VAMPSS study investigators which will be submitted by GSK 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 VAMPSS investigators and in accordance with the current guidelines for STrengthening the Reporting of OBservational studies in Epidemiology (von Elm 2008). VAMPSS investigators will follow the international committee of medical journal editors (ICMJE) recommendations for authorship and acknowledgements. GlaxoSmithKline will be entitled to view the results and interpretations included in the manuscript prior to submission for publication.

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13. APPENDICES

ANNEX 1. LIST OF STAND-ALONE DOCUMENTS

Tables and Figures

Core table shells and figures will be included in the Data Analysis Plan

Stand-Alone Documents

None

ANNEX 2. Additional Information

Known Human Teratogens

**For most agents, consider post-conception exposure only. Exceptions: acitretin and etretinate (see notes next to these exposures).*

Exposure	Notes
ACE Inhibitors	
Acitretin	Any exposure within 2 years of LMP.
Alcohol, Heavy	**>5 drinks per week or ≥ 5 drinks in 1 day: Week = Sun-Sat**
Aminopterin	
Antiseizure / Anticonvulsant Medications	
Antineoplastics, Other	
Cocaine	
Cytomegalovirus (CMV)	
Diabetes, Type I	Type II Diabetes is also a disqualifier
Etretinate	Any exposure within 10 years of LMP.
Fever, High	**102 degrees or higher for 24 hours or longer**
Fluconazole, Systemic	
Isotretinoin	
Lenalidomide	
Lithium	
Methimazole	
Methotrexate	
Propylthiouracil (PTU)	
Radiation, High Dose	≥ 5 rads to the uterus
Rubella	
Thalidomide	
Toxoplasmosis	
Varicella	Primary case of chicken pox
Warfarin (Coumadin, Jantoven) derivatives	

PERSONAL INFORMATION

PREVIOUSLY ENROLLED? ***Y N***
If Yes, previous PREG ID # (s):
1.) PREG #: _____
2.) PREG #: _____
3.) PREG #: _____

PPD Case Number: _____

Primary Group: _____ *Other Enrollments →*

Budget Number: _____

Enrollment Date: _____
(= consent date)

CTIS: *Yes* *No*

LMP: _____

EDC: _____

1.) Budget Number: _____
Group: _____
Enrollment Date: _____
2.) Budget Number: _____
Group: _____
Enrollment Date: _____
3.) Budget Number: _____
Group: _____
Enrollment Date: _____

Name: _____ Mother's DOB: _____

Address: _____ Subject's Initials: _____

Best Home Phone: _____ *Okay to leave message:* Yes No

Best Work Phone: _____ *Okay to leave message:* Yes No

Best Cell Phone: _____ *Okay to leave message:* Yes No

Best time to contact: _____ *Okay to talk to anyone in household?* Yes No

Time Zone: PST MST CST EST

PREFER SAME INTERVIEWER: YES NO

Email Address: _____ Other Contact Name: _____

Other Contact Relationship: _____

Other Contact Phone: _____

FOB (or partner) Name: _____

FOB (biological/donor sperm) DOB: _____

Notes:

Interviewer: _____

DE Date: _____ Validated by: _____

DE Initials: _____ Date Validated: _____

INTAKE

DEMOGRAPHICS & MEDICAL HISTORY

Primary Group: _____

PPD Case Number: _____ Budget: _____

Subject's Initials: _____ Intake Date: _____

REFERRAL SOURCE: TIS Physician/Health-Care Worker Internet Pharmaceutical Company Self-Referral Other

Referral source specifics: _____

DEMOGRAPHICS

MOB Ethnicity (biological/egg donor):
- Hispanic / Latina
- Non-Hispanic / Non-Latina

MOB Race (biological/egg donor):
- Caucasian
- Native American/AK Native
- Black
- Asian
- Pacific Islander
- *Other:_____ *MUST SPECIFY

Primary language at home:
- English
- Spanish
- Other: _____

MOB JOB TITLE: (☐ Full-time or ☐ Part-time)

_____

- Description [*military- rank; chef/cook- type of restaurant; business owners- # of people employed; engineers without BA or Post Grad need to ask for tasks; teachers- what grade and what subject]:

MOB Education:
- < 9th grade
- Junior HS (9th)
- Partial HS (10th or 11th)
- HS Grad/ Trade without HS Grad
- Some College / Specialization (at least 1 year)
- College / University Grad (*Degree:* _____)
- Post Grad (*Degree:* _____)

Is the FOB (partner) providing financial support?*
Yes No

FOB (biological/sperm donor) Ethnicity:
- Hispanic / Latino
- Non-Hispanic / Non-Latino

FOB (biological/sperm donor) Race:
- Caucasian
- Native American/AK Native
- Black
- Asian
- Pacific Islander
- *Other:_____ *MUST SPECIFY

*If "Yes", FOB (partner) JOB TITLE: (☐ Full-time or ☐ Part-time)

_____

- Description [*military- rank; chef/cook- type of restaurant; business owners- # of people employed; engineers without BA or Post Grad need to ask for tasks; teachers- what grade and what subject]:

*If "Yes", FOB (partner) Education:
- < 9th grade
- Junior HS (9th)
- Partial HS (10th or 11th)
- HS Grad/ Trade without HS Grad
- Some College / Specialization (at least 1 year)
- College / University Grad (*Degree:* _____)
- Post Grad (*Degree:* _____)

*If **BOTH** MOB and FOB not working (or only receiving unemployment, disability, social security, welfare, student loans), will anyone else be providing support for the baby? YES NO

*If "Yes", Supporter's # 1 Education:
- < 9th grade
- Junior HS (9th)
- Partial HS (10th or 11th)
- HS Grad/ Trade without HS Grad
- Some College / Specialization (at least 1 year)
- College / University Grad (*Degree:* _____)
- Post Grad (*Degree:* _____)

If yes, Supporter's # 1 Occupation:
- Job Title: (☐ Full-time or ☐ Part-time)

_____
- Description:
- Relationship:

Case Number: _____

*If "Yes", Supporter's # 2 Education:

- < 9th grade
- Junior HS (9th)
- Partial HS (10th or 11th)
- HS Grad/ Trade without HS Grad
- Some College / Specialization (at least 1 year)
- College / University Grad (*Degree:* _____)
- Post Grad (*Degree:* _____)

If yes, Supporter's # 2 Occupation:

- Job Title: (☐Full-time **or** ☐ Part-time)
  _____
- Description:
- Relationship:

→ Total (pre-tax) Household Income: <$10,000 $10,000 - $49,000 >$50,000 Unknown

PREGNANCY HISTORY

Current Pregnancy →

Per Maternal Report:

LMP: _____ *Check if unsure* ☐
DOC: _____
EDC: _____
Cycle: _____ *Check if unsure* ☐

MOB-Reported EDC Determined by:

☐LMP ☐U/S: *date:* _____
☐IVF/ICSI ☐Artificial Insemination
☐Other: _____

Per Database Calculations:

LMP: _____
DOC: _____
EDC: _____
Cycle: _____

Database Calculation of EDC Determined by:

☐LMP ☐U/S: *date:* _____
☐IVF/ICSI ☐Artificial Insemination
☐Other: _____

ART:

☐IVF ☐Fertility Drugs
☐ICSI ☐Donor Egg / Sperm
☐Artificial Insemination
☐Other: _____

1. Have you ever been treated for infertility in this or any previous pregnancy? *[IF YES, please select "Infertility" in "MOB history section" of database (PREG tab)]*	YES	NO
2. Did you use any assistive reproductive methods in this pregnancy (i.e. fertility meds, IVF, etc.)	YES	NO
2a. **If YES**, what treatment:		

Was this pregnancy planned? (*Actively trying to become pregnant?*) Yes No

Date you found out you were pregnant: _____ Pre-pregnancy Wt (lbs): _____ Ht (ft/in): _____

Case Number: _____

Pregnancy Information →

Gravida: _____ *#total pregnancies*
Para: _____ *#livebirths + stillbirths*
SAB*: _____ *Includes ectopic & mole*
TAB: _____

Previous Pregnancies:

Month/Year of Outcome	Single or Multiple	Outcome (Livebirth, Stillbirth, SAB, TAB, ectopic, mole)	GA Weeks at completion of pregnancy	Change in paternity from previous pregnancy (i.e. Was there a change in the father/sperm donor for this reported pregnancy?)
1st.	☐ Single ☐ Multiple			N/A
2nd.	☐ Single ☐ Multiple			Y N
3rd.	☐ Single ☐ Multiple			Y N
4th.	☐ Single ☐ Multiple			Y N
5th.	☐ Single ☐ Multiple			Y N
6th.	☐ Single ☐ Multiple			Y N
7th.	☐ Single ☐ Multiple			Y N
8th.	☐ Single ☐ Multiple			Y N
9th.	☐ Single ☐ Multiple			Y N
10th.	☐ Single ☐ Multiple			Y N
Current Pregnancy	☐ Single ☐ Multiple ☐ Unknown	N/A	N/A	Y N

For Data Entry Purposes *(Use information gathered above regarding previous pregnancies to answer):*	
Change in paternity ever? Y N	Change in paternity in THIS pregnancy? Y N

Previous Pregnancies →

• Preterm delivery *(< 37 wks gestation)*	Yes	No	Preg #:	*Notes:*
• Pregnancies w/ birth defect *(includes SABs and TABs)*	Yes	No	Preg #:	
• Child w/ IUGR *(Dx w/ being small)*	Yes	No	Preg #:	
• Preeclampsia / Toxemia	Yes	No	Preg #:	
• Oligohydramnios *(too little amniotic fluid)*	Yes	No	Preg #:	
• Hydramnios *(too much amniotic fluid)*	Yes	No	Preg #:	
• Pregnancy Induced Hypertension	Yes	No	Preg #:	
• Other	Yes	No	Preg #:	

Additional Notes:

Case Number: _____

Family History →

(MOB/FOB, mother, father, brothers/sisters, aunts/uncles)	Maternal* Yes	Maternal* No	Paternal* Yes	Paternal* No	*Relation*	*Notes:*
• Down Syndrome						
• Neural Tube Defect						
• Cystic Fibrosis						
• Heart Defect						
• Other Birth Defect						
• Genetic Disease						
• Mental Disability						
• Multiple Sclerosis* **MS for MOB should be recorded under MOB history*						
• Other						

**FOB/paternal (biological/sperm donor); *MOB/maternal (biological/egg donor)*

Additional Notes:

MOB (person pregnant) Medical History → ***(*if "Yes", explain...)***

	Yes	No	Date Dx		*Notes:*
• Ankylosing Spondylitis				☐ Current ☐ Resolved	
• Antiphospholipid Syndrome				☐ Current ☐ Resolved	
• Celiac				☐ Current ☐ Resolved	
• Connective Tissue Disease (mixed / undifferentiated)				☐ Current ☐ Resolved	
• Crohn's **Qualify for AI study? Y N**				☐ Current ☐ Resolved	
• Lupus				☐ Current ☐ Resolved	
• Multiple Sclerosis **Qualify for AI study? Y N**				☐ Current ☐ Resolved	
• Psoriasis **Qualify for AI study? Y N**				☐ Current ☐ Resolved	
• Psoriatic Arthritis				☐ Current ☐ Resolved	
• Raynaud's				☐ Current ☐ Resolved	
• Rheumatoid Arthritis **Qualify for AI study? Y N**				☐ Current ☐ Resolved	
• Juvenile Rheumatoid Arthritis				☐ Current ☐ Resolved	
• Sjogren's				☐ Current ☐ Resolved	
• Ulcerative Colitis				☐ Current ☐ Resolved	
• Other AI Disease **Qualify for AI study? Y N**				☐ Current ☐ Resolved	

AI Primary Dx (if applicable)_____

If MOB has 2 or more AI diagnoses, ask which one her doctor considers to be her primary diagnosis.

Case Number: _____

MOB (person pregnant) Medical History Continued… → *(*if "Yes", explain...)*

	Yes	No	Date Dx		Notes:
• Anxiety				☐ Current ☐ Resolved	
• Depression				☐ Current ☐ Resolved	
• Other Psychiatric Conditions				☐ Current ☐ Resolved	
• Anemia				☐ Current ☐ Resolved	
• Asthma **Qualify for Asthma study? Y N**				☐ Current ☐ Resolved	
• Diabetes *(specify type)* ☐ Type 1 ☐ Type 2 ☐ Gestational				☐ Current ☐ Resolved	
• Endometriosis/Other Uterine Pathology				☐ Current ☐ Resolved	
• Epilepsy				☐ Current ☐ Resolved	
• Fibromyalgia				☐ Current ☐ Resolved	
• Genetic Disease				☐ Current ☐ Resolved	
• Guillain Barre				☐ Current ☐ Resolved	
• Heart Disease				☐ Current ☐ Resolved	
• Hepatitis/Liver Disease				☐ Current ☐ Resolved	
• High Blood Pressure				☐ Current ☐ Resolved	
• History Blood Transfusions				☐ Current ☐ Resolved	
• Infectious Disease				☐ Current ☐ Resolved	
• Infertility				☐ Current ☐ Resolved	
• Kidney Disease/Recurrent UTI				☐ Current ☐ Resolved	
• Lung Disease				☐ Current ☐ Resolved	
• Neurological Conditions				☐ Current ☐ Resolved	
• Ovarian Cysts or Uterine Fibroids				☐ Current ☐ Resolved	
• Polycystic Ovarian Syndrome (PCOS)				☐ Current ☐ Resolved	
• Thyroid Dysfunction				☐ Current ☐ Resolved	
• Other				☐ Current ☐ Resolved	

Case Number_____

Primary Group Number_____

Subject's Initials_____

Budget Number_____

If enrolled in asthma study, remember asthma survey monkey

Asthma survey monkey: ☐ Completed

INTAKE DATE:_____wks GA	20 WK DATE:	32 WK DATE:	OUTCOME DATE:	6 MO POST-PARTUM DATE:
Consented:	Due:	Due:	Due:	Due:
Completed:	Completed:	Completed:	Completed:	Completed:

Case Number_____

Prenatal Vitamins* **Yes** **No** **Not Asked**

**Record brand and actual start date; enter this info in notes field*

Product:	**Indication:**	**Dose:**	**Intake** **Y** **N**		**20 Week** **Y** **N**		**32 Week** **Y** **N**		**Outcome** **Y** **N**	
			Start	Stop	Start	Stop	Start	Stop	Start	Stop
1.)										
2.)										
3.)										

Other Vitamins **Yes** **No** **Not Asked**

Product:	**Indication:**	**Dose:**	**Intake** **Y** **N**		**20 Week** **Y** **N**		**32 Week** **Y** **N**		**Outcome** **Y** **N**	
			Start	Stop	Start	Stop	Start	Stop	Start	Stop
1.)										
2.)										
3.)										
4.)										
5.)										

Case Number_____

Other Supplements **Yes** **No** **Not Asked**

Product:	**Indication:**	**Dose:**	**Intake** Y N		**20 Week** Y N		**32 Week** Y N		**Outcome** Y N	
			Start	Stop	Start	Stop	Start	Stop	Start	Stop
1.)										
2.)										
3.)										

Birth Control **Yes** **No** **Not Asked**

- Oral Contraceptive Yes No
- Injection Yes No
- Condoms Yes No
- Spermicide Yes No
- Diaphram Yes No
- IUD Yes No
- Other Yes No

Product:	**Indication:**	**Dose:**	**Intake** Y N		**20 Week** Y N		**32 Week** Y N		**Outcome** Y N	
			Start	Stop	Start	Stop	Start	Stop	Start	Stop
1.)										
2.)										

Case Number_____

Caffeine **Yes** **No** **Not Asked**

Product:	**Indication:**	**Dose:**	**Intake**	**Y N**	**20 Week**	**Y N**	**32 Week**	**Y N**	**Outcome**	**Y N**
			Start	Stop	Start	Stop	Start	Stop	Start	Stop
1.)										
2.)										
3.)										
4.)										
5.)										
6.)										

Cigarette Smoking **Yes** **No** **Not Asked**

Explanation	**Indication:**	**Dose:**	**Intake**	**Y N**	**20 Week**	**Y N**	**32 Week**	**Y N**	**Outcome**	**Y N**
			Start	Stop	Start	Stop	Start	Stop	Start	Stop
1.)										
2.)										
3.)										

Case Number_____

Second Hand Smoke **Yes** **No** **Not Asked**

Product: **Indication:** **Dose:**	**Intake Y N**		**20 Week Y N**		**32 Week Y N**		**Outcome Y N**	
	Start	Stop	Start	Stop	Start	Stop	Start	Stop
1.)								
2.)								
3.)								

Were there any days, even before you knew that you were pregnant, that you had 5 or more drinks of beer, wine or any other kind of alcohol in one day? Yes No Not asked

Were there any weeks, even before you knew that you were pregnant, that you had 6 or more drinks of beer, wine or any other kind of alcohol in one week? Yes No Not asked

Alcohol **Yes** **No** **Not Asked**

Non-disease controls (INTAKE ONLY): ***Stop interview & tell MOB not qualified if:** >5 drinks per week or ≥ 5 drinks in 1 day

Product: **Indication:** **Dose:**	**Intake Y N**		**20 Week Y N**		**32 Week Y N**		**Outcome Y N**	
	Start	Stop	Start	Stop	Start	Stop	Start	Stop
1.)								
2.)								
3.)								
4.)								
5.)								

Case Number_____

Street Drugs

Have you used any street drugs or illicit drugs for recreational purposes or for medicinal purposes? Yes No Not Asked

Product: **Indication:** **Dose:**	**Intake Y N**		**20 Week Y N**		**32 Week Y N**		**Outcome Y N**	
	Start	Stop	Start	Stop	Start	Stop	Start	Stop
1.)								
2.)								
3.)								

Illness/ER Visits Yes No Not Asked (For flu-like illnesses, see next section)

Explanation: **Indication:**	**Intake Y N**		**20 Week Y N**		**32 Week Y N**		**Outcome Y N**	
	Start	Stop	Start	Stop	Start	Stop	Start	Stop
1.)								
2.)								
3.)								
4.)								
5.)								
6.)								

Case Number_____

Influenza

Did you suspect that you had the flu or have you had a flu-like illness? **Yes No Not Asked**

Explanation:	**Intake Y N**		**20 Week Y N**		**32 Week Y N**		**Outcome Y N**	
	Start	Stop	Start	Stop	Start	Stop	Start	Stop
1.)								

Did you have:
Fever: **Yes No** Diarrhea: **Yes No** Fatigue/tiredness: **Yes No**
Headache: **Yes No** Sore throat: **Yes No** Vomiting: **Yes No**
Cough: **Yes No** Chills: **Yes No** Body aches: **Yes No**
Stuffy/Runny nose: **Yes No**

Were you treated with an Anti-viral med (Tamiflu, Relenza, or Other)? **Yes No**
Other antiviral
Name:

*If so, where did you obtain the medication - **Doctor, Health Dept, Friend, Other** ?*

Were you given a prescription (antiviral)? **Yes No**

Did you see a doctor or other health provider? **Yes No**
Were you hospitalized for the flu? **Yes No**
Did you have a lab test to test for the flu? **Yes No**

If yes, what was the test and result:

Rapid flu test	Yes	No	Unk	Positive	Negative
PCR	Yes	No	Unk	Positive	Negative
Blood test at HCP	Yes	No	Unk	Positive	Negative
Swab test	Yes	No	Unk	Positive	Negative
Other:	Yes	No	Unk	Positive	Negative

Name_____

	Intake Y N		**20 Week Y N**		**32 Week Y N**		**Outcome Y N**	
	Start	Stop	Start	Stop	Start	Stop	Start	Stop
2.)								

Did you have:
Fever: **Yes No** Diarrhea: **Yes No** Fatigue/tiredness: **Yes No**
Headache: **Yes No** Sore throat: **Yes No** Vomiting: **Yes No**
Cough: **Yes No** Chills: **Yes No** Body aches: **Yes No**
Stuffy/Runny nose: **Yes No**

Were you treated with an Anti-viral med (Tamiflu, Relenza, or Other)? **Yes No**
Other antiviral
Name:

*If so, where did you obtain the medication - **Doctor, Health Dept, Friend, Other** ?*

Were you given a prescription (antiviral)? **Yes No**

Did you see a doctor or other health provider? **Yes No**
Were you hospitalized for the flu? **Yes No**
Did you have a lab test to test for the flu? **Yes No**

If yes, what was the test and result:

Rapid flu test	Yes	No	Unk	Positive	Negative
PCR	Yes	No	Unk	Positive	Negative
Blood test at HCP	Yes	No	Unk	Positive	Negative
Swab test	Yes	No	Unk	Positive	Negative
Other:	Yes	No	Unk	Positive	Negative

Name_____

Have you had any close/personal contact with anyone (home, work, etc) diagnosed with the flu? Yes No Not Asked

Explanation: If yes, indication how many people and when	**Intake Y N**		**20 Week Y N**		**32 Week Y N**		**Outcome Y N**	
	Start	Stop	Start	Stop	Start	Stop	Start	Stop
1.)								

Case Number_____

Pertussis/Cough
Have you or anyone in your household been sick with pertussis or whooping cough? Yes No Not Asked

Explanation: If yes, whom? And any diagnosis?	**Intake Y N**		**20 Week Y N**		**32 Week Y N**		**Outcome Y N**	
	Start	Stop	Start	Stop	Start	Stop	Start	Stop
1.)								
Any diagnosis? Y N If yes, diagnosis:								
2.)								
Any diagnosis? Y N If yes, diagnosis:								
3.)								
Any diagnosis? Y N If yes, diagnosis:								

Fever Yes No Not Asked

Please probe for details: Did fever break or was it consistent? What was the highest temperature? How long did it stay at that peak temperature? Etc.

Explanation: Degrees: Hours/Days:	**Intake Y N**		**20 Week Y N**		**32 Week Y N**		**Outcome Y N**	
	Start	Stop	Start	Stop	Start	Stop	Start	Stop
1.)								
2.)								
3.)								

Case Number_____

Autoimmune Medications of Special Interest Pre-Conception ☐ MOB does not have an autoimmune disease; questions in this section not asked.

If exposed to MTX, Stelara, CellCept, Leflunomide, or Teriflunomide, record details in Prescription Medication section. Record actual start date.

Methotrexate (MTX) (within 3 months of LMP)? Yes No Not Asked

Stelara (within 3 months of LMP)? Yes No Not Asked

CellCept (generic: Mycophenolate Mofetil) (after DOC)? Yes No Not Asked

Leflunomide / Teriflunomide (within 2 yrs of DOC)? Yes No Not Asked;

If Yes, which manufacturer? Apotex Sanofi-Aventis Barr Par Sandoz Teva Other:_____

If Yes, did she undergo a washout procedure (Cholestyramine or Charcoal)? Yes No Not Asked

Leflunomide / Teriflunomide Blood Test Result:	Intake Y N	20 Week Y N	32 Week Y N	Outcome Y N
1.)	Test date:	Test date:	Test date:	Test date:
2.)	Test date:	Test date:	Test date:	Test date:
3.)	Test date:	Test date:	Test date:	Test date:

Washout Medications (Cholestyramine, Charcoal)

Product: Indication: Dose:	Intake Y N		20 Week Y N		32 Week Y N		Outcome Y N	
*Record actual start date (not LMP date).	Start*	Stop	Start	Stop	Start	Stop	Start	Stop
1.)								
2.)								
3.)								

Case Number_____
Any fertility drugs within 1 month of LMP? Yes No **AI Condition** _____
For fertility drugs, record actual start date (not LMP date)

Exposure within 5 half-lives of LMP to TNF(s) / biologic(s)? Yes No Not Applicable
If Yes, record actual start date (not LMP date)

Exposed post-LMP to an AI study drug *(e.g. biologics, TNFs, etc.)* AND/OR another drug in the same class? Yes No Not Applicable
If Yes, record actual start date (not LMP date)

INTAKE ONLY: *If MOB reports exposure to a medication that would disqualify her from the study, stop interview & tell MOB not qualified

Prescription Medication **Yes** **No** **Not Asked**

Product: **Indication:** **Dose:**	**Intake**	**Y N**	**20 Week**	**Y N**	**32 Week**	**Y N**	**Outcome**	**Y N**
	Start	Stop	Start	Stop	Start	Stop	Start	Stop
1.)								
Category/Class:								
2.)								
Category/Class:								
3.)								
Category/Class:								
4.)								
Category/Class:								

Case Number_____

INTAKE ONLY: *If MOB reports exposure to a medication that would disqualify her from the study, stop interview & tell MOB not qualified

Prescription Medication Continued…

Product: **Indication:** **Dose:**	**Intake**	**Y N**	**20 Week**	**Y N**	**32 Week**	**Y N**	**Outcome**	**Y N**
	Start	Stop	Start	Stop	Start	Stop	Start	Stop
5.)								
Category/Class:								
6.)								
Category/Class:								
7.)								
Category/Class:								
8.)								
Category/Class:								
9.)								
Category/Class:								

Case Number_____

Have you ever had an allergic reaction to: ☐Eggs ☐Gelatin ☐Previous Vaccination ☐No/None

Have you ever received the pertussis vaccine? Yes No Don't Know

Vaccinations (w/in 3 mos. of LMP and ALL pertussis vaccines ever received) Yes No Not Asked

Product: **Indication:** **Dose:**	**Intake** Y N		**20 Week** Y N		**32 Week** Y N		**Outcome** Y N	
	Start	Stop	Start	Stop	Start	Stop	Start	Stop
1)								

Determined Brand of Vaccine: Yes No Pending **Vaccine Manufacturer/Brand**_____ **Lot #**_____
Source of Vaccine Information: _____

Vaccine Dose: ☐Single/Unit Dose ☐Multi-dose Vial ☐Unknown **Route of Administration:** ☐Intramuscular ☐Intradermal ☐Unknown

Facility/Location/Physician where administered:_____ **Phone/Fax:**_____ ☐ **MR** ☐ **HIPAA**
Received Vaccine at Employee Health: Yes No ☐ **MOB unable to obtain vaccine info *OR* prefers MRRF** ☐ **Sent email to MOB** [*Date*:_____]

2)								

Determined Brand of Vaccine: Yes No Pending **Vaccine Manufacturer/Brand**_____ **Lot #**_____
Source of Vaccine Information: _____

Vaccine Dose: ☐Single/Unit Dose ☐Multi-dose Vial ☐Unknown **Route of Administration:** ☐Intramuscular ☐Intradermal ☐Unknown

Facility/Location/Physician where administered:_____ **Phone/Fax:**_____ ☐ **MR** ☐ **HIPAA**
Received Vaccine at Employee Health: Yes No ☐ **MOB unable to obtain vaccine info *OR* prefers MRRF** ☐ **Sent email to MOB** [*Date*:_____]

3)								

Determined Brand of Vaccine: Yes No Pending **Vaccine Manufacturer/Brand**_____ **Lot #**_____
Source of Vaccine Information: _____
Vaccine Dose: ☐Single/Unit Dose ☐Multi-dose Vial ☐Unknown **Route of Administration:** ☐Intramuscular ☐Intradermal ☐Unknown

Facility/Location/Physician where administered:_____ **Phone/Fax:**_____ ☐ **MR** ☐ **HIPAA**
Received Vaccine at Employee Health: Yes No ☐ **MOB unable to obtain vaccine info *OR* prefers MRRF** ☐ **Sent email to MOB** [*Date*:_____]

Case Number_____

Over-the-Counter Medications **Yes** **No** **Not Asked**

INTAKE ONLY: *If MOB reports exposure to a medication that would disqualify her from the study, stop interview & tell MOB not qualified

Product: **Indication:** **Dose:**	**Intake** **Y N**		**20 Week Y N**		**32 Week: Y N**		**Outcome Y N**	
	Start	Stop	Start	Stop	Start	Stop	Start	Stop
1.)								
Category/Class:								
2.)								
Category/Class:								
3.)								
Category/Class:								
4.)								
Category/Class:								
5.)								
Category/Class:								

Case Number_____

INTAKE ONLY: *If MOB reports exposure to a medication that would disqualify her from the study, stop interview & tell MOB not qualified

Over-the-Counter Medications Continued…

Product: Indication: Dose:	Intake Y N		20 Week: Y N		32 Week: Y N		Outcome Y N	
	Start	Stop	Start	Stop	Start	Stop	Start	Stop
6.)								
Category/Class:								
7.)								
Category/Class:								
8.)								
Category/Class:								
9.)								
Category/Class:								
10.)								
Category/Class:								

Case Number_____

Occupational Exposures **Yes** **No** **Not Asked**

Product: **Indication:** **Dose:**	**Intake** **Y** **N**		**20 Week** **Y** **N**		**32 Week** **Y** **N**		**Outcome** **Y** **N**	
	Start	Stop	Start	Stop	Start	Stop	Start	Stop
1.)								
2.)								

Environmental **Yes** **No** **Not Asked**

Indication: **Dose:**	**Intake** **Y** **N**		**20 Week** **Y** **N**		**32 Week** **Y** **N**		**Outcome** **Y** **N**	
	Start	Stop	Start	Stop	Start	Stop	Start	Stop
1.)								
2.)								

Physical Trauma **Yes** **No** **Not Asked**

Indication: **Dose:**	**Intake** **Y** **N**	**20 Week** **Y** **N**	**32 Week** **Y** **N**	**Outcome** **Y** **N**
	Date	Date	Date	Date
1.)				
2.)				

Case Number_____

X-Rays **Yes** **No** **Not Asked**

Indication: **Dose:**	**Intake** **Y** **N**		**20 Week** **Y** **N**		**32 Week** **Y** **N**		**Outcome** **Y** **N**	
	Start	Stop	Start	Stop	Start	Stop	Start	Stop
1.)								
2.)								
3.)								

Hospitalizations (*admitted* into hospital) **Yes** **No** **Not Asked**

Product: **Indication:** **Dose:**	**Intake** **Y** **N**		**20 Week** **Y** **N**		**32 Week** **Y** **N**		**Outcome** **Y** **N**	
	Start	Stop	Start	Stop	Start	Stop	Start	Stop
1.)								
2.)								
3.)								

Case Number_____

INTAKE ONLY: *If MOB reports prenatal diagnosis of malformation (CVS, Amnio, U/S) AND is NOT in a registry group, stop interview & tell MOB not qualified

Pregnancy Related Tests	INTAKE	20 WEEK	32 WEEK	OUTCOME	Date	Result
CVS **done btw 10-12 wks*	Y N Not Asked	Y N Not Asked	Y N Not Asked	Y N Not Asked		
1st trimester serum screen ** done btw 10-13w6d*	Y N Not Asked	Y N Not Asked	Y N Not Asked	Y N Not Asked		
Nuchal Translucency ** Btw 11w2d-14w2d *Data entry under U/S*	Y N Not Asked	Y N Not Asked	Y N Not Asked	Y N Not Asked		
AFP (Quad screen, 2nd trimester screening) **done btw 15-20 wks*	Y N Not Asked	Y N Not Asked	Y N Not Asked	Y N Not Asked		
Amnio	Y N Not Asked	Y N Not Asked	Y N Not Asked	Y N Not Asked		
NIPT	Y N Not Asked	Y N Not Asked	Y N Not Asked	Y N Not Asked		
Glucose Tolerance Test	Y N Not Asked	Y N Not Asked	Y N Not Asked	Y N Not Asked	#1: _____ #2: _____ GTT Notes:	#1: ☐1hr ☐2hr ☐3hr ☐Nl ☐Abnl #2: ☐1hr ☐2hr ☐3hr ☐Nl ☐Abnl
Non-Stress Test	Y N Not Asked	Y N Not Asked	Y N Not Asked	Y N Not Asked		
Other	Y N Not Asked	Y N Not Asked	Y N Not Asked	Y N Not Asked		

Case Number_____

INTAKE ONLY: *If MOB reports prenatal diagnosis of malformation (CVS, Amnio, U/S) AND is NOT in a registry group, stop interview & tell MOB not qualified

INTAKE: Y N Not Asked	20 Week: Y N Not Asked	32 WEEK: Y N Not Asked	OUTCOME: Y N Not Asked

Ultrasound Date	Level	Indication	Results	I	20	32	O
1.	I II Unknown						
2.	I II Unknown						
3.	I II Unknown						
4.	I II Unknown						
5.	I II Unknown						
6.	I II Unknown						
7.	I II Unknown						
8.	I II Unknown						
9.	I II Unknown						
10.	I II Unknown						
11.	I II Unknown						
12.	I II Unknown						

Case Number_____

Mom Reported Intake EDC	DB Calculated EDC	Mom Reported 20 Week EDC	Mom Reported 32 Week EDC

Trimester ultrasound completed	Ultrasound Accuracy	Change EDC if difference is greater than:
1	5 - 7 days	7 days from dates by LMP
2	10 - 14 days	14 days from dates by LMP
3	21 days	21 days from dates by LMP

Intake

Has EDC changed any time in pregnancy Yes No NA

If yes, when did it change_____

For data entry purposes
If yes, according to U/S accuracy chart were dates changed in DB? Yes No NA

20 Week

Has EDC changed any time in pregnancy Yes No NA

If yes, when did it change_____

For data entry purposes
If yes, according to U/S accuracy chart were dates changed in DB? Yes No NA

32 Week

Has EDC changed any time in pregnancy Yes No NA

If yes, when did it change_____

For data entry purposes
If yes, according to U/S accuracy chart were dates changed in DB? Yes No NA

Case Number_____

	Intake	20 Week	32 week	Outcome
Fetal Movement	Yes No Not Begun Not Asked	Yes No Not Begun Not Asked	Yes No Not Begun Not Asked	NA
Onset of Fetal Movement	Date:	Date:	Date:	NA
Fetal Activity	Active Not Active Very Active	Active Not Active Very Active	Active Not Active Very Active	NA
Phone / Address Changes	N/A	Yes No N/A	Yes No N/A	Yes No N/A
CTIS	Yes No N/A	Yes No N/A	Yes No N/A	Yes No N/A
Depression Scale Survey	Yes No N/A	Yes No N/A	Yes No N/A	Yes No N/A
AI Enrolled	Yes No N/A	Yes No N/A	Yes No N/A	N/A
Flu Enrolled	Yes No N/A	Yes No N/A	Yes No N/A	N/A
Pertussis Enrolled	Yes No N/A	Yes No N/A	Yes No N/A	N/A
Asthma Enrolled	Yes No N/A	N/A	N/A	N/A
Written consent	Sent N/A	Sent Received N/A	Sent Received N/A	Sent Received
HIPAA consent	Sent N/A	Sent Received N/A	Sent Received N/A	Sent Received
Referred to breastfeeding study?	Yes No N/A	Yes No N/A	Yes No N/A	Yes No N/A
Interviewer				
DE Date				
DE Initials				
Validated By				
Date Validated				

Date/Time Contact Attempts:		
Previous Call Date: _____ Call Date: _____	**OUTCOME** DELIVERY & BIRTH INFORMATION	Exam Due Date: _____ Exam Preferences: _____

OTIS Case Number: _____ Primary Group: _____

Subject's Initials: _____

EDC: _____ Budget Number: _____

PREGNANCY & DELIVERY

	Yes	No	DK	NA	Date Dx
• Pre-term Labor *(before 37 weeks)*					
• Preeclampsia / Toxemia *(PIH, protein in the urine, swelling)*					
• PIH *(Pregnancy Induced Hypertension)*					
• Group B Strep					
• Maternal Fever *(at delivery)*					
• Placenta Previa *(placenta blocking the birth canal, at delivery)*					
• Placenta Abruptio *(placenta detached before baby was born)*					
• Excessive Bleeding/Hemorrhage *(Dx by Dr)*					

→ Diabetes:	Yes	No	If "Yes": • Gestational (*Date Dx:* _____) • Type I (*Date Dx:* _____) • Type II (*Date Dx:* _____)
→ Other:	Yes*	No	

Explanation / Notes:*

_____

_____

_____

→ Maternal Weight Gain for Pregnancy: _____ *(lbs)* *Notes:*

Case Number: _____

BIRTH INFORMATION → Single → Multiple (#: _____)

- Liveborn
- Stillborn
- SAB
- Ectopic
- Mole
- TAB

Baby's Name:		DOB:	*Male* *Female*
Apgars: *1 min:* _____ *5 min:* _____	Birth Weight: _____ *lbs* _____ *oz*	Birth Length: _____ *in*	OFC: _____ *cm or in*

DELIVERY DETAILS

Vaginal:	C-Section:	Presentation:	Forceps:	Vacuum:
Yes No	Yes* No	Vertex Breech Transverse	Yes No	Yes No

→ *if C-Section"	Primary Repeat	Reason for c/s	Elective Emergency Repeat	Had labor started when the c/s was performed? Yes No

Notes:

NEWBORN COMPLICATIONS *(continued on next page)*

	Yes	No	DK	NA	Dates *Dx/Resolved*
• Jaundice					
• Meconium Aspiration *(did the baby inhale meconium)*					
• Transient Tachypnea *(temporary, rapid, shallow breath)*					
• Bradycardia *(pulse rate too slow)*					
• Cyanosis *(blue skin)*					

Case Number: _____

NEWBORN COMPLICATIONS *(continued)*

	Yes	No	DK	NA	Dates *Dx/Resolved*
• Respiratory Problems/Difficulty					
• Cord Gases Taken					
• Resuscitated					
• Hypoglycemia *(low blood sugar)*					
• Jitteriness					
• Hypotonia *(floppy muscles)*					
• Hypertonia *(excessive muscle tone)*					
• Temperature Regulation Problems					
• Other neonatal complications (i.e. abnormal lab test, tachycardia, etc.)					
• Dx Abnormalities / Birth Defects 1. Who diagnosed? 2. What details were you given / what did they tell you? 3. Was/is surgery required? 4. Is any follow-up required? 5. If yes to 4, what type of hcp will be following? **Let supervisor know & enter in "MALFS" tab (check "Follow up on Malf" box; write details in "Malf Notes")* ***If SAE (i.e. malformation) has already been reported prenatally & the same SAE is pending an outcome update, please update the supervisor on diagnosis once outcome has been collected.*					

Other: _____

_____

→ Admission to Level II Nursery: Yes No **if "Yes", Reason / # days:* _____
→ Admission to NICU: Yes No **if "Yes", Reason / # days:* _____

Notes:

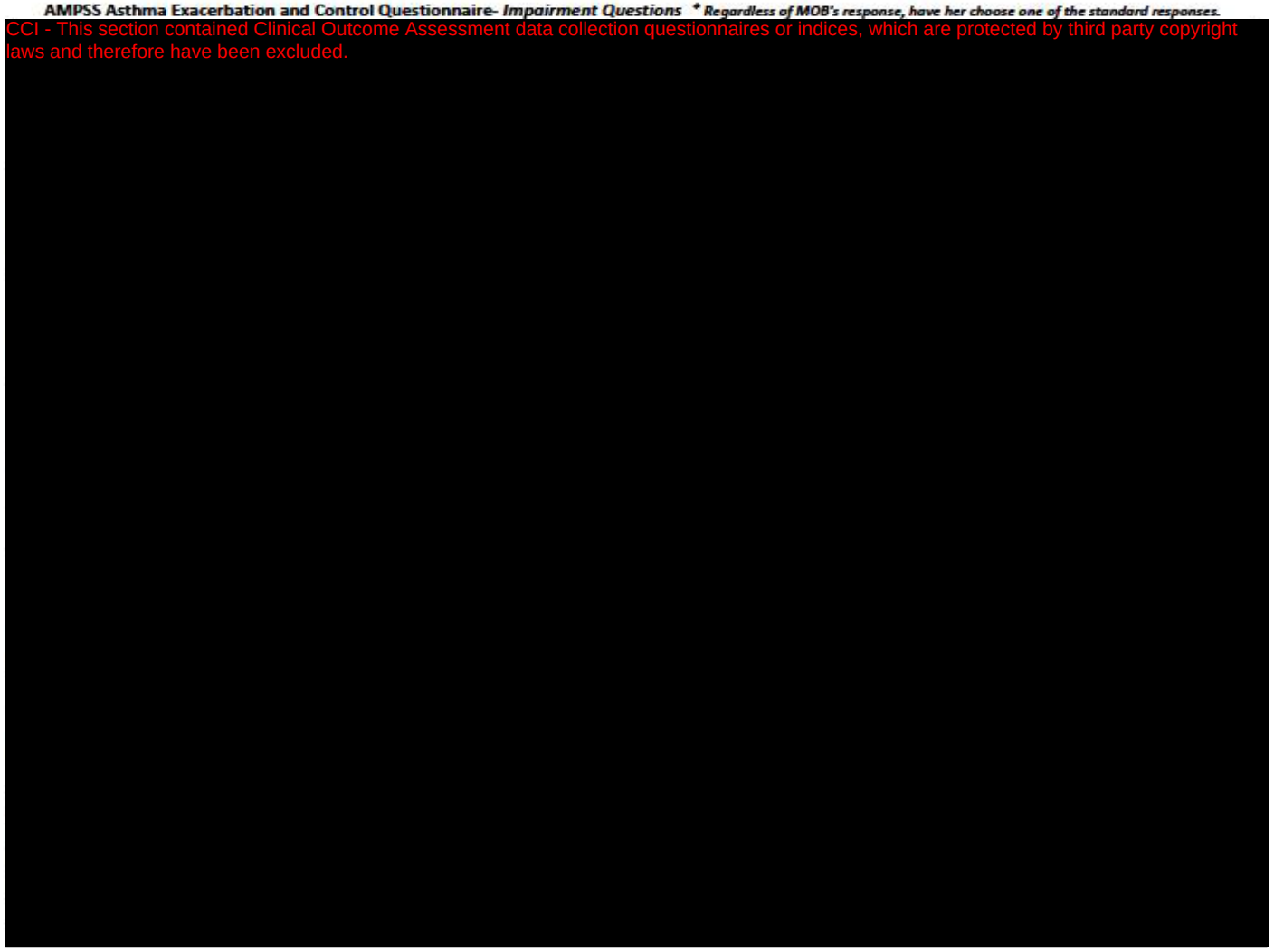
_____

_____

→ Breastfeeding: Yes No **if "Yes", exclusively for 2 weeks?* Yes No
Length of time: _____

Completed pregnancy diary? Yes No Which is more accurate? Diary Interview

AMPSS Asthma Exacerbation and Control Questionnaire- *Impairment Questions* ***Regardless of MOB's response, have her choose one of the standard responses.***



Pregnancy ID # _____

Allergist for MOB *Medical Record Abstraction Form*

Group # _____

PPD **Provider?** ☐ **Yes** ☐ **No**

If yes, date HIPAA signed by MOB: _____

Asthma Diagnosis

Diagnosed? ☐ Yes ☐ No Date of Diagnosis: _____ Agrees with MOB report? ☐ Yes ☐ No

Notes: _____

_____

_____

Unscheduled Clinic Visits for increased asthma symptoms

Date	Notes (including changes or additions to medications)	Agrees with MOB report?
		Y N
		Y N
		Y N

ER Visits for increased asthma symptoms

Date	Notes (including changes or additions to medications)	Agrees with MOB report?
		Y N
		Y N
		Y N

Hospitalizations for increased asthma symptoms

Date	Notes (including changes or additions to medications)	Agrees with MOB report?
		Y N
		Y N
		Y N

Form Color: Purple

Pregnancy ID # _____

Obstetrician *Medical Record Abstraction Form* **Group #**

OB History G_____ P_____ S_____ T_____

	Month/Year	Outcome	GA	Birth Defect?	IUGR?	Pre-eclampsia?	Oligohyd?	Polyhyd?	Notes *SAB-suspected cause; TAB-personal reasons or medical; if GA not noted, indicate whether preterm; etc.*
1st									
2nd									
3rd									
4th									
5th									
6th*									

**If more than 6 prior pregnancies, list additional pregnancies on a separate sheet.*

Maternal Height and Weight

Height: _____ Consistent w/MOB? Y N

Pre-Preg Wt: _____ on _____ *date* Final Preg Wt: _____ on _____ *date* Wt Gain: _____ Consistent w/MOB? Y N

Assisted Reproductive Technologies

None IVF ICSI Artificial Insem Fertility Rx Donor Egg/Sperm Other Consistent w/MOB? Y N

Pregnancy Dates

Final EDC per OB: _____ Determined on _____ *date determined* based on LMP U/S: _____ *date of U/S* Other: _____

EDC per MOB (from Intake form): _____ EDC in db: _____ OB & db are: 0-3d diff (term) Same (premie) Discrepant

If discrepancy, explain:

_____

General Notes:

_____

Medical Record Abstraction Form: Delivery/Birth Information

PPD **Provider? Yes No** Pregnancy ID _____
Group Code: _____

If yes, date Baby HIPAA signed by MOB:

Date records received: _____

Birth Information	**Agree w MOB?**
☐ Liveborn ☐Stillborn	☐Y ☐N
☐ Male ☐ Female	☐Y ☐N
EDC: _____	☐Y ☐N
Date of Birth: _____	☐Y ☐N
GA at Delivery: _____ wks	
Estimate of GA by Exam: _____ wks	
Weight: _____ ☐ gm ☐ lb/oz	☐Y ☐N
Length: _____ ☐ cm ☐ in	☐Y ☐N
OFC: _____ ☐ cm ☐ in	☐Y ☐N
Apgars 1 min: _____ 5 min: _____	☐Y ☐N
☐Single ☐ Multiple: # ____ *of* ____	☐Y ☐N
Chorionicity/Amnionicity:	
☐ Di-Di	
☐ Mono-Di	
☐ Mono-Mono	
☐ Triplets+	
☐ NN	

Delivery Information	**Agree w MOB?**
Mode: ☐ Vaginal ☐ C/S ☐ *1°* ☐ *Rpt* ☐ *NN** ☐ NN	☐Y ☐N
Presentation: ☐Vtx ☐Breech ☐Other _____ ☐ NN	☐Y ☐N
Intervention: ☐ Forceps ☐ Vacuum ☐ Neither ☐ NN	☐Y ☐N
Rupture of Membranes: ☐ SROM ☐ AROM ☐ NN	
Labor: ☐ None ☐ **Induced** ☐ Spontaneous ☐ NN	
If spontaneous, **augmented**? ☐Yes ☐No ☐NN	
If C/S, or if labor was Induced or Augmented, reason(s):	
☐ Repeat C/S	☐Y ☐N
☐ Failure to Progress →	☐Y ☐N
☐Arrest of Descent ☐Arrest of Dilation ☐Arrest of Labor	☐Y ☐N
☐CPD ☐NN ☐ Other:_____	
☐ Fetal Malpresentation	☐Y ☐N
☐ Non-Reassuring Fetal Status: _____	☐Y ☐N
☐ IUGR	☐Y ☐N
☐ Pregnancy-Related Condition: _____	☐Y ☐N
☐ Pre-Existing Maternal Condition: _____	☐Y ☐N
☐ Multiples	☐Y ☐N
☐ Non-Medical Reason: _____	☐Y ☐N
☐ Premature Rupture of Membranes	☐Y ☐N
☐ Post-Term (GA ≥ 42 weeks)	☐Y ☐N
☐ Other: _____	☐Y ☐N
☐ NN	

For any discrepancies w/MOB report, describe discrepancy and note which account is entered in database and why:

Throughout this form "NN" = Not Noted

Form Color: Pink

Medical Record Abstraction Form: Pediatrician – 0-6 Months

PPD **Provider?** ☐ Yes ☐ No Pregnancy ID _____

If yes, date Baby HIPAA signed by MOB: _____ Group Code: _____

Date records received: _____

Measurements

Birth

DOB: _____ Apgars 1min: ____ 5 min: ____

Weight: _____ ☐ gm ☐ lb/oz

Height: _____ ☐ cm ☐ in

OFC: _____ ☐ cm ☐ in

Interval Growth (preferably between 3 and 6 mos)

Visit Date: _____

Weight: _____ ☐ gm ☐ lb/oz

Height: _____ ☐ cm ☐ in

OFC: _____ ☐ cm ☐ in

Validation of Feeding Method

Breastfeeding ☐ Yes ☐ No ☐ Not Noted

Exclusive breastfeeding for the first two weeks? ☐ Yes ☐ No ☐ Not Noted

Supplementation/Formula Feeding? ☐ Yes ☐ No ☐ Not Noted

Feeding Notes, including when supplementation started, how much/how often:

Potential Malformations ☐ Not Noted

Include physical details, date first noted, date diagnosed, test results, referrals, planned follow-up, etc.

Malignancy *Include dates, biopsy information and other test results, specialist who made the dx.* ☐ Not Noted

Medical Record Abstraction Form: Pediatrician - Yearly Records

PPD **Provider?** ☐ Yes ☐ No Pregnancy ID _____
If yes, date Baby HIPAA signed by MOB: _____ Group Code: _____
Date records received: _____

Baby's DOB: _____ MR through age: ☐1 yr ☐ 2 yr ☐ 3 yr ☐ 4 yr ☐ 5 yr

Measurements *Record annual measurements; if earlier data were not previously recorded, include those also.*

Date: _____ Wt: _____ ☐gm ☐lb/oz Ht: _____ ☐cm ☐in OFC: _____ ☐cm ☐in

Date: _____ Wt: _____ ☐gm ☐lb/oz Ht: _____ ☐cm ☐in OFC: _____ ☐cm ☐in

Validation of Feeding Method ***If not captured from earlier records.*** ☐ Previously abstracted ☐ Not Noted

Breastfeeding ☐ Yes ☐ No ☐ Not Noted Exclusive BF first 2 weeks? ☐ Yes ☐ No ☐ Not Noted
Supplementation/Formula? ☐ Yes ☐ No ☐ Not Noted

Feeding Notes, including when supplementation started, how much/how often:

Potential Malformations ☐ Not Noted
Include physical details, date first noted, date diagnosed, test results, referrals, planned follow-up, etc.

Hospitalizations *Include date range of hospitalizations, reasons, and other relevant details.* ☐ Not Noted