Postapproval Pregnancy Safety Studies

Guidance for Industry

DRAFT GUIDANCE

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For questions regarding this draft document, contact (CDER) Denise Johnson-Lyles at 301-796-6169 or (CBER) the Office of Communication, Outreach, and Development at 800-835-4709 or 240-402-8010.

U.S. Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research (CDER)
Center for Biologics Evaluation and Research (CBER)

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Postapproval Pregnancy Safety Studies Guidance for Industry[1]

This draft guidance, when finalized, will represent the current thinking of the Food and Drug Administration (FDA or Agency) on this topic. It does not establish any rights for any person and is not binding on FDA or the public. You can use an alternative approach if it satisfies the requirements of the applicable statutes and regulations. To discuss an alternative approach, contact the FDA staff responsible for this guidance as listed on the title page.

I. INTRODUCTION

The purpose of this guidance is to provide sponsors[2] and investigators with recommendations on how to design investigations to assess the outcomes of pregnancies in women exposed to drugs and biological products regulated by FDA (i.e., pregnancy safety studies). The goal of postapproval pregnancy safety studies is to provide clinically relevant human safety data that can inform health care providers treating or counseling patients who are pregnant or anticipating pregnancy about the safety of drugs and biological products through inclusion of the information in a product's labeling.

In the years since FDA issued guidance on this topic, pregnancy safety studies required by FDA have expanded beyond those using data from pregnancy exposure registries (pregnancy registries)[3] to also include other types of epidemiologic studies and pregnancy surveillance programs. This guidance should be used in conjunction with other epidemiological literature on the design, conduct, and interpretation of observational studies. The development of pregnancy safety studies requires specialized knowledge in a variety of areas, including expertise in the fields of epidemiology, clinical teratology, obstetrics, pediatrics, clinical genetics, and statistics when designing a study.[4]

[1] This guidance has been prepared by the Postapproval Pregnancy Safety Studies working group in the Center for Drug Evaluation and Research in cooperation with the Center for Biologics Evaluation and Research and the Office of Women's Health in the Office of the Commissioner at the Food and Drug Administration.

[2] For the purposes of this guidance, *sponsors* refer to persons or entities that conduct or fund studies for approved products.

[3] A pregnancy registry collects data that are then analyzed to address a safety question. For the purposes of this guidance, *pregnancy registry* refers to both the data collection and the study that uses the data.

[4] The previous guidance for industry *Establishing Pregnancy Exposure Registries* published August 23, 2002, has been withdrawn.

In general, FDA's guidance documents do not establish legally enforceable responsibilities. Instead, guidances describe the Agency's current thinking on a topic and should be viewed only as recommendations, unless specific regulatory or statutory requirements are cited. The use of the word *should* in Agency guidances means that something is suggested or recommended, but not required.

II. BACKGROUND

Pregnant women represent an important segment of the population, with over 6 million pregnancies occurring per year, based on national vital statistics (Curtin et al. 2015). Pregnant women may have chronic conditions, such as diabetes, seizure disorders, or asthma, that need to be treated during pregnancy, or pregnant women may develop acute or serious medical conditions during pregnancy that require treatment. In addition, nearly half of all pregnancies in the United States may be unintended, which could result in potential inadvertent exposure to drugs and biological products in pregnancy if a woman is exposed to a drug when she is not aware she is pregnant (Finer 2016). Therefore, there is an important need for safety information on product exposure during pregnancy.

During clinical development of most drugs and biological products, pregnant women are actively excluded from trials, and if pregnancy does occur during a trial, the usual procedure is to discontinue treatment and monitor the women to assess pregnancy outcomes. Consequently, at the time of a drug or biological product's initial marketing, except for drugs and biological products developed to treat conditions unique to pregnancy, there are no or limited human data to inform the safety of a drug or biological product taken during pregnancy.

Section 505(o)(3) of the Federal Food, Drug, and Cosmetic Act (FD&C Act) (21 U.S.C. 355(o)(3)), added by section 901 of the Food and Drug Administration Amendments Act of 2007 authorizes FDA to require certain postmarketing studies or clinical trials for prescription drugs approved under section 505(b) of the FD&C Act and biological products approved under section 351 of the Public Health Service Act (42 U.S.C. 262). Under section 505(o)(3), FDA can require such studies or trials at the time of approval to assess a known serious risk related to the use of the drug, to assess a signal of serious risk related to the use of the drug, or to identify an unexpected serious risk when available data indicates the potential for a serious risk. Under section 505(o)(3), FDA can also require such studies or trials after approval if FDA becomes aware of *new safety information*.[5] Postapproval studies using data collected in pregnancy registries may be required to assess potential serious risks to the pregnancy that may affect the health of the fetus or the woman due to drug or biological product use during pregnancy.[6] However, gaps in safety data in pregnant women still exist.

[5] Defined at section 505-1(b)(3) of the FD&C Act. Also see the guidance for industry *Postmarketing Studies and Clinical Trials — Implementation of Section 505(o)(3) of the Federal Food, Drug, and Cosmetic Act* (April 2011). We update guidances periodically. For the most recent version of a guidance, check the FDA guidance web page at https://www.fda.gov/RegulatoryInformation/Guidances/default.htm.

[6] See the guidance for industry *Postmarketing Studies and Clinical Trials — Implementation of Section 505(o)(3) of the Federal Food, Drug, and Cosmetic Act*.

FDA held a 2-day public meeting in 2014 where stakeholders, including birth defect experts from academia, industry, professional organizations, and patient groups, discussed the conduct of pregnancy registries and epidemiologic studies using different study designs.[7] In addition, FDA conducted reviews of pregnancy registries listed on the FDA's Office of Women's Health web page (Gelperin et al. 2017). Based on FDA reviews and the 2014 public meeting, FDA understands that pregnancy registry data have contributed to labeling changes and clinical guidelines, but their potential has not been fully realized, often because of feasibility issues.

Pregnancy registries remain an important tool for safety data collection in the postmarketing setting because of the prospective design and the ability to collect detailed patient level data. However, because of the recurring challenges of achieving sufficient enrollment, pregnancy registries generally are not sufficient by themselves to assess the safety of products during pregnancy; therefore, other study methods capable of appropriately assessing the occurrence of specific major congenital malformations (MCMs) (e.g., birth defects and congenital anomalies)[8] and other pregnancy outcomes are needed. In addition, use of complementary approaches may help address the limitations inherent to a specific study design and provide greater confidence in the conclusions. Input received from the 2014 public meeting and findings from FDA reviews were used to develop this guidance.

The following sections describe three general approaches (pharmacovigilance, pregnancy registries, and complementary data sources) that can be used in the postmarket setting to evaluate drug or biological product safety during pregnancy. These approaches are not intended to imply a hierarchy of evidence from the different study methods. Rather, each approach may uniquely contribute to the overall safety assessment of a product during pregnancy. When considering postmarketing approaches, the selection of any one or combination of these assessments and timing of initiation may vary by drug or biological product. Consideration can be given to experience with similar drugs and biological products, knowledge of the underlying disease and its risks (maternal and fetal), potential use of the drug or biological product in females of reproductive potential and pregnant women, existing knowledge of a safety concern, and the potential for capturing the same pregnancy in two different assessments (*double counting*). Moreover, evaluation of the strengths and limitations inherent to each type of assessment allows FDA to recommend or require the appropriate method of postapproval risk assessment.[9]

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[7] See transcripts from the FDA public meeting "Study Approaches and Methods to Evaluate the Safety of Drugs and Biological Products During Pregnancy in the Post-Approval Setting," May 28-29, 2014, at https://www.fda.gov/Drugs/NewsEvents/ucm386560.htm.

[8] For the purposes of this guidance, the following terms are used interchangeably: *congenital malformations*, *congenital anomalies*, and *birth defects*, and are referred to as MCM throughout this guidance.

[9] The authority to require a responsible person to conduct a postapproval study or studies or clinical trial(s) of a drug under section 505(o)(3) includes the authority for FDA to set parameters for the study or trial to be conducted, including how the study or trial is to be done and the population and indication. In other words, under section 505(o)(3), we can require a study or clinical trial that is well designed and adequate to address the serious safety concern. Our current thinking on this and other matters is set forth in the guidance for industry *Postmarketing Studies and Clinical Trials — Implementation of Section 505(o)(3) of the Federal Food, Drug, and Cosmetic Act*.

III. PHARMACOVIGILANCE — CASE REPORTS AND CASE SERIES

Good pharmacovigilance practice involves the collection of comprehensive data on adverse pregnancy outcomes to detect safety signals and develop a case series for analysis. Sources can include spontaneous reports submitted to the sponsor and FDA, as well as case reports from the medical literature or clinical studies. Well-documented and informative case reports can be used to identify a signal, particularly if the pregnancy outcome is rare in the absence of drug exposure. Safety signals generally indicate the need for further investigation, which may or may not lead to the conclusion that the product caused the outcome or increased the risk of the outcome. The importance of astute clinicians and clinical judgment in identifying a distinctive and unique pattern of congenital malformations associated with a particular pregnancy exposure has been critical in identifying teratogens (Shepard 1994; Obican and Scialli 2011). The quality of the reports is critical for appropriate evaluation of the potential relationship between the product and adverse outcomes. FDA recommends that sponsors make a reasonable effort to obtain complete information for case assessment during initial contacts and subsequent follow-up.

Case reports are the most common source of reports of adverse pregnancy outcomes but can often be challenging to interpret because information is often incomplete or there are additional risk factors for the adverse pregnancy outcome, which case reports may not address. In addition, one needs to consider the background rates of adverse pregnancy outcomes. Good case reports include numerous important elements for conducting adequate pharmacovigilance. Specific critical factors in evaluating the effects of product exposure in human pregnancies may include, but are not limited to, the following:[10]

- A detailed description of the adverse pregnancy outcome
- A detailed description of the exposure including the specific medication, the dose, frequency, route of administration, and duration
- The timing of the exposure in relation to the gestational age
- The maternal age, medical and pregnancy history, and use of concomitant medications, supplements, and other substances
- Exposures to known or suspected environmental teratogens

FDA has occasionally considered case reports and case series to be adequate data sources for establishing a causal association for a human teratogenic exposure, such as with isotretinoin (Centers for Disease Control and Prevention (CDC) 1984; Rosa 1983), or a serious adverse event, such as oligohydramnios with trastuzumab (Zagouri et al. 2013). In general, such evidence has been evaluated on a case-by-case basis. Case reports have been most useful and influential in situations where the adverse pregnancy outcome rarely occurs as a background

[10] See the guidance for industry *Good Pharmacovigilance Practices and Pharmacoepidemiologic Assessment* (March 2005).

event, and the adverse outcome is well-documented. A suspected safety signal arising from case reports and case series that is not initially confirmed should be viewed as the start of an iterative process, and not necessarily conclusive evidence of absence of risk.

Known limitations of spontaneous postmarketing reports (such as under-reporting, lack of a denominator, and incomplete information) pose considerable challenges in analyzing cases and determining whether a causal relationship exists between a product exposure and an adverse pregnancy outcome.[11] Thus, routine pharmacovigilance usually will be insufficient for a conclusive assessment regarding the potential risk of an exposure during pregnancy because of the inability to quantify risk. Observational studies such as pregnancy registries and other pharmacoepidemiological studies usually are needed to provide additional information including a control group to derive and compare rates on safety outcomes of drugs and biological products used during pregnancy. A sponsor should have a structured approach for pregnancy surveillance with targeted questionnaires to obtain follow-up information on all potentially exposed pregnancies of which the sponsor becomes aware, regardless of whether the pregnant woman chooses to enroll in a registry. Pregnant women should be able to decline participation or additional follow-up at any time at their discretion.

IV. PREGNANCY REGISTRIES

A. Overview

A pregnancy registry actively collects information on drug or biological product exposure during pregnancy and associated pregnancy outcomes, which can be used to conduct a prospective observational study (women are enrolled before the pregnancy outcome). Pregnancy registries depend on the voluntary participation of women who have been exposed to a specific drug or biological product during pregnancy and unexposed women who enroll into the comparator cohort. Pregnancy registry data are prospectively collected by maternal interview and medical record documentation and may include results of the clinical examination of the newborn. Because of the prospective design of pregnancy registries, they may support assessment of multiple maternal, obstetrical, fetal, and infant outcomes, including pregnancies that do not result in a live birth.

A pregnancy registry may be U.S.-based or international in its scope. When submitting interim and final pregnancy registry study reports, sponsors should include cumulative analyses of worldwide pregnancy surveillance data to provide perspective on registry feasibility and updates on available safety data in pregnant women that may not be included in the registry.

Pregnancy registries have the following strengths:

- By enrolling women exposed to the product of interest, pregnancy registries can be an efficient way to collect data on the effects of rare exposures during pregnancy.

[11] Ibid.

- A pregnancy registry can be initiated and start to accrue real-time data as soon as a product becomes commercially available, in contrast to the use of claims data and electronic health records where there will be a lag time in data availability.

- Prospective enrollment facilitates ascertainment of an exposure of interest close to the time it occurs and before information about the pregnancy outcome is known.

- Pregnancy registries have the potential to obtain accurate information about whether exposure occurred and the timing of the exposure in relation to gestational age, dose, frequency, and duration of the exposure, as well as covariates, and may therefore reduce exposure misclassification, recall bias, and confounding.

- A pregnancy registry can potentially collect data on a variety of pregnancy and infant outcomes, including postnatal outcomes.

- A pregnancy registry can be designed to include data from physical examination of the newborn, and periodic clinical assessment of the offspring of exposed mothers, enabling access to detailed clinical information about outcomes of interest, without relying on International Classification of Diseases (ICD) codes.

Pregnancy registries have the following limitations:

- Analyses of collected data may have minimal statistical power to detect associations for rare pregnancy outcomes.

- Most pregnancy registries are designed primarily to collect data used to assess the overall risk of MCMs. Effects on less common, specific MCMs may be missed for all but the most potent teratogens.

- Patient recruitment and retention are often challenging, and identification of an appropriate comparator group may not always be feasible.

- Data from pregnancy registries generally are not sufficient by themselves to assess the safety of products during pregnancy, and other study methods such as retrospective cohort studies or case control studies may be needed to corroborate registry findings.

The ability of a pregnancy registry to provide safety data that can be used to inform product labeling depends on factors such as the availability and quality of key clinical data and the number of patients enrolled into the registry. Sponsors should address registry design considerations (discussed below) in a written protocol and statistical analysis plan that include considerations of study feasibility.

B. Registry Design Considerations

A well-written protocol for a pregnancy registry should describe its objectives, which may range from open-ended safety surveillance to testing a specific hypothesis. The following issues

should be addressed in the protocol to ensure consistency of data collection and analysis that will provide scientifically valid results.

1. Objectives

The protocol should state the objectives of the registry for all study outcomes. An effective pregnancy registry has the potential to serve as an early warning system to identify a previously unrecognized major teratogen soon after market introduction by identifying MCMs in infants of exposed mothers. For less potent teratogens or for drugs and biological products that cause other adverse pregnancy outcomes, a pregnancy registry can function as a signal detection study and generate hypotheses that can be tested using other methods that may be better powered to assess specific birth defects or other abnormalities.

2. Study Population for Inclusion

Ideally, women in the exposed and unexposed cohort should be enrolled in a pregnancy registry prospectively (i.e., before the conduct of any prenatal tests that could provide knowledge of the outcome of pregnancy). If the condition of the fetus has already been assessed through prenatal testing (e.g., targeted ultrasound, amniocentesis), such reports traditionally have been considered retrospective. However, because it may be difficult to obtain enrollment before prenatal testing on a consistent basis, the study population should include all women, including those who have had early prenatal testing, and the protocol should address how pregnancies with prenatal testing before enrollment will be evaluated in statistical analyses to avoid potential bias.

3. Outcome Definition(s) and Ascertainment

A pregnancy can result in live birth, miscarriage (loss before 20 weeks), elective termination, or fetal death/stillbirth (loss after 20 weeks). Within each of these categories the fetus or infant can be evaluated for the presence or absence of the primary outcome. As part of the study design, the protocol should state a priori criteria for defining study outcomes. Criteria for defining birth defects as *major* should be clearly stated. For example, MCMs might be defined as "abnormalities in structural development that are medically or cosmetically significant, are present at birth, and persist in postnatal life unless or until repaired." Similarly, criteria should be established for abnormalities that will be excluded from the definition of outcome (e.g., those that are minor, transient, chromosomal abnormalities, genetic syndromes, positional defects, prematurity related) (Holmes and Westgate 2011). A standardized classification system should be used, as appropriate. An expert clinical geneticist or dysmorphologist should review and classify medical records and reports of all MCMs. The clinical expert reviewer and method of assessment should be the same for both the exposed and comparator group(s) and the reviewer should be blinded to the exposure status.

Some examples of other outcomes that may be primary or secondary on a case-by-case basis include:

- Measures of fetal growth deficiency (small for gestational age)
- Preterm delivery

- Other pregnancy complications
- Developmental milestones or neurologic abnormalities in offspring of exposed mothers
- Abnormalities of immune system development in offspring of exposed mothers

4. Sample Size and Statistical Power

A written protocol for a pregnancy registry should include a statistical analysis plan with a description of target sample size based on power calculations, and assessment of feasibility of the study in the patient population of interest. When estimating the target sample size, it is important to take into consideration the expected background rate of pregnancy loss, and cases that may be lost to follow-up or otherwise unevaluable. Estimated rates based on the general population may not apply to specific disease groups (e.g., diabetes).

Determination of an adequate sample size depends on the objective(s) and design of the registry and the background rate of the outcome in the study population. If more than one pregnancy outcome is considered, sample size determination should be based on the outcome with the lowest background rate (e.g., MCMs). Consideration should be given to the prevalence of the disease in females of reproductive potential and pregnant women and anticipated frequency of product exposure in pregnant women.

No known teratogen increases the risk of all MCMs. Typically, a specific defect or pattern of defects is associated with a specific teratogenic exposure during a critical period. Specific MCMs occur rarely in the general population (i.e., fewer than 1 in 1,000 live births). Historically, pregnancy registries have not had sufficient sample size or power to evaluate increased risks for specific MCMs unless the relative risks are large (Gelperin 2017; Bird et al. 2018). Therefore, most registries compare the overall proportion of the total combined number of various MCMs observed in the exposed group to the overall proportion in the comparator group(s). Sponsors should include justification for the choice of expected background rates for outcomes of interest in their proposed sample size and power calculations.

5. Safety Evaluation When a Pregnancy Registry Is Not Feasible

In some situations, a pregnancy registry may never have adequate power to allow statistical inference. Achievement of an adequate sample size may not occur when the likelihood of exposure in pregnancy is low, or use of a product is not recommended during pregnancy. Anticipated issues with registry study feasibility should be stated in the protocol and appropriately addressed, for example by expanding the inclusion criteria to include all reports of exposed pregnancies (both prospective and retrospective). For products that are anticipated to be used rarely during pregnancy (e.g., treatment of advanced cancer), sponsors can consider a pregnancy surveillance program (a structured approach for data collection with targeted questionnaires to obtain follow-up information on all exposed pregnancies of which sponsors become aware). This type of case series of exposed pregnancies can inform clinical and regulatory decision-making. Worldwide safety data collection is usually needed to identify a sufficient number of exposed pregnancies for clinical safety assessment.

6. Comparator Selection — Reference Group(s)

The strategy for selection of an appropriate comparison group(s) should be made when designing the pregnancy registry and should be included in the protocol. Ideally, the registry should enroll a concurrent internal comparison group of pregnant women unexposed to the evaluated treatment. In addition, patients with the same disease (and disease severity, if feasible) should be compared, because confounding due to the underlying condition may arise. Cohorts exposed to different treatment regimens, when available, can serve as additional internal comparator groups when evaluating a specific drug or biological product used as one treatment in a multiproduct or disease-based registry study (for example, autoimmune diseases).

A background rate or the prevalence of congenital anomalies in a population-based surveillance system (e.g., Metropolitan Atlanta Congenital Defects Program (MACDP))[12] or from another pregnancy registry may be the only available comparator in certain situations. However, if background rates or information from the external population-based surveillance system are chosen as a comparison group, it is important to be aware of the limitations of whatever existing system is used so that appropriate analyses can be designed, and results interpreted correctly. For example, while MACDP prevalence data are well-documented and stable over time, they have several characteristics that limit their validity as a comparator group for a pregnancy registry. Limitations include the small geographic region from which the data are drawn (metropolitan Atlanta); inclusion and exclusion criteria for outcomes of interest that differ from the registries (particularly with regard to chromosome abnormalities); and the duration of postnatal follow-up. Importantly, because external comparators typically estimate risk in the general, mostly healthy, population, they may not be helpful to discern effects of the exposure of interest and the underlying disease of the pregnant woman undergoing treatment, such as diabetes or asthma.

When available and feasible, sponsors can consider use of external databases with data on background rates in the disease population of interest to ensure comparability of groups. Selection of an appropriate comparator is important because comparing dissimilar populations could bias the study results, indicate a risk when none exists, or mask an increased risk that exists. When feasible, selection of multiple comparator groups may be informative.

7. Exposure Definition and Ascertainment

Sponsors should collect detailed information on start and stop dates for all products taken during pregnancy, as well as dose, frequency, duration, and indication. Exposure information in the time period just before pregnancy is also often important, especially for products with a long half-life. Accurate information about specific gestational timing of exposure(s) can help identify critical exposure periods during gestation and biological plausibility for specific effects.

8. Covariates — Potential Confounders

Sponsors should consider the potential for confounding by indication, which makes it difficult to determine whether any observed effects are caused by the drug or biological product or the

[12] https://www.cdc.gov/ncbddd/birthdefects/macdp.html

underlying disease. Data should be collected on the pregnant woman's pertinent medical history, current disease status, and overall management. Other potential confounders for which data should be collected include, for example: socioeconomic status, maternal age, tobacco and alcohol use, illegal drug use, maternal body mass index, folic acid and vitamin use during the pregnancy, obstetrical history, medical history, family history of adverse pregnancy outcomes including MCMs, and other relevant confounders (Caton 2012).

9. Data Collection

The value of the pregnancy registry depends on the accuracy and comprehensiveness of its data. All data collection efforts should be identical among exposed and comparator study groups to minimize bias.

The objective(s) of the registry should determine the type, extent, and length of patient follow-up. The feasibility of obtaining reliable pregnancy and infant outcome information is a critical consideration in pregnancy registry design. Although prenatal health care providers are a good source of information on outcomes, such as miscarriage, elective terminations, live births, and pregnancy complications, they are not a good resource for information on infant conditions not readily diagnosed at or soon after birth. The infant's health care provider is the best resource for full information on the health status of the infant after birth. The protocol should also specify inclusion of pertinent findings from postmortem examination of pregnancies with nonlive birth outcomes to avoid bias due to under-ascertainment of major malformations (Holmes and Westgate 2011).

The protocol should include a plan and rationale for follow-up contacts during and/or after pregnancy. The follow-up contact should obtain details on the pregnancy course, outcome, status of the infant, and any evidence of abnormalities.

See Appendix A for a list of recommended data elements to include when designing a pregnancy registry.

10. Data Analysis and Presentation

Validation of cases should be performed through medical record review and adjudication of outcomes by a clinical dysmorphologist or appropriate specialist for both the exposed and comparator group(s).

Inferential statistics should be applied to test prespecified hypotheses regarding the potential association between the exposure and the outcome(s) of interest.

Potential biases should be discussed, as well as possible methods for mitigation, if applicable. Descriptive statistics are the primary approach for summarizing patient characteristics and additional data from a pregnancy registry. Given the heterogeneous nature of data obtained in pregnancy registries, there is no one format for data presentation that is applicable for all studies. The choice of a final format depends on outcomes identified in the registry protocol, unanticipated findings, and expert advice. We encourage sponsors to develop forms of data

presentation and analysis that fully capture outcomes of concern within their particular registry. Separate analyses should be performed for each pregnancy outcome (miscarriage, elective termination, fetal death/stillbirth, live birth) and stratified by gestational timing of exposure (with a separate analysis of first trimester exposures for MCMs). Additional analytical approaches should be used to assess covariates and factors that may affect the study findings, such as gestational timing of enrollment (Margulis et al. 2015).

11. Privacy and Human Subject Protection Issues

Sponsors should consider privacy (including data protection) and human subject protection (including obtaining informed consent and institutional review board (IRB) oversight) when designing a pregnancy registry and developing protocols for the subsequent use of the data from the registry. FDA recommends that an IRB be consulted when developing a pregnancy registry to ensure that the collection of data and all other procedures associated with the registry will withstand scientific and ethical scrutiny.

Because pregnancy registries typically do not involve the administration of an investigational product, there is not likely to be any foreseeable risk or harm to the pregnant woman, fetus, or resulting child from participating in the registry other than risk associated with inappropriate disclosure of identifiable private information. The patient should be requested to sign medical record release forms to allow collection of the records from the health care provider(s) of the mother and infant. Investigators are responsible for ensuring that any data releases are compliant with the Health Insurance Portability and Accountability Act and that all research performed complies with standards of privacy of individually identifiable health information.

If the registry involves the collection of information on the child after birth, either through a physical examination or specimen collection, considerations should be given to 21 CFR part 50, subpart D, Additional Safeguards for Children in Clinical Investigations (for FDA-regulated human subjects research).

12. Independent Data Monitoring Committee/Scientific Advisory Board

To ensure scientific integrity and appropriate patient protection, we encourage each registry to have an independent data monitoring committee (or scientific advisory board) similar to those used for clinical studies. Members of the committee could include experts in obstetrics, embryology, teratology, pharmacology, epidemiology, pediatrics, clinical genetics, and any relevant therapeutic areas. The committee could assist in the review of data, classification of specific pregnancy outcomes including MCMs when relevant, and the dissemination of information to ensure that results are interpreted and reported accurately. We recommend that the role and duties of the committee or scientific advisory board be specified in the protocol.

13. Recruitment and Retention Plans

Successful recruitment and retention strategies are critical to the success of pregnancy studies such as registries or other studies requiring enrollment of study subjects. We recommend a robust recruitment and retention plan that includes a multipronged approach to ensure

widespread coverage of the eligible population. Early enrollment also may improve detection of pregnancy outcomes such as miscarriage. These plans should be flexible and continuously reassessed throughout the study to ensure the registry maintains an adequate number of eligible pregnant women in both the exposure and comparator groups.

a. Recruitment

Engaging health care providers and patients before the initiation of recruitment increases awareness of the study and provides an opportunity to seek feedback from these stakeholders regarding the study plan. We encourage sponsors to collaborate with entities such as existing registries, patient advocacy groups, medical societies, and other relevant organizations to engage in awareness activities.

Under the Pregnancy and Lactation Labeling Rule requirements, if there is a pregnancy registry for the product, relevant contact information must be included in product labeling under the subheading Pregnancy Exposure Registry.[13] Suggested modes of contact information include a toll-free telephone number or a website's uniform resource locator (URL).

The FDA's Office of Women's Health (OWH) maintains an online list of pregnancy registries that are actively enrolling women to raise awareness about pregnancy registries and connect consumers and health professionals to registries. The registries are posted to the FDA's OWH web page based on a sponsor's or investigator's request to list its registry. FDA encourages sponsors and investigators to submit a pregnancy registry listing to OWH at Registries@fda.hhs.gov. FDA does not endorse any registry and is not responsible for the content of registries listed on the web page.[14]

Recruitment strategies can be described as facility-based, health care provider-initiated, or patient-initiated.

- Facility-based recruitment can occur at the level of a practice or health system. Electronic health records can be used to identify drug or biological product users to facilitate the enrollment process for providers. For example, an automated alert of a pregnancy registry can be generated in response to positive pregnancy test results and/or specific drug or biological product prescriptions.

- Health care provider-initiated recruitment of patients is an important deciding factor for many pregnant women. Provider recruitment approaches include:

  – Announcement of the registry study and contact information in the product labeling
  – Promotional materials and product Internet pages

[13] 21 CFR 201.57(c)(9)(i)(A).

[14] The Pregnancy Registries web page is located at https://www.fda.gov/ScienceResearch/SpecialTopics/WomensHealthResearch/ucm251314.htm. The OWH mailbox address and the web page URL may change. See the FDA website for the most recent information (https://www.fda.gov/).

- Announcements in professional journals and newsletters
- Personal mailings to specialists
- Presentations and exhibits at professional meetings

- Patient-initiated recruitment efforts rely on patients to contact the registry study staff and self-enroll. Because pregnancy is often recognized by the patient first, registries that enroll patients directly can allow for recruitment of patients earlier in pregnancy. Useful avenues to notify pregnant women of pregnancy registries include:

  - Print media including publications, press releases, and articles in newspapers and magazines with pregnant women among their readership

  - Distribution of flyers and posters in locations such as hospitals, ultrasound clinics, laboratories, prenatal classes, community centers, stores, and coffee shops (Webster et al. 2012)

  - Social media

  - Downloadable applications for mobile devices or personal computers could enable broader participation through ease of providing information[15]

Successful strategies to encourage the participation of pregnant women in medical research that may be applicable to postapproval safety studies include:

- Incentives that facilitate study participation (Webb et al. 2010)

- Employing empathetic, culturally sensitive, and personable study staff (El-Khorazaty et al. 2007).

b. Retention

Even though recruitment materials may yield strong initial recruitment results, we recommend implementing a robust retention plan to ensure that an adequate number of pregnant women remain in the registry. The retention plan should address specifics of patient retention strategies, contingency plans to obtain follow-up information, methods to track follow-up rates over time, and implementation steps to improve follow-up if expected follow-up rates are not met.

FDA also recommends that retention efforts focus on participating health care providers to improve retention rates and reduce the burden of data collection (e.g., implementing streamlined processes and succinct forms). Access to pregnancy registry results provides a strong incentive for the participation of health care providers, particularly obstetric care providers, and the provision of interim data reports to participating health care providers may bolster retention. Additionally, high levels of retention have been achieved by pregnancy registries that communicate directly with patients. Emphasizing the mission of the pregnancy registry may

[15] See the FDA's MyStudies Application (App) web page at https://www.fda.gov/Drugs/ScienceResearch/ucm624785.htm.

reinforce participants' motivation to remain in the study. Sharing study results through a newsletter or website has been found to be effective in reinforcing patients' altruistic reasons for participation. Establishing and maintaining a longitudinal relationship between participant and interviewer can reduce loss to follow-up. As with other longitudinal studies, collecting contact information of family members or friends in case the patient cannot be reached can aid in retention. Recruitment and retention of pregnant women may be aided by a flexible follow-up schedule (e.g., conducting follow-up interviews by telephone, during evening and weekend hours or over a secure online platform), because participants may be balancing work and childcare responsibilities.

14. Multiproduct Pregnancy Registries

To prevent overburdening patients, physicians, and health delivery systems with multiple requests to participate in individual studies, we encourage sponsors to work together directly or through consortiums to develop or support multiproduct registries. A multiproduct pregnancy registry actively collects information on exposure to various product therapies in specific diseases, such as human immunodeficiency virus or epilepsy (Hernández-Díaz et al. 2012). In some cases, a general multiproduct registry, such as that conducted by a teratogen information service, collects information on products for unrelated indications.[16] Multiproduct registries have advantages over single-product registries with respect to efficiency and economy. They also have the advantage of having comparison groups of pregnant women unexposed to the drug or biological product of interest readily available (see section IV.B.6., Comparator Selection — Reference Group(s)).

15. Pregnancy Registry Discontinuation

We recommend that a pregnancy registry be continued until one or more of the following occurs:

- Sufficient information has accumulated to meet the scientific objectives of the registry
- The feasibility of collecting sufficient information diminishes to unacceptable levels because of low exposure rates, poor enrollment, or loss to follow-up
- Other methods of gathering appropriate information become achievable or are deemed preferable

16. Lactation Study Added on to a Pregnancy Registry

There is also often a need to collect lactation data to provide information on the safety of drugs and biological products during breast-feeding. Pregnancy registries can be used to recruit and enroll breast-feeding women in lactation studies. Some women enrolled in a pregnancy registry are already taking a drug or biological product during pregnancy, and because they may be likely to continue treatment after delivery, these women are an ideal population in which to study

[16] See the MotherToBaby pregnancy studies conducted by the Organization of Teratology Information Specialists available at https://mothertobaby.org/pregnancy-studies/.

product levels in milk. For information on how to conduct a lactation study, see the draft guidance for industry *Clinical Lactation Studies: Considerations for Study Design*.[17]

V. COMPLEMENTARY STUDIES

Use of complementary studies with different study designs may help address the limitations inherent to a pregnancy registry. Additionally, as more postmarketing safety information becomes available from interim registry reports, spontaneous reports, or case series, a more specific safety signal may become apparent. Thus, additional studies that complement data obtained from pregnancy registries and other sources, referred to as *complementary studies* in this guidance, can be implemented as the need arises to better understand the specific effects of using a drug or biological product during pregnancy, and to more precisely quantify the magnitude of an association between a pregnancy exposure and a specific outcome.

Complementary studies can be retrospective in design, using secondary data (i.e., data collected for purposes other than to assess the safety of one specific drug or biological product).[18] Common retrospective data sources and study designs used for complementary studies for purposes of pregnancy-related research can include the following:

- Electronic data sources (e.g., insurance claims and electronic health record databases)
- Population-based surveillance and national registries or registers
- Population-based case control studies

These data sources and designs are discussed in the following subsections.[19]

A. Electronic Data Sources

Electronic data sources often contain a large number of records available for research. At the time of publication of this guidance, electronic data sources readily available for pregnancy research include electronic administrative claims databases and/or electronic health record (EHR) databases, referred to collectively as *electronic health care data (EHD)* in this guidance. Best practices for studies using these data sources have been described in guidance[20] and also apply to pregnancy studies using EHDs.

[17] When final, this guidance will represent the FDA's current thinking on this topic. For the most recent version of a guidance, check the FDA guidance web page at https://www.fda.gov/RegulatoryInformation/Guidances/default.htm.

[18] As the need arises, secondary data can be supplemented with additional data collection (e.g., maternal interview).

[19] Methods used to identify and evaluate pregnancy outcomes in a pregnancy registry study described in section IV., Pregnancy Registries (e.g., study objective(s), outcome(s), comparators, exposure, confounders, statistical analysis plan) also apply when considering complementary studies and will not be repeated in this section. This section addresses concerns specific to the data sources selected for complementary studies.

[20] See the guidance for industry and FDA staff *Best Practices for Conducting and Reporting Pharmacoepidemiologic Safety Studies Using Electronic Healthcare Data* (May 2013).

Regardless of the specific type of electronic data sources and study design used, investigators should fully understand and describe the strengths and limitations of the data source proposed (including the population(s) covered, data elements captured and their validity, system(s) of care, and system-specific clinical and pharmacy data) to evaluate whether the data source is appropriate to address specific pregnancy-related hypotheses.

Pregnancy and/or live birth data from EHD sources have been developed and used in a variety of ways to evaluate product exposure and/or safety during pregnancy (Devine et al. 2010; Andrade et al. 2012; Taylor et al. 2015; Huybrechts et al. 2014). Despite its successful and growing use, selection of an EHD source to evaluate drug or biological product safety in pregnancy should reflect consideration of methods used to identify pregnancies, estimates of conception and gestational age, linkage to offspring records, and ascertainment and validation of pregnancy and birth outcomes. Each of these considerations is discussed below.

1. Methods to Identify Pregnancies

The ability to identify clinically recognized pregnancies and births using EHD is central to use of any database capable of assessing product safety during pregnancy. Identifying live births in an EHD is relatively straightforward because delivery codes are available and relatively reliable.

Sponsors should consider the implications of limiting a study population to that of only live births, because birth defects likely to result in non-live birth outcomes would not be captured. Failure to include non-live births in a study population primarily affects study generalizability; however, it also may result in a biased relative risk estimate if the rate of pregnancy loss or termination caused by the defect is higher in one group than the other.

Use of EHD to identify non-live birth pregnancy outcomes for assessment of safety signals is challenging. Non-live birth outcomes may be identified in EHD by the presence of diagnostic and/or procedure codes specific to the outcome. However, gestational age at the time of the outcome may be difficult to estimate if gestational age-specific codes accompanying the outcome codes are unavailable or unreliable. Without a reasonable estimate of gestational age, a reliable assessment of pregnancy exposure is difficult unless the investigator has access to ultrasound or laboratory data.

2. Estimates of Conception and Gestational Age

A valid estimate of gestational age, from which a conception date may be estimated, is critical for determining the timing of an exposure during pregnancy. For studies assessing pregnancy outcomes among live births only, several methods exist for identifying gestational age. These include:

- U.S. birth certificates (when available)
- Diagnostic ICD codes found in EHD databases[21] and algorithms using these codes
- EHR or ultrasound report

[21] Given the potential variability in code validity by data source and outcome type (e.g., live birth versus stillbirth), codes to identify gestational age should be validated in each database.

3. Linkages to Offspring

Common methods for mother-infant linkages in the United States include linkages using birth certificates and linkages using unique data elements within the same EHD source (Andrade et al. 2012). Linkages of pregnancies identified in EHD to offspring using birth or fetal death certificates or other sources (e.g., medical records, national or state birth defect surveillance registries) can provide the investigator access to several important variables that are not captured, poorly captured, or captured with inadequate detail in EHD sources (e.g., maternal/paternal race/ethnicity, maternal smoking status, parity, birth defects, some drug exposure, and precise estimates of gestational age and birthweight of the newborn).

Even when only EHD sources are available, study data can be enhanced by linking those from the mother to the offspring. Many EHD sources contain unique identifiers assigned to both the mother and infant that may reflect the relationship to the primary health insurance policyholder. Matching this number, as well as the mother's delivery date, to the newborn's date of birth often successfully links the mother's pregnancy to the infant's health records. However, if the newborn is covered under a different insurance policy than the mother, the linkage may be impossible or at least limited to the clinical information available on the birth certificate or other data sources.

In the United States, linkages of non-live birth outcomes identified in EHD sources to other data sources are limited. Some states require reporting of fetal deaths (after 20 weeks), and this information may be available to investigators on a case-by-case basis via the state's vital records department. Information collected by the state is often similar to that collected on a birth certificate, but specific data elements vary by state.

4. Study Outcome Ascertainment and Validation

Diagnostic and procedure codes contained in EHD sources can be used to identify and study product-associated MCMs. However, the presence of any single diagnostic code does not necessarily imply a correct diagnosis. Diagnostic codes may reflect coding errors, rule-out diagnoses, actual diagnoses, or the presence of an abnormality that has not yet been validated or characterized. The validity of diagnostic codes for specific birth defects varies greatly by specific defect and data source (Cooper et al. 2008; Palmsten et al. 2014). Outcome validation is still needed for all outcomes unless a high-performing algorithm has been previously validated for the specific outcome in the same (or similar) database under consideration. Some outcomes can be ascertained in multiple ways. For instance, preterm birth and "small for gestational age" may be identified through the presence of diagnostic codes or may be calculated using gestational age and birth weight data found on the birth certificate and/or medical record. Investigators should validate these outcomes in the specific database of interest if considering their use as endpoints in EHD studies.

For all birth outcomes identified using EHD, sponsors should use a *gold standard* method of validation such as a medical chart for the development of a testable algorithm. For MCMs, sponsors should use reviews by clinical experts (geneticists or dysmorphologists) and/or linkage

to birth defect registries and/or birth certificate data. The use of only EHD without access to such gold standard sources or, at a minimum, a high-performing validated algorithm measuring the same outcome in the specific database being considered may result in inaccuracy.

B. Population-Based Surveillance and National Registries or Registers[22]

Population-based birth defect data sources are part of surveillance networks that extend to an entire group of people having similar demographics (e.g., the entire nation in some European countries), or to similar groups of people (e.g., state or regional births in the United States). The advantage of using birth defect surveillance registries for MCM identification or validation is that the identified MCM cases have already been adjudicated. Many of these registries capture and adjudicate birth defect information for live births, stillbirths/fetal deaths, and elective terminations. Some international birth defect registries follow guidelines developed by the World Health Organization, in collaboration with the CDC and the International Clearinghouse for Birth Defects Surveillance and Research (ICBDSR). Birth defect definitions in these registries include MCMs associated with chromosomal abnormalities, which may not be applicable to outcomes associated with drug or biological product exposures.

If maternal exposure information is collected, much of it is obtained from obstetrical records. If sponsors consider population-based birth defect registries for exposure-based complementary studies, they may need to supplement the registries with drug or biological product exposure information from targeted maternal interviews and/or link to prescription information when personal interviews are not possible.[23]

Population-based birth defect registries have the substantial advantage of having large sample sizes that allow the study of relatively rare MCMs.

Examples of population-based birth defect surveillance networks include:

- State-based Surveillance (United States)
- Vaccine and Medications in Pregnancy Surveillance System (VAMPSS) (United States)[24]
- The ICBDSR[25]

[22] For the purposes of this section, the term *registry* is used interchangeably with *register* (a term more commonly used in Europe).

[23] International population-based birth defect registries, usually European, can link to other databases to obtain drug or biological product exposure and outcome information.

[24] http://www.bu.edu/slone/research/studies/vampss/

[25] http://www.icbdsr.org/resources/annual-report/

- The European Registration of Congenital Anomalies and Twins, registries[26]

Those that capture MCMs as a result of mandatory reporting allow for an accurate estimate of incident birth defects in the network, especially when the numerator can be easily linked to the number of pregnant women in the country or the region as the denominator during the study period.

Regardless of the type of surveillance or registry selected for analysis, limiting observation only to MCMs increases the risk of missing important toxic product effects that may be incompatible with life or that may occur at different times during the pregnancy. Some registries, however, do include stillbirths and elective terminations. Therefore, it is important to thoroughly understand and describe what information is and is not available in the population-based registries considered for a study, including what information is available on maternal drug or biological product exposures.

C. Population-Based Case Control Studies

Case-control study designs (including nested designs) are frequently considered when there is a need to collect additional information from the mothers through personal interviews, to obtain additional information on infants, to request permission to review medical records, or to perform long-term follow-up of the offspring. Case-control studies also may be needed if the registry is unable to collect sufficient data to assess a safety signal previously identified from another data source.

1. Selection of Pregnancy-Related Cases and Controls

Cases with pregnancy or infant outcomes of interest can be identified from EHD, or regional, national, or international birth defect registries. The same concerns identified earlier in this guidance for selection of controls or comparators for pregnancy registry studies (internal or external controls) also apply to selection of controls or comparators for complementary case-control studies (see section IV.B.6., Comparator Selection — Reference Group(s)). For any study, it is most important to ensure that comparators or controls are selected from the same disease population (internal controls) when possible. Controls can be identified from the same EHD or vital statistics departments or from general (state, regional, or national) birth records giving rise to the cases; alternatively, birth outcomes (cases and controls) can be identified from exposure- or disease-based registries.

When a case-control design is considered to evaluate a pregnancy outcome, regardless of the source from which cases and controls were identified, sponsors should validate case or control status using medical records or other reliable sources such as birth defect registries or review by clinical experts. Documentation of validation should be provided when selecting cases from these data sources. Case status identified from national or international networks are usually already validated.

[26] http://www.eurocat-network.eu/aboutus/datacollection/guidelinesforregistration/malformationcodingguides

2. Exposure Assessment

The advantages of obtaining additional information by interviewing the mother as part of a case-control study include the ability to collect data on all types of drug or biological product exposures, including those not covered by insurance (e.g., over-the-counter, supplements). An additional strength is the ability to extend or adapt the interview to capture information not available from other databases: personal or family history; race and other demographics; dose, timing, and duration of product use; history of maternal disease or indication for medication; comorbidities; and potential confounders such as body mass index, tobacco and alcohol use, reproductive history, occupation (maternal and paternal), and the occurrence of breast-feeding. At the interview, investigators can obtain informed consent to review medical records to confirm diagnoses or to identify brand or lot, among others. If relevant, investigators can request biological specimens (e.g., breast milk samples, buccal swabs for DNA testing) to test for product penetrance or assess hereditary effects. Direct access to the mothers allows specialized physical examinations and developmental follow-up of the offspring.

Exposure recall bias is always a concern for information obtained from maternal interviews, because such self-reported data are collected after the pregnancy outcome (i.e., case status) is known. Recall bias could be introduced if the accuracy of reported exposure is different between cases and controls, for example mothers of birth defect cases may more accurately recall exposures during pregnancy versus mothers of unaffected infants. Attempts to minimize this bias could include selecting as controls mothers with other adverse pregnancy outcomes (e.g., malformed infants with chromosomal defects or with malformations other than the one(s) of interest) or other serious medical problems. Another approach to minimize recall bias is the use of pharmacy records among cases and controls to confirm reported drug or biological product exposures, when available, although pharmacy data only provide information on prescription fills and not necessarily on quantity consumed and may not include over-the-counter products.

3. Examples of Pregnancy Case-Control Studies in the United States

Examples of case-control studies are listed below and can be used as a starting point for designing a study. Note, however, that data from these studies, although population-based, are only specific to the populations studied and may not be relevant to the study population under consideration. If comparisons are to be made to these studies, every effort should be made to understand and explain the similarities and differences and to identify resulting confounding and biases.

- The National Birth Defects Prevention Study[27]

- Birth Defects Study to Evaluate Pregnancy exposures[28]

[27] http://nbdps.org/

[28] http://www.bdsteps.org/

842 • Pregnancy Health Interview Study (Birth Defects Study), a multicenter case-control study
843 based at the Slone Epidemiology Center at Boston University, a collaborator of the
844 VAMPSS[29]
845

[29] http://www.bu.edu/slone/research/studies/phis/

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Guidances[1]

Draft guidance for industry *Clinical Lactation Studies: Considerations for Study Design*[2]

Draft guidance for industry *Postmarketing Safety Reporting for Human Drug and Biological Products Including Vaccines*[3]

Guidance for industry *Good Pharmacovigilance Practices and Pharmacoepidemiologic Assessment*

Guidance for industry *Postmarketing Studies and Clinical Trials — Implementation of Section 505(o)(3) of the Federal Food, Drug, and Cosmetic Act*

[1] We update guidances periodically. To make sure you have the most recent version of a guidance, check the FDA guidance web page at https://www.fda.gov/RegulatoryInformation/Guidances/default.htm.

[2] When final, this guidance will represent the FDA's current thinking on this topic. For the most recent version of a guidance, check the FDA guidance web page at https://www.fda.gov/RegulatoryInformation/Guidances/default.htm.

[3] When final, this guidance will represent the FDA's current thinking on this topic.

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APPENDIX A: LIST OF DATA COLLECTION ELEMENTS

The following data elements should be included when designing a pregnancy registry.

General

Patient identifier
Name of reporter at initial contact with the registry
Date of initial contact with the registry
Dates of any follow-up contacts
Telephone number and email address of reporter
Additional contact names, telephone numbers, and email addresses (if reporter is the patient)

Maternal Information

Source of information (e.g., obstetrician, pregnant woman)
Birth date
Race
Occupation
Height, weight, body mass index
- Maternal medical history (e.g., hypertension, diabetes, seizure disorder, autoimmune disease, known risk factors for adverse pregnancy outcomes including environmental or occupational exposures)

Obstetrical history:
- Number of pregnancies and outcome of each (live birth, miscarriage, pregnancy termination (elective or therapeutic), ectopic pregnancy)
- Previous maternal pregnancy complications
- Previous fetal/neonatal abnormalities and type

Current pregnancy:
- Date of last menstrual period
- Ultrasound results for gestational dating
- Prenatal test results (including dates)
- Pregnancy weight gain of mother
- Obstetric complications (e.g., preeclampsia, premature delivery)
- Complications during pregnancy (including any adverse product reactions) and dates
- Number of fetuses
- Disease course(s) during pregnancy and any complications
- Drug or biological product exposures (prescription drugs, over-the-counter products, and dietary supplements):
  - Name
  - Dosage and route
  - Date of first use and duration
  - Indication
- Recreational drug use (e.g., tobacco, alcohol, illicit drugs) and amount

Family history (specify type, maternal or paternal, among others):
- Malformations
- Genetic disorders
- Multiple fetuses/births

Neonatal Information

Initial:
- Source of information (e.g., obstetrician, pediatrician, mother)
- Date of receipt of information
- Date of birth or termination
- Gestational age at birth or termination
- Gestational outcome (live born, fetal death/stillborn, miscarriage, elective termination, and termination for a fetal anomaly)
- Sex
- Obstetric complications (e.g., preeclampsia, premature delivery)
- Pregnancy order (singleton, twin, triplet)
- Results of neonatal physical examination including
  - Anomalies diagnosed at birth or termination (including autopsy results)
  - Anomalies diagnosed after birth
  - Weight at birth indicating whether small, appropriate, or large for gestational age
  - Length at birth
  - Head circumference at birth indicating whether small, appropriate, or large for gestational age
  - Condition at birth (including, when available, Apgar scores at 1 and 5 minutes, umbilical cord vessels and gases, need for resuscitation, admission to intensive care nursery)
- Neonatal illnesses, hospitalizations, drug therapies

Follow-up:
- Source of information (e.g., pediatrician, mother)
- Date of receipt of information
- Anomalies diagnosed since initial report
- Developmental assessment
- Infant illnesses, hospitalizations, drug therapies