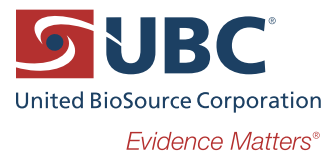


## References

1. Watts DH, Covington DL, Beckerman K, et al. Assessing the risk of birth defects associated with antiretroviral exposure during pregnancy. *Am J Obstet Gynecol*. 2004;191(3):985-992.
2. Holmes LB, Wyszynski DF, Lieberman E. The AED (anti-epileptic drug) pregnancy registry: a 6-year experience. *Arch Neurol*. 2004;61(5):673-678.
3. Wide K, Winbladh B, Kallen B. Major malformations in infants exposed to antiepileptic drugs in utero, with emphasis on carbamazepine and valproic acid: a nation-wide, population-based register study. *Acta Paediatr*. 2004;93(2):174-176.
4. Guidance of Industry: Establishing Pregnancy Exposure Registries. 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). August 2002; Clinical/Medical.
5. Reviewer Guidance: Evaluating the Risks of Drug Exposure in Human Pregnancies. 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). April 2005; Clinical/Medical.
6. Guideline on the Exposure to Medicinal Products During Pregnancy; Need for Post-Authorisation Data: European Medicines Agency. November 2005.
7. Cunnington M, Messenheimer J. Pregnancy registries: strengths, weaknesses, and bias interpretation of pregnancy registry data. *Int Rev Neurobiol*. 2008;83:283-304.
8. Cooper WO, Hernandez-Diaz S, Gideon P, et al. Positive predictive value of computerized records for major congenital malformations. *Pharmacoepidemiol Drug Saf*. 2008;17(5):455-460.
9. Devine S, West SL, Andrews E, et al. Validation of neural tube defects in the full featured—general practice research database. *Pharmacoepidemiol Drug Saf*. 2008;17(5):434-444.

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## Evaluating Pregnancy Outcomes: Prospective Pregnancy Registries vs. Administrative Database Analyses

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### Introduction

Women of childbearing age are susceptible to a wide range of medical conditions that require chronic therapy such as diabetes, depression, epilepsy and asthma. If they become pregnant, they must also face questions regarding the potential impact of their medication on the risk of birth defects. Those who seek materials regarding the potential effect of medications on risk of malformation are often disappointed by the lack of specific information available in most product labels and from medical information sources. While useful observational data have been systematically collected for some drug classes such as the antiretroviral<sup>1</sup> and antiepileptic medications,<sup>2,3</sup> many important drugs and biologics have very limited available information. To fill the knowledge gap, investigators or sponsor companies may choose to either begin new registry studies or use large administrative databases that have both prescription drug use and birth outcome information. This paper reviews strengths and weaknesses of these approaches.

The US Food and Drug Administration (FDA)<sup>4,5</sup> and European Medicines Agency (EMA)<sup>6</sup> have issued valuable guidance on relevant topics. Even with guidance from regulatory agencies, the design, conduct and interpretation of observational studies of birth outcomes following prescription drug use is a challenging venture. In addition to the challenges inherent in observational studies (e.g., non-randomized, potential confounding, no ideal comparison group), the exposure of interest, prescription drug use, brings its own set of issues (e.g., not always collected, same drug called multiple names, confounding by indication, small sample size). The outcome of interest, typically rates of major malformations, also has inherent methodological challenges (e.g., lack of standardization in collection and categorization, high rates of minor malformations). Learning from the experiences of prior work is critical to the success of these important studies.

A positive development in increasing the knowledge base on prescription drug use and pregnancy outcome is the trend toward sponsors making post-marketing commitments to create and maintain pregnancy registries for new drug or biologic products or to conduct database studies. These registries or database studies should collect additional information that will eventually be useful in guiding the prescription drug and biologic use of women of childbearing age.

Against the backdrop of a great need for more information and the inherent challenges of the topic, this white paper describes the contrasting practical and methodological challenges of 2 approaches: de novo pregnancy registries and the use of administrative databases.

### Pregnancy Registries

A pregnancy registry is an organized, prospective, observational, longitudinal study designed to estimate the overall risk of birth defects and in some cases, the risk of infant developmental delays associated with a particular drug. Pregnancy registries exist both for specific medical conditions, such as HIV/AIDS, cancer and epilepsy, as well as for specific products used to treat these conditions and other common conditions such as type two diabetes, multiple sclerosis and rheumatoid arthritis. Both the EMA and the FDA have issued guidelines on when it is appropriate to conduct a pregnancy registry.

Guidelines on When to Establish a Pregnancy Registry<sup>7</sup>

- When the medication has a high likelihood of being used in women of childbearing age.
- When the medication is for chronic therapy use and it is unadvisable to discontinue the therapy during pregnancy.
- The medication has special circumstances, such as the potential for fetal infection through administration of live attenuated vaccines.

- Animal studies or human case reports have shown the potential for fetal harm.
- When the medication belongs to a drug class or has similar components or mechanisms of action as drugs known to have teratogenic effects.

While many design issues inherent in typical registries hold true for pregnancy registries, there are special elements unique to pregnancy registries that must be addressed. Sample size in a typical non-safety registry is often determined by the commercial goals for the product, rather than power to detect events of interest. In a pregnancy registry, sample size is dictated by the frequency of the outcome of interest in both the registry (exposed) group and the comparator group.

The selection of an appropriate comparator group in a pregnancy registry is essential and can be accomplished by directly enrolling a non-exposed cohort or, more commonly, by looking to external sources of comparable cohorts and associated outcomes, most often found in hospital, state or nationwide surveillance systems and databases. Regardless of how the comparator cohort is identified, care must be taken to ensure that the cohort is as generalizable as possible, with complete reporting of all pregnancy outcomes.

Finally, successful patient recruitment and retention is dependent on a multi-faceted outreach program to healthcare providers and patients. On the provider front, data may be obtained from family practitioners, obstetricians, pediatricians and midwives, requiring the patient to provide an upfront medical release to acquire data from these many sources. Additionally, maintaining a schedule of patient contact that reinforces the importance of complete data collection while respecting patient privacy and showing sensitivity in cases of negative birth outcomes can be challenging. Data collection must be targeted, streamlined, and above all, as complete as possible to minimize any bias. The issue of bias can be a major limitation of pregnancy registries, as having a complete denominator of all pregnant women taking a particular product can be virtually impossible. Even some of the larger pregnancy registries do not capture all pregnancies. For example, the combined enrolled population of the six largest epilepsy pregnancy registries totals approximately 12,500 women; clearly this does not represent this population in its entirety.

Collecting data in a prospective manner allows for:

- A priori specification of required data elements, rather than “making due” with available data found in automated databases.
- The inclusion of vital lifestyle data, such as socioeconomic status, smoking status and drinking habits. These data may not always be found in an automated database.
- The fostering of goodwill on the part of the sponsor among prescribers and patients. Supporting these relationships also supports the commercial goals of the product.

Conversely, prospective pregnancy registries have the following downsides:

- Cost—The cost of program outreach, call-center maintenance, and data collection is high, compared to the small number of expected pregnancies.
- Image—Publicizing a pregnancy registry may lead some patients to believe that the drug is unsafe and must be discontinued.
- Analytical challenges—Again, finding a suitable comparator cohort that is generalizable and complete enough to support analyses can be challenging.

## Automated Databases

Whether a drug has been on the market for many years, or is not yet approved, automated databases can serve a useful role in planning and executing risk assessment strategies. To conduct meaningful studies of pregnancy outcomes, at a minimum, we need to identify the occurrence of a pregnancy, approximate date of conception or last menstrual period (LMP), pregnancy outcome occurrence and details by date and medication exposures by date. This information is usually either contained in or can be derived from most administrative databases. For example, the LMP is recorded in some electronic medical record (EMR) databases and can be estimated from delivery date or first medical visit for pregnancy in claims databases. With this information, it is possible to assess the frequencies of various pregnancy outcomes in association with the use of prescription medications at certain times during pregnancy (e.g., first trimester) in large populations containing thousands of women.

The best database for a particular study depends on the details of the situation. For example, the choice of database is notably different when the drug of interest is prescribed on an outpatient basis rather than for a drug used primarily in the hospital. Most databases capture pharmacy prescriptions, but only a subset of databases capture inpatient data with sufficient detail to identify exposure to specific medications. With regard to the endpoint(s) of interest, the choice of data source may depend on whether there is broad examination of many pregnancy outcomes or whether there is a focus on a particular type of birth defect. If the aim of the study is to identify a small number of specific defects, it would need to be determined whether those outcomes are identifiable with sufficient accuracy through the coding systems of the various databases. For example, Medicaid inpatient claims coded to ICD-9 codes have been found to provide good positive predictive value (PPV) (>70%) for cardiac, gastrointestinal and orofacial defects, but were less accurate for defects of the central nervous system.<sup>8</sup> In the General Practice Research Database (GPRD) database in the United Kingdom, however, there was good PPV for neural tube defects as a group, although codes were less accurate for spina bifida, specifically.<sup>9</sup> It is possible though to identify databases that allow for details around the pregnancy outcomes through text in an EMR or via a manual chart review to confirm events; the number of databases that allow for this capability is growing in both the United States and in Europe. In addition, certain defects, such as cleft palate, are readily identified at birth, while other defects, such as some heart defects or developmental delays, may become apparent only later in life.

To identify defects that come to attention after birth, a database must be able to link the mother (and her exposures) with the child. A growing number of databases now offer this capability.

In general, database studies bear no cost of patient enrollment or data collection, so obtaining information rapidly and at relatively low cost are strengths of the database approach. On the other hand, databases do not necessarily include all of the data of interest for particular research objectives. Categories of data that are sometime absent in databases include lifestyle factors, such as smoking, diet and use of over-the-counter and herbal medications. For studies where the potential influence of these factors is large, certain databases offer the opportunity to augment the automated data with additional data collected from questionnaires. Often, the additional data is minimal, and can be efficiently and effectively collected for a sample of the study population.

Database studies may not be well suited to new products for which information is needed urgently because product uptake is not immediate and most databases have some notable lag-time until the analyzability of their data (typically at least 3–6 months). Depending on the indication and market penetration, it could take some time for a product to have a sufficient number of users among pregnant women in any particular database. Finally, database studies are not necessarily an alternative to prospective studies, but are often complementary. For example, prospective pregnancy registries are often uncontrolled. While uncontrolled studies can be useful in identifying strong teratogenic effects or unique types of birth defects, weak to moderate effects or common birth defects may not be apparent without a control group. In many situations, a suitable comparison group can be developed using automated databases.

## Conclusions

The choice of study approach (registry vs. database) will depend heavily on the primary pregnancy research objectives. While both study designs are viable methods to answering questions of pregnancy outcomes associated with pharmaceutical exposures, each type of study has its own strengths and limitations. Given the restraints on timing of study conduct, clinical outcomes of interest and available resources, these strengths and limitations should be carefully considered before deciding which approach to employ. Some of the major strengths and limitations associated with registries and database studies in pregnancy outcomes research are noted in **Table 1**.

While the research question may often identify a clear choice of study design (e.g., a registry when identification of a very particular clinical event of interest or risk factor is required or a database when population-based prevalence estimates are needed quickly), it is potentially beneficial to conduct both a database study and registry in parallel. This approach could provide immediate evidence via a database study and more clinically detailed information via the registry study.

As regulatory agencies require increased vigilance regarding pharmaceutical risk management, including that of terato-

genic outcomes associated with new pharmaceutical products, it is important to understand the various options for identifying valid answers to important safety research questions. Both pregnancy registries and analysis of large individual patient databases provide viable and high quality research approaches to gaining insight into the effects of pharmaceutical products on pregnancy outcomes.

**Table 1. Strengths and Limitations of Registries and Database Studies for Pregnancy Outcomes**

	Registry	Database Study
<b>Identification of Exposed Population</b>	Referral by healthcare practitioner or self-referred.	Identifiable via pregnancy diagnosis/billing codes.
<b>Identification of Pregnancy Outcomes</b>	Routine follow-up with patient and healthcare provider throughout the pregnancy with documentation of final birth outcome.	Identifiable via diagnosis/procedure codes. Validity of coding varies by clinical event of interest.
<b>Comparator Group</b>	Generally derived from an enrolled comparator cohort within the registry or, most often, from external surveillance sources.	Easily identifiable and matchable.
<b>Detail on Risk Factors</b>	Captured a priori on data collection forms.	Limited to those identifiable via diagnosis codes, procedure codes, prescriptions, and other variable database elements (e.g., laboratory values).
<b>Generalizability</b>	May be biased due to lack of complete pregnant population enrolled in the pregnancy registry.	Generalizable to population represented by database (e.g., Managed care, Medicaid, etc.)
<b>Timeline for Results</b>	Results compiled on a periodic basis but dependent on enrollment rates and pregnancy status.	3–4 months
<b>Budget (US Dollars)</b>	\$1.0M+	\$125,000–\$250,000