Pregnancy Registries and Lactation Studies
Best Practices to Support Product Labeling

Deborah Covington, DrPH
Senior Research Leader, Real-World Evidence, Evidera

Fewer than 10% of drugs on the market have adequate data on safety of use in pregnancy and lactation,[1] yet over 90% of pregnant women use some type of medication while pregnant.[2] There are many reasons for the use of these drugs, including chronic conditions that require continuous treatment (e.g., asthma, epilepsy, diabetes); acute conditions that arise during pregnancy (e.g., infections, high blood pressure); and inadvertent drug exposure before the woman realizes she is pregnant. All patients, and especially pregnant patients, should have access to needed medications that have been adequately studied and be provided with information to enable them to assess the risks and benefits of using this medication. Thus, the need for studies focusing on the safety of medication use among pregnant and breastfeeding women is clear.

Regulatory Landscape

Since the thalidomide tragedy 50 years ago, the U.S. Food and Drug Administration (FDA) has required that medicinal products undergo testing to determine reproductive effects in animal models. However, animal models are not always reflective of the human experience. There is increasing interest in monitoring safety of drug use in human pregnancies. In 2002, the FDA issued guidance for industry in establishing pregnancy exposure registries.[3]

EMA followed with guidance on Exposure to Medicinal Products During Pregnancy in 2005.[4] With the passage of the Food and Drug Administration Amendments Act (FDAAA) in 2007, pregnant women were designated a special population and the FDA was granted the authority to mandate pregnancy registries. More recently, the FDA's Pregnancy and Lactation Labeling Rule (PLLR)[5,6] was issued which specifies the content and format of information presented in prescription drug labeling. The new Rule is intended to assist health care providers (HCPs) in assessing benefit versus risk and subsequent counseling of pregnant women and breastfeeding mothers regarding medication use. While the PLLR went into effect on June 20, 2015, it applies retroactively to all human prescription drug and biological products approved after June 2001 and requires companies to comply with these new regulations for all medications from that date (with a three-year grace period).

Overall, the new labeling requirements provide a much more robust description of product safety related to human reproductive issues *(Figure 1)*.

According to the FDA, there are currently 102 active pregnancy exposure registries,[7] which is a significant

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increase in the last three years.[8] Pregnancy registries have a fairly long history, with one of the first pregnancy registries having started over 30 years ago. Lactation studies on the other hand are still relatively rare. Due to the specific nature of these studies, there are clear and major differences compared to clinical trials and other observational studies and registries. Pregnancy and lactation studies have unique needs in terms of study design, recruitment and retention, data collection, and comparator data, and often require hybrid methodologies or innovative study designs to ensure a successful study.

Figure 1.
Examples of New Labeling Requirements under the PLLR[6]

- State if a pregnancy registry exists for that product, and if so, provide the contact information for the registry
- Include a risk summary of what is known about the potential risk of exposure during pregnancy, preferably based on human data. If there is no data to inform risk, include a statement to that effect
- Include a brief description of the data used to support statements made in the risk summary (if a pregnancy registry exists that has sufficient data to be able to make a statement about the risk of the product, the registry and data should be described)
- In the clinical considerations section, include information about the possible impact of untreated disease so that prescribers and their patients can make more informed decisions about the risk versus the benefit (e.g., for an asthma treatment, include a description of the effects of poorly controlled asthma on pregnancy)
- Include information on special dosing adjustments in pregnancy, if applicable
- Include a lactation section to provide information on the use of the product while breastfeeding, such as the amount of product in breast milk and the effects of the breast milk on the infant (data to include in this section typically comes from clinical lactation studies)
- Include a section on male reproductive risks

Pregnancy Registries

Prospective pregnancy registries are voluntary, observational, exposure-registration, and follow-up studies. Women are enrolled prospectively while still pregnant and before any knowledge of the pregnancy outcome through prenatal testing. This prospective orientation helps avoid bias that may be introduced by retrospective reporting. An active data collection system is used as opposed to a passive surveillance system and typically collects data from multiple reporters, including the pregnant woman herself, her HCPs, and the infant's pediatrician if a live infant is born.

Enrollment Process

To maximize enrollment, all eligible pregnant women exposed to the product of interest are allowed to participate. This remote enrollment process is facilitated by a central site and Principal Investigator (PI) to remotely oversee the registry and monitor participants and their infants for safety. Participants do not need to be located near a registry site and can enroll from anywhere in the country. For global pregnancy registries, there is a central PI in each country who then submits the country-specific regulatory and ethics committee documents and monitors women from their respective country. A registry contact or call center is established to assist the PI in all aspects of the pregnancy registry including awareness, enrollment, and data collection. Once a woman is made aware of a registry, she reaches out to the contact center where a representative provides a description of the registry and answers any questions she might have about enrollment or participation. If the woman is interested, the contact staff then assess her eligibility to participate in the registry. Once the woman is determined to be eligible, the contact staff facilitate the informed consent process, which includes medical release consent for HCPs to report data to the registry. The contact staff collect enrollment data from the participant over the phone and then they contact the applicable health care providers to collect clinical data.

How and from whom data are collected can affect the accuracy of the data. It is critical to collect the right data from the right reporter. Women typically know more about their habits and drug compliance than HCPs. Women can provide information on whether prescribed medication was actually taken, as well as habits and lifestyle factors that could impact the pregnancy. HCPs can provide more complete and accurate data on maternal, fetal, and neonatal diagnoses and clinical outcomes, especially clinical outcomes of interest (e.g., congenital malformations, preterm birth, small for gestation age, etc.). For example, the prescriber or treating physician can provide important data on the disease and disease severity. The obstetrician can provide data on the pregnancy and pregnancy outcome, and the pediatrician can provide data on the infant. These data are collected at various time points: 1) at enrollment or shortly after

enrollment; 2) midway through the pregnancy; and, 3) at pregnancy outcome. If a live infant is born, the pediatrician provides pediatric follow-up data. The FDA and other regulatory authorities generally require a twelve-month infant follow up, but this can vary. Some registries only collect information at pregnancy outcome, while others collect information as far out as three to five years of age for the child.

For optimum enrollment, it is critically important to keep things simple and allow multiple means for enrollment (e.g., phone, website, mobile devices). Depending on the country regulatory and privacy regulations, streamlining the consent process may also be possible. For example, in the U.S. and a few other countries, post-marketing requirements allow for a verbal consent process, which can greatly facilitate enrollment. Also, a simple data collection process will facilitate enrollment and retention. Thus, it is important to ensure the case report forms are as short and simple as possible. There is often a temptation to add more data fields than are truly needed, which can dissuade participation by both patients and health care providers.

> Patient recruitment is one of the greatest challenges faced by pregnancy registries.

Timing of enrollment is also critical. Enrolling patients as soon as possible after conception or after the exposure is extremely important for two reasons. First, it allows the capture of early pregnancy events. Second, enrolling pregnancies early before the outcome or the presumed outcome is known through prenatal testing is important to avoid selection into the registry based on presumed knowledge of the potential outcome. For example, some women may be relieved to know their baby does not have any problems after prenatal testing and are therefore more willing to enroll in the registry. Alternatively, some women may enroll because their baby does have a birth defect identified on a prenatal test. Either scenario can introduce bias either towards a lower or higher risk of birth defects. Understanding which types of prenatal tests can assess birth defects is also important. The first trimester dating ultrasounds do not assess fetal malformations, but tests, such as the nuchal translucency, chorionic villus sampling, amniocentesis, alpha fetal protein measurements, and second trimester ultrasound do assess for malformations. Thus, enrolling patients before these tests are performed is important.

Recruitment

Patient recruitment is one of the greatest challenges faced by pregnancy registries. Because registries typically use the patient-centered approach rather than a traditional site-based approach, it is important that the registry casts a broad net in their awareness efforts including outreach to both health care providers and pregnant women. A robust awareness plan should be designed specifically for each registry accounting for the particular product, target population, geographic scope, and most importantly, the goals of the registry. The internet and social media are important recruitment sources for pregnant women and personal mailings, medical science liaisons (MSLs), and scientific venues are important recruitment initiatives for health care providers. Awareness plans typically include a mixture, if not all, of the avenues outlined below.

- **The FDA requirement** that the registry and contact information be mentioned in the product label is very helpful in ensuring providers and patients are made aware of each registry.
- **Outreach to clinicians** (not only physicians, but nurses, nurse practitioners, midwives, etc.) is crucial to the recruitment effort. The vast majority of women are referred to pregnancy registries through their health care providers, and since women often spend time with nurses as well as doctors, it is important to include all types of clinicians.
- **A registry brochure** is typically created to provide information on the registry, why it is being conducted, and the procedures involved in participating. This brochure, an introductory letter, and sample data collection forms are then sent to all applicable health care providers to educate them on each registry.
- **Medical science liaisons** outreach - they visit prescribers on a regular basis and can provide more in-depth information about the registries.
- **Attendance at scientific and professional conferences,** including exhibit booths where knowledgeable staff can distribute the brochure and answer questions and conference presentations on the registry methods (or data if available).
- **A registry website** should be established where women and HCPs can find information on the specific registry, including contact information.
- **Social media** is growing in popularity as a means of awareness as well, especially with younger women spending so much time on social media outlets. LinkedIn, Twitter, and Facebook are all examples of social media outreach channels.
- **Advocacy groups** can also be a great source of awareness, especially for certain diseases where active advocacy groups exist. Often advocacy groups will provide a link to the pregnancy registry website from their website, informational articles or ads about the pregnancy registry in group newsletters, etc.

There is limited hard evidence on the effectiveness of awareness activities for pregnancy registries, however, systematic examination of enrollment patterns in

pregnancy registries following various awareness initiatives have indicated that multiple, persistent awareness activities have the greatest impact on enrollment, especially activities tapping into the internet and social media.[9]

Comparator Data

Given the inherent difficulties in identifying an appropriate comparison group, multiple methods may be used to review the data for signals. There are two basic types of comparators used to put potential signals into context in pregnancy registries including internal comparators and external comparators.

Internal comparators include pregnant women who are enrolled concurrently into the registry who do not have the exposure of interest. These women may: 1) have the disease of interest but they have not been exposed to the registry product; 2) be healthy volunteers; or, 3) be a combination of both. Many registries use both a disease comparator and a healthy volunteer comparator. The advantage of using internal comparators is that they undergo the same processes as the exposed group, including definitions and assessments of outcomes and covariates that could impact outcomes. Additionally, adjustments for differences in characteristics and covariates can be done in the analysis. While internal comparators are generally thought to be scientifically superior to external comparators, it is important to remember these studies are still observational and not carefully controlled clinical trials. Thus, the comparator group, even if enrolled internally, could still vary on important characteristics from the exposed group. Other limitations include difficulty in enrolling an internal comparator, as there is little incentive for unexposed women to participate in a pregnancy registry. Finally, enrolling an internal comparator has an impact on study size and costs since two to three times as many participants are needed.

External comparators can include other prospective registries or studies; secondary data sources, such as electronic medical records (EMR) or claims databases; published data; national vital statistics; or population-based comparators, such as the CDC's Metropolitan Atlanta Congenital Defects Program (MACDP)[10] or the European Surveillance of Congenital Anomalies (EUROCAT).[11] This approach requires a detailed evaluation of background rates from external surveillance sources and published literature to identify comparable rates of pregnancy outcomes and congenital anomalies. Background rates in the general population on infant mortality and other pregnancy outcomes, such as premature birth, are readily available from national vital statistics or publications in the scientific literature. Published rates of birth defects are available from the CDC's MACDP or EUROCAT. These population-based comparators are commonly used because they typically have large sample sizes and can provide stable risk estimates for specific birth defects.

However, rates in the general population are not an ideal comparator because the methods of ascertainment differ from those of a pregnancy registry and the population may differ greatly on important characteristics or factors that could impact pregnancy outcome. When relying on external comparators it is critical to identify differences between the registry population and comparator group and to thoroughly understand the methodology and factor these differences into the analysis plan.

When studying a population with a disease that impacts the pregnancy outcome, such as asthma, multiple sclerosis (MS), or diabetes, it is important to identify a comparator with the underlying disease rather than using a population-based comparator. The comparator should be appropriate to the population under study, and when possible, use the same methodology and definitions as the registry. However, this may not always be possible. What is important to remember is that there is no ideal comparator for a pregnancy registry. Using multiple comparators may improve the validity of your findings.

Summary

Over the last 30 years, pregnancy registries have been used to systematically collect much needed data on safety of medication use in pregnancy. Well-designed pregnancy registries offer a unique opportunity to collect information on pregnancy exposures early in a product's life cycle, when interest in the product and safety is highest. Pregnancy registry data have been used to support label changes[3] and will continue to provide much needed human data to support the new Pregnancy and Lactation Labeling Rule.

Lactation Studies

Lactation studies are relatively new and much less common than pregnancy registries, Thus, there is still much to be learned. Study approaches are evolving and there are numerous barriers to overcome in developing the ideal study design. Some lactation studies have been conducted in Phase I units where the mother is required to spend a 24-hour period in the unit providing breast milk samples. Other studies require that mothers collect breast milk samples at home and deliver them to a study site on a periodic basis. These study designs are onerous for new mothers who rarely have the time or inclination to make this commitment to a study when their priority is spending time with their newborn. There is also the challenge of finding pregnant women during the narrow window of pregnancy or shortly thereafter, who have the exposure of interest and who intend to breastfeed. Additionally, while pregnancy registries are observational in nature (participants are observed and data on outcomes are collected), lactation studies are considered interventional because they require the collection of biological samples. Because they are considered interventional, lactation studies often have more rigorous regulatory and ethics

requirements than observational pregnancy registries. One advantage of lactation studies is that they require fewer subjects, typically fewer than 20, while pregnancy registries usually require 250 to 500 participants.

Since lactation studies have numerous barriers and challenges, it is important to try different approaches to designing these studies. Below is a case study of an innovative approach that has proved successful in conducting lactation studies.

Conclusion

Prospective pregnancy registries and lactation studies, if conducted properly, can be very effective tools to support the new FDA labeling rule, as well as provide much needed human data to help health care providers and prospective parents in making informed treatment decisions during pregnancy and lactation. ■

For more information, please contact Deborah.Covington@evidera.com.

Case Study

Background

A post-authorization safety surveillance study was conducted in several countries in North America and Europe. The objective of the study was to determine whether the product of interest was transferred to breast milk. The ultimate goal of the study was to generate robust data to include in the product label so that women treated with the product considering breastfeeding and their treating physician could make informed decisions for the benefit of mother and child.

Approach

A traditional site-based approach was combined with a remote enrollment model whereby women were allowed to self-enroll through a central site. This hybrid approach sought to enroll all eligible women, even those that were not located near a traditional study site. Investigators had the option to enroll subjects treated at their site (i.e., traditional model) or monitor subjects who self-enrolled remotely via phone.

Traditional sites would identify appropriate patients from their practices and enroll them in a standard site-based study approach. The remote enrollment approach permitted all eligible women to enroll through a central PI. In this model, women would call the Remote Coordinating Center (RCC), the remote study coordinator would screen the woman for eligibility over the phone, and obtain her consent to a physical assessment. The woman would then undergo the physical assessment by her local health care provider, who then completed the necessary

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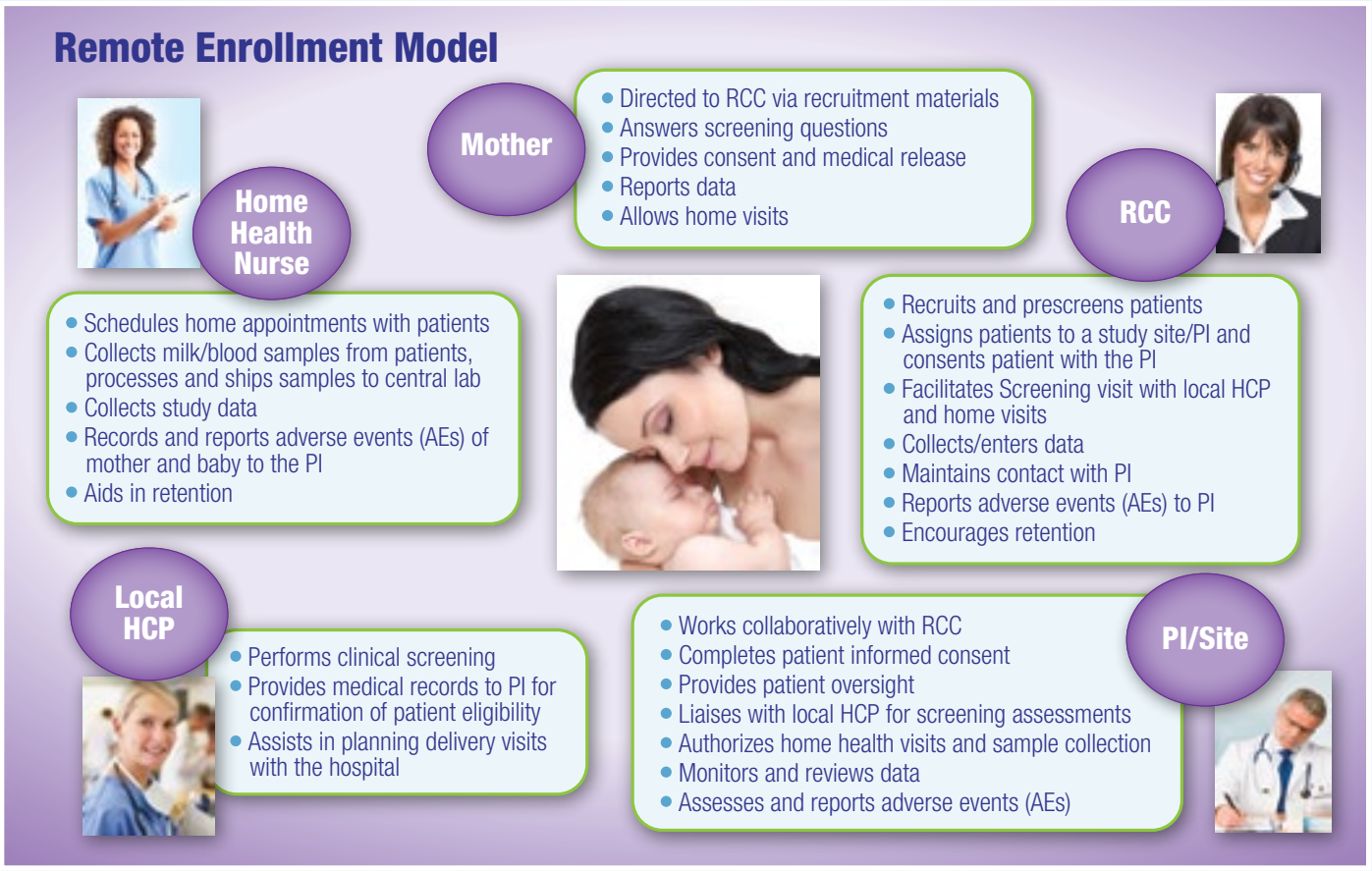

Case Study - CONTINUED

paperwork and sent it into the RCC. Since these studies are interventional, informed consent was required and those discussions occurred over the phone and then forms were sent by courier, signed, and returned to the RCC. The remote enrollment process allowed all eligible women to participate without traveling to a specific study site.

Study subjects enrolled through either process were visited by home health nurses who collected the breast milk samples and other relevant information, as well as any adverse events experience by the mothers or their babies. The study required that breast milk samples be collected nine times within 28 days starting at six weeks post-partem. All samples were then sent to the central lab for processing. This simplified the process for the new mothers, removing significant time and travel barriers.

Results

This hybrid model proved to be very successful and was generally accepted by the regulatory agencies and ethics committees in all the participating countries. However, not all the investigators accepted the remote enrollment option. For example, many investigators in the European countries chose the traditional site model or used a modified version where a single investigator served as the national coordinator for multiple sites within that country. In North America, the hybrid model boosted enrollment by 75% which never would have been accomplished using only traditional site enrollment. While the remote enrollment model was not accepted by most European investigators, enrollment flourished using the traditional sites.

The collection of samples and information by the home health nurses resulted in 100% of the visits being completed, 99% were completed within the specified timeframe, and 100% of the data collection forms were accurate and complete.

Impact

While lactation studies present unique challenges, using a hybrid approach provided access to a subject population that may not otherwise have been willing or able to participate. The home health approach helped reduce the burden on the new mothers making them more willing to participate and ensuring timely and accurate collection of the samples and data. By conducting these studies, robust data can be provided to better inform treatment decisions for women with chronic diseases considering breastfeeding. Within one year of study completion, the product label was updated with data from the study and submitted and approved by regulatory authorities.

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