PART A ONLY

PROJECT TITLE:

Evaluating the Quality of Interview Data Collected by Teratology Information Services About Pregnancy Outcomes, Maternal and Infant Health, Following Medication Use During Pregnancy and Lactation

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INFORMATION COLLECTION REQUEST

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A. Justification

1. Circumstances Making the Collection of Information Necessary

The use of a number of medications during pregnancy is known to be associated with serious adverse effects in children. Thalidomide and isotretinoin (Accutane®) are the most notable examples, but there are others. Controversies surrounding the use of medications specifically to increase breast milk production also have brought renewed attention to safety concerns about medication use during lactation. However, because pregnant and lactating women are traditionally excluded from clinical trials, and because premarketing animal studies do not necessarily predict the experience of humans, little information is available about the safety of use of most prescription medications during pregnancy and lactation at the time they are marketed. In addition, reproductive animal studies may not be conducted routinely for non-prescription drugs, herbal preparations, or dietary supplements. While it is considered prudent to avoid taking medications when pregnant or breastfeeding, this is not always possible. Half of pregnancies in the United States each year are unplanned, so that many women inadvertently use medications early in gestation during the critical period of fetal development before realizing they are pregnant. In addition, many maternal conditions (e.g., asthma, epilepsy, depression) require treatment during pregnancy and breastfeeding, the cessation of which could pose a risk to the health of both mother and infant.

Currently, the United States does not conduct comprehensive monitoring for pregnancy or infant outcomes related to medication exposures. The U.S. Food and Drug Administration (FDA) collects reports of adverse health events associated with medication use, but the extended length of time between many pregnancy exposures and outcomes makes underreporting a major limitation of this system for monitoring pregnancy outcomes. Spontaneously reported events are not routinely analyzed by FDA to assess pregnancy and lactation risk. Further, healthcare providers may be unaware that a woman is breastfeeding, and thus even less likely to report an event related to lactation. Additionally, pediatric healthcare providers may not recognize breastfeeding as a potential source of medication exposure in a child. Because use of individual medications among child-bearing aged women can be low, it can take years for case control studies and birth defects surveillance systems to identify effects of medications after they are marketed.

To try to address these concerns, a number of pharmaceutical manufacturers have established pregnancy drug registries to monitor the effects of use of selected medications during pregnancy

on pregnancy outcomes and fetal and infant health. The FDA has developed guidance specific to pregnancy drug registries to assist manufacturers in standardizing these efforts (http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM071639.pdf). In some instances, FDA has required postmarketing monitoring of pregnancy outcomes after medication exposure as a condition of new drug approval. However, registries such as these monitor only a small number of medications, and many suffer from methodologic limitations including high loss to follow-up rates and incomplete or nonspecific outcome information. Many registries administered by pharmaceutical companies contract with a third party, such as a private research organization, to receive reports of medication exposure during pregnancy and follow pregnant women to collect outcome information. In some registries, outcome information about the infant's health is obtained only from the mother's obstetrician, her subspecialist, or from a pharmacist. Typically, these registries do not collect information about the effects of medication exposures during breastfeeding, and are not conducted for exposures to herbal preparations or dietary supplements.

Teratology Information Services (TIS) throughout the United States and Canada utilize trained specialists to provide free phone consultation, risk assessment, and counseling about environmental exposures during pregnancy and breastfeeding—including prescription and over-the-counter medications, herbal preparations, and dietary supplements—to women and healthcare providers. These teratology information specialists research the effects of exposures during pregnancy and lactation using multiple sources (e.g., drug companies, the medical literature, and other specialists). Altogether, they respond to approximately 70,000-100,000 inquiries each year.

Because they have direct contact with pregnant and breastfeeding women, and because women contact these services specifically to obtain information about these exposures, TIS are in a unique position to monitor the effects of medication use during pregnancy and lactation on pregnancy outcomes and maternal and infant health. Advantages of using TIS for this purpose include the fact that they accept calls about exposure to any medication, including prescription and non-prescription drugs, herbal preparations, and dietary supplements; they typically ascertain the dose and timing of exposure directly from the woman taking the medication close to the time it is taken, which can minimize recall bias; they obtain information about the pregnancy outcome and maternal and infant health directly from the woman and not from a third party; and, as a group, they accept calls from throughout the U.S. These characteristics could improve the ability to generate information about the effects of a wide variety of medications in an accurate and timely manner, particularly newly marketed medications that have not been widely used during pregnancy or lactation. Direct contact with women who call them could improve participation in and completion of follow-up interviews. Teratology information services thus could potentially offer an alternative and more effective venue for monitoring pregnancy outcomes and maternal and infant health after medication exposure during pregnancy and breastfeeding.

A few TIS, most notably the California Teratology Information Service and the MotherRisk program in Canada, have conducted follow-up studies of pregnant women who contacted them

after taking specific medications, and other TIS have referred callers to these programs for participation. However, because these programs are centered in academic institutions, they are unique in their capacity to conduct this type of follow-up study. Monitoring of pregnancy and breastfeeding outcomes has never been conducted on a large scale by other TIS.

It is the goal of this project to assess the quality of information on pregnancy outcomes and maternal and infant health following medication use during pregnancy and lactation that can be obtained from maternal interviews conducted in a few TIS in the U.S.; and to assess the extent of additional time and resources required for individual TIS to do this successfully. If it is found that TIS can collect accurate data, a study of the feasibility of a larger TIS network may be conducted in conjunction with FDA. Such a TIS based network might contribute to the following health outcomes:

- Improved decision-making by pregnant and breastfeeding women and their healthcare providers about the safe use of medications—including prescription and non-prescription drugs, herbal preparations, and dietary supplements—before, during, and after pregnancy.
- Improved maternal health through the safe use of medications to manage acute and chronic conditions during pregnancy and breastfeeding.
- Improved infant health through identification of the effects of medication exposure during gestation, including congenital malformations and fetal loss.
- Ensuring a healthy start in life through breastfeeding.

These health outcomes relate to CDC goals for (1) people—infants and toddlers, and adults, specifically women of childbearing age; and (2) places—health care settings, specifically pregnancy and lactation counseling.

Data collection for this project is based on the following components of the Public Health Service Act: (1) 42 USC 241, Section 301, which authorizes "research, investigations, experiments, demonstrations, and studies relating to the causes, diagnosis, treatment, control, and prevention of physical and mental diseases and impairments of man."; (2) 42 USC 247b-4, Section 317 C, which authorizes the activities of the National Center on Birth Defects and Developmental Disabilities. This section was created by Public Law 106-310, also known as "the Children's Health Act of 2000". Copies of the authorizing legislation are attached as Attachments A1 and A2.

2. Purpose or Use of the Information Collection

The information gathered will be used to assess the quality of information on pregnancy outcomes and maternal and infant health following medication use during pregnancy and lactation, including use of prescription and non-prescription drugs, herbal preparations, and dietary supplements, that might reasonably be obtained from maternal interviews conducted by a few TIS in the U.S., and the extent of additional time and resources required for individual TIS to do this successfully. The information will be used to estimate:

- the range and types of medication exposures that could be ascertained by TIS
- the specificity and completeness of information obtained about pregnancy outcomes, and maternal and infant health

- the extent of additional time and resources required for individual TIS to successfully generate quality information on pregnancy outcomes and maternal and infant health following medication use during pregnancy and lactation through conduct of maternal interviews

3. Use of Improved Information Technology and Burden Reduction

All interviews will be conducted by telephone. Enrollment will be restricted to pregnant and breastfeeding women who are at least 18 years of age, live in the United States, and are not incarcerated. When a pregnant or breastfeeding woman contacts a TIS during the project period for information or counseling about a medication exposure—including exposure to a prescription drug, a non-prescription drug, herbal preparation, or dietary supplement—the TIS counselor will provide information and counseling per the usual practice of that TIS. Once that has been completed, the TIS counselor will inform the woman about the project and ask if she would like to be contacted by the project coordinator for that site to learn more about the project and potential enrollment. If she agrees, the TIS counselor will obtain the best phone number, email address, and time for the study coordinator to contact her within the coming week. At the agreed upon time, the site's project coordinator will call her back, explain the project, answer any questions she has about the project, and determine if she is interested in participating. If so, the coordinator will obtain verbal informed consent by phone and proceed with the enrollment interview and either initial pregnancy or initial breastfeeding interview. In most instances, the project coordinator will not be the same person as the TIS counselor who answered the woman's initial call to the TIS. In the event that the project coordinator is the same person as the TIS counselor who initially speaks with the woman about her exposure, the coordinator might provide information about the study, obtain the woman's consent, and conduct the enrollment and initial interviews all on the same phone call. Whether this is done in one, two, or more calls will depend on individual circumstances, such as whether it is a convenient time for the woman to learn about the study and complete the interviews.

For each pregnant woman who agrees to participate, 4 telephone interview sessions will be conducted: (1) at enrollment to conduct the enrollment and initial pregnancy questionnaires; (2) during the third trimester of pregnancy to conduct the follow-up pregnancy questionnaire; (3) approximately one month after delivery to conduct the initial infant questionnaire and, if the woman is breastfeeding and has taken a medication, the initial breastfeeding questionnaire and (4) when the infant is about 3 months old to conduct the follow-up infant questionnaire and, if the woman is breastfeeding and has taken a medication, the follow-up breastfeeding questionnaire. For each breastfeeding woman who agrees to participate, either 2 or 3 telephone interview sessions will be conducted: (1) at enrollment to conduct the enrollment and initial breastfeeding questionnaires; (2) at approximately one month after enrollment to conduct the follow-up breastfeeding questionnaire; and (3) if the woman is taking a chronic medication or frequently takes an episodic medication, at approximately 3 months after enrollment to conduct another follow-up breastfeeding questionnaire. Women participating in the project will only be required to provide verbal responses. While conducting the telephone interviews, the study coordinator will enter the participant's responses either directly into an electronic data base that contains the interview questionnaires or onto a paper form containing the questionnaires from

which the responses will subsequently be entered into an electronic data base. Scripts for referring callers to the study coordinator, explaining the study, obtaining informed consent, and conducting the questionnaires are included in Attachments C1, C2, and D1-D7. An information sheet explaining the study in question and answer format that is to be mailed to study participants and those who need more time to consider whether to participate is included in Attachment C3. We request a three year period of approval from OMB due to the lengthy nature of this data collection activity.

4. Efforts to Identify Duplication and Use of Similar Information

Currently, the United States does not conduct comprehensive monitoring for pregnancy or infant outcomes related to medication exposures. FDA collects reports of adverse health events associated with medication use, but the extended length of time between many pregnancy exposures and outcomes makes underreporting a major limitation of this system for monitoring pregnancy outcomes. Spontaneously reported events are not routinely analyzed by FDA to assess pregnancy and lactation risk.

A number of pharmaceutical manufacturers have established pregnancy drug registries to monitor the effects of use of selected medications during pregnancy on pregnancy outcomes and fetal and infant health. However, these registries monitor only a small number of medications, and many suffer from methodologic limitations including high loss to follow-up rates, lack of a comparison group, incomplete and nonspecific outcome information especially regarding the occurrence of malformations, small sample sizes, and lack of generalizability. Large existing data bases, such as those from health maintenance organizations (HMOs), have been used to identify pregnancy outcomes after medication use based on prescription data. These data can be useful for evaluating medications that are frequently used by pregnant women, but are often restricted to specific medications on the HMO formulary. Their ability to monitor newly marketed medications as they begin to be used by women in general and pregnant women in particular, and to monitor non-prescription drugs, herbal preparations, and dietary supplements, is limited. In addition, neither the pharmaceutical company-based registries nor the HMO data ascertain medication exposures during breastfeeding.

Case-control studies, such as the National Birth Defects Prevention Study funded by CDC and those conducted by the Slone Epidemiology Center at Boston University, have also been used to evaluate pregnancy outcomes and fetal and infant health after medication use during pregnancy through maternal interviews. While such case-control studies are efficient to evaluate the occurrence of rare outcomes such as individual types of malformations, they do not efficiently ascertain rare exposures such as newly marketed medications that are only beginning to be used by pregnant or breastfeeding women. National data bases from other countries, such as the General Practitioners Research Database in Great Britain and the Swedish Birth Registry, can provide useful information about the effects of medication use on pregnancy outcomes and fetal and infant health. However, they do not ascertain all medications that are marketed in the U.S., and can be limited by sample size.

Because they have direct contact with pregnant and breastfeeding women, and because women contact the services specifically to obtain information about these exposures, TIS are in a unique position to monitor the effects of medication use during pregnancy and lactation on pregnancy outcomes and maternal and infant health. Advantages of using TIS for this purpose include the fact that they accept calls about exposure to any medication, including prescription and non-prescription drugs, herbal preparations, and dietary supplements; they typically ascertain the dose and timing of exposure directly from the woman taking the medication close to the time it is taken, which can minimize recall bias; and, they obtain information about the pregnancy outcome and infant health directly from the woman and not from a third party. These characteristics could improve the ability to generate information about the effects of a wide variety of medications in an accurate and timely manner, particularly newly marketed medications that have not been widely used during pregnancy or lactation.. Direct contact with women who call them could improve participation in and completion of follow-up interviews.

A few TIS, most notably the California Teratology Information Service and the MotherRisk program in Canada, have conducted their own follow-up studies of pregnant women who contacted them after taking specific medications, and other TIS have referred callers to these programs for participation. However, because these programs are centered in academic institutions, they are unique in their capacity to conduct this type of follow-up study. Monitoring of pregnancy and breastfeeding outcomes has never been conducted on a large scale by other TIS. It is the goal of this project to assess the quality of information on pregnancy outcomes and maternal and infant health following medication use during pregnancy and lactation that can be obtained from maternal interviews conducted by more a few TIS in the U.S.; and to assess the extent of additional time and resources required for individual TIS to do this successfully.

In order to obtain sufficient data to fulfill these goals, the services of at least 3 different TIS are needed. The program contacted the Organization of Teratology Information Specialists (OTIS), the not-for-profit umbrella organization of TIS and individuals interested in teratology, to identify TIS in the U.S. with a large enough call volume to identify 200-250 women with a medication exposure during pregnancy or lactation within a 6-month period. OTIS recommended 5 services that met this criterion. The program selected 3 of these based on their ability to obtain local IRB approval and to secure sufficient staff to collect the project data in a timely fashion, both of which are essential for carrying out the project. A separate but identical purchase order for the data was awarded to each of the 3 TIS. No other vendors were considered because TIS are uniquely positioned to engage pregnant and breastfeeding women in follow-up studies of the effects of medication use. The program knows of no other vendors who have this direct connection with a large number of women who use medications while pregnant or breastfeeding.

5. Impact on Small Business or Other Small Entities

No small businesses or small entities will be impacted by this project. Only individual women will be interviewed.

6. Consequences of Collecting the Information Less Frequently

Data will be collected for only one pregnancy and/or one period of breastfeeding, per individual respondent. The frequency of follow-up interviews outlined in Attachment E is needed to maintain contact with respondents throughout pregnancy (up to a maximum of 40 weeks) and through the early months of breastfeeding; to update information about medication use close to the time it is used in order to minimize recall bias; and to allow sufficient time to ascertain relevant fetal and infant health outcomes that present at different times after delivery. For example, some internal congenital malformations may not be evident immediately after delivery, but present with symptoms weeks or even months later. A follow-up period of 3 months after delivery should be sufficient to ascertain most health outcomes without placing additional burden on the respondents. If CDC did not conduct or sponsor the proposed data collection, it would be impossible to assess whether TIS can more effectively and efficiently monitor the effects of medication use during pregnancy and lactation on pregnancy outcomes, and maternal and infant health, than existing activities (see section 4).

7. Special Circumstances Relating to the Guidelines of 5 CFR 1320.5

The schedule of interviews in Attachment E was established with the intent of requiring respondents to be interviewed no more often than quarterly (every 3 months). Exceptions are the follow-up infant interview which is conducted 2 months after the initial infant interview and, for women who first contact a participating TIS while breastfeeding, the follow-up breastfeeding interviews which are conducted one month after the initial breastfeeding interview and again 2 months after that if the mother is taking a chronic medication. These interviews are scheduled more often than 3 months in order to ascertain relevant infant health outcomes close to the time of exposure without unduly extending the overall length of the project. For pregnant women, the schedule of interviews is based on the time during pregnancy when they voluntarily contact a participating TIS and then enroll in the study. This is expected to vary among women so that for some, individual follow-up interviews may occur more frequently than 3 months apart. There are no other special circumstances relating to the guidelines of 5CFR 1320.5.

8. Comments in Response to the Federal Register Notice and Efforts to Consult Outside the Agency

The 60–day federal register notice (date 11/23/2007, page 65737-65738) appears in Attachment B. Only one public comment was received. This comment was deemed non-substantive. A prompt response was sent by the CDC OMB office.

The program discussed the project by phone and by email with the following persons outside of CDC within the past year to obtain their views on the content of data to be collected, format of questions to be asked, and logistics of conduct of the project including maintenance of contact with participants throughout the project period:

1) Christina Chambers, PhD
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2) Thomas Hale, R.Ph., Ph.D.
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3) Lewis B. Holmes, MD
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4) Caitlin Reilly Smith
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Each of the 3 participating TIS conducted a test of each interview with women of child-bearing age during a 3-month period in the fall, 2007 (5 interviews total) in order to assess the length of time each interview would take to complete, whether instructions to the interviewer contained in the questionnaires were clear and accurate, whether the questions asked were clear and understandable to the respondent, whether the questions generated the intended type and quality of information from the respondent, and to obtain the women's input on the nature, content, and acceptability of the interviews.

9. Explanation of Any Payment or Gift to Respondents
No payment or gift will be offered to respondents.

10. Assurance of Confidentiality Provided to Respondents
In order to assure privacy of the information collected to the extent allowable under federal regulations, approval from the local Institutional Review Boards (IRBs) for each of the three participating TIS, and a Certificate of Confidentiality from CDC, are being sought for this project. Because CDC staff will not interact with study participants and study data received by CDC will not contain identifiers (e.g., name, phone numbers, email address, the expected date of delivery, date of the last menstrual period, birth or delivery date), CDC is not engaged in the

research (see Attachment I) and the CDC IRB declined to review the study protocol. The Connecticut site has current IRB approval for the project (Attachment H1). The Texas site is in the process of obtaining an extension for its local IRB approval (Attachment H1). The Utah site is in the process of applying for local IRB approval for the project. The project will not proceed with data collection until all IRB approvals and a Certificate of Confidentiality for the data collection are obtained, and all study staff at the 3 TIS sites have reviewed and signed confidentiality pledges (Attachment F).

The three TIS contractors are creating a new and separate additional system of records to collect and record the identifiable, sensitive data for this research project, which includes the names of the participants. As this new system of records goes beyond the scope of their existing system of records at the three TIS sites and is being created solely for the purposes of this contractual research activity, the Privacy Act (5 U.S.C. 552a) applies to this data collection activity. As stated by CDC policy, if the "contract requires extensive additional data collection such that a separate record system must be established" then the Privacy Act applies. Furthermore, as stated above, the data includes and is retrieved by the name of the participating individuals at the three contractor sites. This new system of records falls under existing CDC System of Records Notice 09-20-0136 "Epidemiologic Studies and Surveillance of Disease Problems". Please see the CDC intranet site for complete description of the justification for the Privacy Act criteria for contractors at: http://intranet.cdc.gov/od/ocso/osrs/faq_privacy.htm.

Once all interviews at a TIS site have been completed and the responses have been entered into an electronic data file, the identifying information (e.g., name, phone numbers, email address, expected date of delivery, date of the last menstrual period, birth or delivery dates) maintained by the study for all participants will be destroyed. In addition, the subject IDs will be removed from the files containing questionnaire responses. However, information obtained by the TIS counselor related to the participant's initial call before she agreed to participate in the study, including identifying information, will be kept by the TIS at their site per their usual practice. A final anonymized file containing only the individual study questionnaire responses will be transmitted to CDC by each participating TIS over CDC's Secure Data Network. CDC study staff, including programmers who maintain the final electronic data files transmitted to CDC from each site, will have access only to responses to the questionnaires provided during each interview that are not linked to the identifiers. CDC staff will not have access to identifying information (e.g., name, phone numbers, email address, the expected date of delivery, date of the last menstrual period, birth or delivery date).

TIS will need to collect identifying information (e.g., name, phone numbers, and email address) for each woman who agrees to participate, as well as information from which to estimate the timing of events during gestation and after delivery (e.g., the expected date of delivery, date of the last menstrual period, the baby's birth date), in order to conduct follow-up interviews throughout pregnancy and during breastfeeding. The identifying and contact information will be maintained on-site by the local study staff until all interviews for that site have been completed and the responses have been entered into an electronic data file. Each participant will be assigned a subject identification number (ID) which will appear on the questionnaires. Identifying and

contact information for each participant will be kept in a separate file linked to the questionnaires only through the subject ID. Identifying and contact information, consent and tracking forms, subject ID numbers, and responses to the questionnaires provided during each interview that are collected by the study in hard copy form will be maintained at the TIS site in locked cabinets with limited access. Identifying and contact information, consent and tracking forms, subject ID numbers, and responses to the questionnaires provided during each interview that are collected by the study in electronic files will be password protected with limited access. Only the local study coordinator, local project staff who conduct the interviews, and local computer programmers or information technologists who maintain the electronic data files at each site will have access to the identifying and contact information, consent and tracking forms, and responses to the questionnaires provided during each interview that are linked to the identifiers. At the time that informed consent is obtained, the participant's U.S. Postal Service (USPS) mailing address will be obtained and written directly onto an envelope through which an information sheet about the project will be mailed to the participant. The participant's USPS mailing address will not be maintained at the local study site.

At the time of enrollment in the study, individual respondents will be informed that providing the information in each interview, in its entirety or for individual questions, is voluntary. At the beginning of each follow-up interview, and periodically during conduct of these interviews, individual respondents will be reminded that providing the information for individual questions is voluntary. At enrollment, individual respondents will be informed that identifying information (e.g., name, phone numbers, email address, expected date of delivery, date of the last menstrual period, birth or delivery dates) will be maintained on-site by the local study staff until all interviews for that site have been completed and the responses have been entered into an electronic data file, at which time the identifying information for all participants will be destroyed; that information provided during her initial call to the TIS will be maintained per the service's usual procedures; that consent to participate in the study includes consent for sharing information collected by the study, excluding identifying information, with CDC; and that findings of the study will be shared with others only in aggregate through presentations and posters at scientific meetings and through publication in peer-reviewed journals. Copies of the consent form are provided in Attachments C2a and C2b.

11. Justification for Sensitive Questions

The proposed information collection is an evaluation project, the goals of which are to assess the quality of information on pregnancy outcomes and maternal and infant health following medication use during pregnancy and lactation, including use of prescription and non-prescription drugs, herbal preparations, and dietary supplements, that can be obtained from maternal interviews conducted by a few TIS in the U.S., and the extent of additional time and resources required for individual TIS to do this successfully. In order to fulfill these goals, the project must ask the same information during participant interviews that would be asked if the purpose of the project was to monitor the effects of medication use during pregnancy and lactation. This includes questions about maternal characteristics, pregnancy outcomes, and maternal, fetal, and infant health, all of which could reveal sensitive information.

The schedule of participant interviews and the questionnaires to be used in each are provided in Attachments D1-D7 and E. Questions about maternal race and ethnicity, educational level, and household income are needed in the enrollment interview in order to assess whether women who participate in the project are similar to all pregnant and breastfeeding women in the U.S. This will help assess whether findings about the effects of medication use in pregnancy and lactation from a monitoring system based in TIS could be generalized to all women. Questions about the date of the participant's last menstrual period, the number and outcomes of her previous pregnancies, history of birth defects in the immediate family or previous pregnancies, and methods used to conceive the current pregnancy are needed in the initial pregnancy interview in order to establish the timing of exposures and outcomes and to assess whether pregnancy, fetal, and infant outcomes could be temporally or causally related to medication use or potentially explained by other reproductive factors or family history. Detailed questions about the identity of medications taken, the timing, dose, and duration of use during pregnancy and breastfeeding, and the conditions for which they were taken, are needed in the initial and follow-up pregnancy and breastfeeding interviews in order to assess whether pregnancy, fetal, and infant outcomes could be temporally related to medication use. These questions potentially could reveal sensitive information such as use of medications for psychiatric conditions or medication addiction or abuse. Questions about the timing and nature of additional maternal conditions are needed in the initial and follow-up pregnancy and breastfeeding interviews, and questions about the timing and nature of injuries or traumas are needed in the initial and follow-up pregnancy interviews, in order to assess whether pregnancy, fetal, and infant outcomes could be explained by factors other than medication use. These questions potentially could reveal sensitive information such as the presence of a sexually transmitted disease, or injuries or traumas that resulted from domestic violence or criminal assault.

Questions about the timing and results of prenatal testing and surgery are needed in the initial and follow-up pregnancy interviews in order to identify the full range of pregnancy, fetal, and infant outcomes following medication use and to assess whether these outcomes could be explained by pregnancy-related factors other than medication use. Questions about smoking, alcohol, and recreational drug use are needed in the initial and follow-up pregnancy and breastfeeding interviews in order to assess whether pregnancy, fetal, and infant outcomes could be explained by these factors. These questions potentially could reveal sensitive information such as addictive or illegal behavior. Questions about the outcome of the current pregnancy are needed in the follow-up pregnancy and initial infant interviews in order to identify pregnancy and fetal outcomes that could result from medication use. These questions potentially could reveal sensitive information such as elective termination of the pregnancy. Questions about the participant's health following pregnancy and detailed questions about the infant's health, growth, medical treatment, and the presence of any birth defects are needed in the initial and follow-up infant questionnaires to identify the full range of maternal and infant outcomes that might be related to medication use. Detailed questions about the timing, frequency, and duration of breastfeeding and formula use are needed in the initial and follow-up breastfeeding interviews in order to assess the quantity of medication exposure received by breastfeeding infants.

At the time of enrollment in the study, individual respondents will be informed that providing the information in each interview, in its entirety or for individual questions, is voluntary. At the beginning of each follow-up interview, and periodically during conduct of these interviews, individual respondents will be reminded that providing information for individual questions is voluntary.

While the purpose of this project is to assess the quality of information on pregnancy outcomes and maternal and infant health following medication use during pregnancy and lactation obtained from interviews conducted by TIS, the project will generate information about the effects of use of individual medications. These data will be examined for pregnancy, fetal, or infant outcomes that appear associated with individual use of medications reported during the project.

12. Estimates of Annualized Burden Hours and Costs

All interviews will be conducted by telephone. Enrollment will be restricted to pregnant and breastfeeding women who are at least 18 years of age, live in the United States, and are not incarcerated. When a pregnant or breastfeeding woman contacts a TIS during the project period for information or counseling about a medication exposure—including exposure to a prescription drug, a non-prescription drug, herbal preparation, or dietary supplement—the TIS counselor will provide information and counseling per the usual practice of that TIS. Once that has been completed, the TIS counselor will inform the woman about the project and ask if she would like to be contacted by the project coordinator for that site to learn more about the project and potential enrollment. We anticipate that approximately 85% of the women invited to participate will do so. This response rate estimate is based upon the fact that all potential participants are in fact calling the TIS of their own volition, due to their high interest in the health of their child. Based upon an 85% response rate estimate, a total of 882 women will be invited to participate in order to obtain a total of 750 participants.

If a caller is interested in learning more about the project, the TIS counselor will complete the tracking form (Appendix C1c) in order to obtain the best phone number, email address, and time for the study coordinator to contact her within the coming week. At the agreed upon time, the site's project coordinator will call her back, explain the project, answer any questions she has about the project, and determine if she is interested in participating. If so, the coordinator will obtain verbal informed consent by phone and proceed with the enrollment and initial pregnancy or breastfeeding interviews. In most instances, the project coordinator will not be the same person as the TIS counselor who answered the woman's initial call. In the event that the project coordinator is the same person as the TIS counselor who initially speaks with the woman about her exposure, the coordinator might provide information about the study, obtain the woman's consent, and conduct the enrollment and initial interview all on the same phone call. Whether this is done in one, two, or more calls will depend on individual circumstances, such as whether it is a convenient time for the woman to learn about the study and complete the interviews. At the end of each interview, information from the tracking form will be updated in order to obtain the best phone number, email address, and time for the study coordinator to contact the woman for the next interview.

Participants will be enrolled in one of three follow-up groups, depending on their medication exposure. For each woman who contacts the TIS about taking a medication during pregnancy, but does not breastfeed, 4 telephone interviews will be conducted: (1) at enrollment to conduct the enrollment and initial pregnancy questionnaires; (2) during the third trimester of pregnancy to conduct the follow-up pregnancy questionnaire; (3) approximately one month after delivery to conduct the initial infant questionnaire; and (4) when the infant is about 3 months old to conduct the follow-up infant questionnaire. For each woman who contacts the TIS about taking a medication while breastfeeding, either 2 or 3 telephone interview sessions will be conducted: (1) at enrollment to conduct the enrollment and initial breastfeeding questionnaires; (2) at approximately one month after enrollment to conduct the follow-up breastfeeding questionnaire; and (3) if the woman is taking a chronic medication or frequently takes an episodic medication, at approximately 3 months after enrollment to conduct another follow-up breastfeeding questionnaire. For each woman who contacts the TIS about taking a medication during pregnancy and who breastfeeds after delivery, 4 telephone interviews will be conducted: (1) at enrollment to conduct the enrollment and initial pregnancy questionnaires; (2) during the third trimester of pregnancy to conduct the follow-up pregnancy questionnaire; (3) approximately one month after delivery to conduct the initial infant questionnaire and, if she has taken a medication, the initial breastfeeding questionnaire; and (4) when the infant is about 3 months old to conduct the follow-up infant questionnaire and, if the woman is breastfeeding and has taken a medication, the follow-up breastfeeding questionnaire. Women participating in the project will only be required to provide verbal responses. While conducting the telephone interviews, the study coordinator will enter the participant's responses either directly into an electronic data base that contains the interview questionnaires or onto a paper form containing the questionnaires from which the responses will subsequently be entered into an electronic data base. Scripts for referring callers to the project coordinator, explaining the study, obtaining informed consent, and conducting the questionnaires are included in Attachments C1, C2, and D1-D7.

The number of respondents in each follow-up group in Tables A.12 was estimated from information provided by the three participating TIS about the proportion of women who typically call them with a question about medication exposure during pregnancy vs. during lactation, the proportion who use a short-term vs. chronic medication during lactation, and the estimated proportion of women in the U.S. who breastfeed after delivery (http://www.cdc.gov/breastfeeding/data/NIS_data/data_2004.htm). The average hourly wage rate in Table A.12 was estimated from the Bureau of Labor Statistics Wage Data for mean hourly earnings for all workers in the U.S. in 2006. As discussed in section A.8, the average burden was estimated by testing the questionnaires with 5 women of childbearing age.

Table A.12-1. Estimated Annualized Burden Hours and Cost to Respondents

Type of Respondent	Form Name	#Respondents	#Responses Per Respondent	Avg. Burden per Response (in hours)	Total Burden (in hours)	Average Hourly Wage Rate	Total Annual Respondent Cost
All Respondents	Telephone script for permission to seek consent (C1a or C1b)	294	1	3/60	15	$20.00	$300
Screened Eligible Respondents-	Tracking Form (C1c)	250	1	5/60	21	$20.00	$420
Pregnancy Exposure (group 1)/Lactation Exposure (group 2) /Pregnancy and Lactation Exposure (group 3)	Consent (C2a or C2b)	250	1	20/60	83	$20.00	$1,660
Groups 1, 2 and 3	Enrollment (D1)	250	1	10/60	42	$20.00	$840
Group 1 and 3	Initial pregnancy Questionnaire (D2)	200	1	30/60	100	$20.00	$2,000
	Follow- up pregnancy questionnaire (D3)	200	1	20/60	67	$20.00	$1,340
	Initial infant questionnaire (D4)	200	1	20/60	67	$20.00	$1,340
	Follow-up infant questionnaire (D5)	200	1	15/60	50	$20.00	$1,000
Groups 2 and 3	Initial breastfeeding questionnaire (D6)	100	1	20/60	33	$20.00	$ 660
	Follow-up breastfeeding questionnaire (D7)	100	1.5	15/60	38	$20.00	$ 760

TOTAL		**250**			**516**	**$20.00**	**$ 10,320**

13. Estimates of Other Total Annual Cost Burden to Respondents and Record Keepers
There are no costs to respondents other than their time.

14. Annualized Cost to the Federal Government
Estimates of the proportion of CDC investigators' time (FTE) includes development of Access software for use by TIS to enter questionnaire responses; review of interim summary reports (initially monthly, then quarterly) from each of the 3 TIS while data are being collected; analysis of the final data file; and preparation of a final manuscript, averaged over the total study period. Estimates of cost and fees for each TIS site include development of enrollment scripts, informed consent, and questionnaires; obtaining local IRB approval; conduct of follow-up interviews with up to 250 women each; preparation of interim summary reports of the project status (initially monthly, then quarterly); preparation of a final summary of the project including an anonymized data file; and assistance in manuscript preparation. The total costs to the federal government for this activity over three years is $262, 500. The Annualized costs are described in Table A. 14-1 below.

Table A.14-1. Estimates of Annualized Costs to the Federal Government

Expense Type	Expense Explanation	Annual Costs (dollars)
Direct Costs to the Federal Government	CDC Project Officer (.10 FTE)	$11,000
	CDC Co-Principal Investigator (.05 FTE)	$9,000
	CDC Co-Principal Investigator (.05 FTE)	$4,000
	CDC Co-Principal Investigator (.03 FTE)	$3,500
	CDC Programmer (.07 FTE)	$5,000
	Subtotal, Direct Costs to the Government	$32,500
Contractor and Other Expenses	Utah Site Cost and Fees	$18,333
	Connecticut Site Cost and Fees	$18,333
	Texas Site Cost and Fees	$18,333
	Subtotal, Contracted Services	$55,000
	TOTAL COST TO THE GOVERNMENT	$87,500

15. Explanation for Program Changes or Adjustments
This is a new request for information collection and has not been previously approved by OMB.

16. Plans for Tabulation and Publication and Project Time Schedule
Table A.16-1. Project Time Schedule

Activity	Time Schedule
Staff hiring and training, set-up computer database	1-3 months after OMB approval
Begin enrolling participants and conducting follow-up interviews	4-6 months after OMB approval
Stop enrolling new participants	10-12 months after OMB approval
Complete final follow-up interviews	21-25 months after OMB approval
Submit final data report to CDC	25-26 months after OMB approval

Initial tabulation of results	25-26 months after OMB approval
Data validation with TIS sites (if needed)	26-28 months after OMB approval
Final data analysis	26-28 months after OMB approval
Dissemination of results	28 months after OMB approval

The proposed information collection is an evaluation project. The information gathered will be used to assess the quality of information on pregnancy outcomes and maternal and infant health following medication use during pregnancy and lactation, including use of prescription and non-prescription drugs, herbal preparations, and dietary supplements, that can be obtained from maternal interviews conducted by a few TIS in the U.S., and the extent of additional time and resources required for individual TIS to do this successfully. The information generated will consist of descriptive measures of the range and types of medication exposures ascertained; the proportion of pregnant and breastfeeding women contacting a TIS about medication exposure who enroll in the study; the proportion of enrolled women who actually participate in each phase of the follow-up; the specificity and completeness of information obtained about pregnancy outcomes, and maternal and infant health; comparison of demographic characteristics and known risk factors for pregnancy outcomes of the women who participate in the follow-up with those of all pregnant and breastfeeding women in the U.S.; the extent of additional time and resources required for individual TIS to successfully monitor effects of medications on pregnancy outcomes, and maternal and infant health. In order to quantify the specificity and completeness of information obtained from open-ended questions, the quality of the response to each of these questions will be rated at the conclusion of each interview by the TIS staff according to predefined categories (e.g., complete/specific; moderately complete/specific; incomplete/nonspecific). These categories will then be used to analyze the quality of responses obtained from open-ended questions for the entire project.

17. Reason (s) Display of OMB Expiration Date is Inappropriate
No exception for display of OMB expiration date is requested.

18. Exceptions to Certification for Paperwork Reduction Act Submission
No exceptions for certification for Paperwork Reduction Act submission are requested.