Birth Defects Study To Evaluate Pregnancy exposureS (BD-STEPS)
OMB # 0920-0010

Supporting Statement B
Revision

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B. Collection of Information Employing Statistical Methods

B.1. Respondent Universe and Sampling Methods

Seven Centers for Birth Defects Research and Prevention (CBDRP) currently participate in BD-STEPS: Arkansas (AR), California (CA), Iowa (IA), Massachusetts (MA), North Carolina (NC), New York (NY), and CDC/NCBDDD's Division of Congenital and Developmental Disabilities (DCDD) serves as the site of record for Georgia (GA) (see **Attachment E** for List of BD-STEPS Centers). Cases for BD-STEPS in Atlanta are selected from the Metropolitan Atlanta Congenital Defects Program (MACDP) surveillance system, and cases for all other Centers are selected from established state surveillance systems. The collection of information for cases of selected birth defects does not employ statistical methods because all infants with one of the 22 birth defects are included (see **Attachment H**) in the state birth defects surveillance systems from which eligible cases are ascertained, and all cases with an eligible defect are included, not just a sample of cases. Individual birth defects are rare occurrences so it is necessary to ascertain all cases in order to have enough cases of specific defects to study. Two Centers will collect information for all stillbirths without major defects in their respective study area. However, the controls in BD-STEPS are selected by a sampling process.

For BD-STEPS, each of the CBDRP will select randomly from the population (from either vital records or hospital birth logs) approximately 100 eligible controls each year for inclusion in the study. Whether hospital records or birth certificates are used as the source for control-infants, the records are reviewed to ensure that, given the available information, the selected control-infant does not have a birth defect. Records are also reviewed to abstract information for the purpose of follow up and contact.

Table B.1. BD-STEPS Potential Sample of Respondents.

		Annual Number of Interviews by Type of Respondent and Site Type				
Center	Type of Respondent	Mothers (Telephone Interview)	Mothers Supplemental Interview (Stillbirth)	Newborn Bloodspots	Online Questionnaire*	Infectious Disease Release Review
Form Type		Attachment F	Attachment J	Attachment R, S, T, and U	Attachment G1-8	Attachment L and N
Arkansas	Case	270		270	87	270
	Control	100	100	100	32	100
	Stillbirth	220	220			
California	Case	270			87	270
	Control	100			32	100
Georgia**	Case	270			87	270
	Control	100			32	100
Iowa	Case	270		270	87	270
	Control	100		100	32	100
Massachusetts	Case	270		270	86	270
	Control	100	100	100	32	100
	Stillbirth	220	220			
New York	Case	270		270	86	270
	Control	100		100	32	100
North Carolina	Case	270		270	86	270
	Control	100		100	32	100
	TOTAL	Total unique respondents = **3,030**	**640**	**1,850**	**830**	**2,590**

B.2. Procedures for the Collection of Information

State-specific birth defects surveillance data are used to identify case subjects for BD-STEPS. The selection of BD-STEPS controls is described in Section B.1. Once potentially eligible subjects are identified for the study, a clinical geneticist reviews the information abstracted from the medical record to determine if they meet the case definition and are eligible for the study. The first contact, sent by mail to the mothers, is an introductory letter, along with a "Human Subjects" fact sheet, and a "Question and Answer" sheet sent by the Center from which the case or control subject originated.

Approximately 10 days after the introductory packet has been sent, the centralized interview contractor makes follow up phone contact with the mother (see **Attachment Q1/Q2** for contact scripts). During this phone call, the interviewer obtains oral consent for the interview and either conducts the interview then or schedules the interview at a time convenient for the mother. The interview is conducted with a computer assisted telephone interview (CATI) (see **Attachment F1/F2** for a hard copy of the questionnaire). The script used in the telephone interview (including oral consent) is in **Attachment Q1/Q2**. The script varies slightly depending on the status of the child: control, living case, deceased case, or stillborn/termination case.

A thank you letter is sent after the telephone interview is completed (**Attachment AA1/AA2 and BB1/BB2**). For the states that allow CBDRP access to newborn bloodspots and require maternal consent, a letter describing the request for collection of residual newborn bloodspots is included with the interview thank you letter (**Attachment AA1/AA2 and BB1/BB2**), as well as a written consent form pertaining to bloodspots (**Attachment R1/R2**). For parents of multiples (e.g. twins or triplets), consent for sharing data (including newborn bloodspots) of the siblings that were part of the multiple birth is requested (**Attachment T1/T2**).

Release of Reportable Infectious Diseases information will be requested (**Attachments AA1/AA2 and BB1/BB2**) from all participants after completing the CATI (see Section B.4); a written informed consent form (**Attachment L1/L2)** for the release of this information is included with the CATI interview thank you letter. After participants sign and send back the infectious disease consent form, they will receive a thank you letter (**Attachment M1/M2**).

In addition, participants are asked during the interview if they work in one of eight occupational categories of interest. If yes, participants are sent an introductory invitation via email that includes information about the online questionnaire and a link to the online questionnaire (**Attachment G1-8**). After participants complete the online questionnaire, a thank you letter is sent.

Finally, two Centers will ask mothers whose pregnancies ended in stillbirth with or without birth

defects and controls to participate in a supplemental telephone interview. Mothers will be sent an invitation that includes information about the supplemental interview. Approximately 10 days after the introductory packet has been sent, the participants will receive a follow up phone call. During this phone call, the interviewer obtains oral consent for the interview and either conducts the interview then or schedules the interview at a time convenient for the mother. The interview is conducted with the supplemental questionnaire (**Attachment J1/J2**). The script used in the telephone interview (including oral consent) is in **Attachment V1/V2**. The script varies slightly depending on the status of the child: control or stillborn case. Participants receive a thank you letter after they complete the supplemental telephone interview (**Attachment P1/P2**).

A large portion of the BD-STEPS interview has been maintained from the NBDPS to make pooling of the CBDRP's NBDPS and BD-STEPS data possible; pooled data will facilitate the analysis of rare exposures and the examination of trends over time. The BD-STEPS interview retained topics including pregnancy history, family history, multiple births, fertility, maternal conditions and illnesses (including diabetes, genitourinary infections, and fevers), medication and herbal use, emotional stress, physical activity, obesity, alcohol and tobacco use, residential history, occupational history, and demographic characteristics (including race, ethnicity, acculturation status, and education).

B.3. Methods to Maximize Response Rates and Deal with Nonresponse

The response rate during the first year of the NBDPS was approximately 60% for cases and controls. With the addition of the $20 money order in the introductory packet, interview participation rates increased to over 70% in 2000. Interview participation rates ranged from approximately 60-70% from 2005-2009. To account for inflation and the well-documented decrease in participation across many studies that employ phone-based interviewing, participants will now be offered an additional incentive upon completing the telephone interview, a $30 gift card included with the thank you letter mailing (**Attachment AA1/AA2 and BB1/BB2**).

The token of appreciation amount for the online questionnaire, the newborn bloodspot consent request, and the release of reportable infectious disease results is ten dollars for each component.

The two Centers contributing to the stillbirth component of the study, will send a $10 gift card to mothers asked to participate in the supplemental telephone interview along with the introductory letter including information about the questionnaire. If the mother chooses to complete the supplemental telephone interview, an additional $10 gift card along will be sent with a thank you letter (**Attachment P1/P2**).

B.4. Tests of Procedures or Methods to be Undertaken

Many of data elements ascertained in the BD-STEPS interviews are consistent with those from the NBDPS interviews, which makes pooling of the CBDRP's NBDPS and BD-STEPS data possible. The current revision includes minor edits to the questionnaire and the addition of questions to the BD-STEPS CATI on infections, travel, and marijuana use during pregnancy.

Innovative questions were added to the BD-STEPS telephone interview in response to some of the findings from NBDPS and to new findings in the literature. Changes included:

- Adding questions about specific maternal diseases and their treatment, including thyroid disease, asthma, autoimmune disease, transplant receipt, cancer, depression, and anxiety;
- Updating the interview instrument to evaluate possible new and emerging birth defects risk factors (e.g. new medications);
- Adding questions about exposures not explored before that have biological plausibility and public health importance (e.g. dental procedures and transplant receipt);
- Expanding sections to provide increased detail (e.g. indication and dose for specific medications).

Additional changes are now being made to the BD-STEPS CATI, specifically the addition of questions on infections during pregnancy, travel, and marijuana use. The modified CATI is included in **Attachment F1**.

BD-STEPS is being conducted at seven locations around the country. The interview data from the CBDRPs will be used in statistical analyses by collaborators at each of the CBDRP. Data will be released at regular intervals based on completed cohorts defined by expected date of delivery for each calendar year. Several data cleaning steps will be implemented before release of the data.

The online occupational questionnaire (**Attachment G1-G8**) represents a newer method for data collection for the study that began in 2017.

In addition, after the telephone interview, requests to obtain consent for newborn screening bloodspots and release of reportable infectious disease information are sent to participants. Reportable infectious disease information includes data reported to the state health department by a medical professional (See **Attachment L1** for infectious disease results informed consent and **Attachment N1** for infectious disease results verbal consent).

B.5. Individuals Consulted on Statistical Aspects and Individuals Collecting and/or Analyzing Data

The statistical aspects of the design of the BD-STEPS data collection are the responsibility of the Principal investigator:

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Additional consultation on the development of the BD-STEPS was obtained from the Principal Investigators of the CBDRP (**Attachment E**). Abt Associates is currently contracted by CDC to manage all BD-STEPS interviewing activities; the Abt Associates primary contact is the following:

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Analysis of BD-STEPS data is the primary responsibility of Dr. Tinker, with assistance from the Principal Investigators of the CBDRP.