6. STUDY DESIGN

6.1 Overview of Study Population

The National Children's Study is a longitudinal study that will enroll and follow over time a nationally representative sample of approximately 100,000 children born in the United States. Participation in the Study is voluntary, so potential Study participants can choose not to participate at any time. The Study calls for collecting information on children from birth through age 21. However, to enable assessments of exposures and risk factors during critical periods of embryonic and fetal development, some information must be collected from women before they become pregnant, and additional information must be collected while the woman is pregnant. Thus the Study plan is to select a sample of women of child-bearing age, to request that each eligible woman participate in the Study, and to follow these women over a fixed period of time. If an eligible woman informs the Study that she is planning on becoming pregnant or she is "at risk" of becoming pregnant, certain information will be collected on preconception exposures and risk factors. If any eligible woman in the selected sample becomes pregnant, information will be collected during her pregnancy. The collection of mother's information will begin as early in the pregnancy as possible and, at the time of birth, her child will be enrolled in the sample of children. It is recognized that not all pregnancies will result in a live birth; the Study protocol addresses human subject concerns and issues related to adverse pregnancy outcomes.

Thus, for the NCS, children/births are sampled through the mothers. Because not all pregnancies are planned, not all mothers will have preconception information collected. The Study target is to enroll at least 25 percent of pregnancies prior to conception and to identify and enroll a cumulative total of 90 percent of pregnancies before the end of the first trimester of the pregnancy. For most Study locations, births will be enrolled during a 4-year period with a target of 250 births per Study location per year. As described below, there are 105 Study locations in the national design. Most locations correspond to a single county, but some are comprised of multiple counties.

6.2 Inclusion and Exclusion Criteria

The sample design described below calls for recruiting women into the Study primarily through household sampling. All women who are in the first trimester of pregnancy at the time of initial contact with the Study are eligible for inclusion. Additionally, women between ages 18 and 44 at the time of initial contact who are not pregnant are eligible for enrollment and follow-up for pregnancy. If at any time in the enrollment period it is determined that a particular woman cannot become pregnant, she will not be followed. The frequency and intensity of follow-up of women who are not pregnant depends on the woman's probability of becoming pregnant as described in Section 6.4.2.

If a woman enrolled in the Study gives birth during the 4-year enrollment period, the newborn is included in the Study provided the mother resides in a household that is part of the Study sample at the time of the delivery. All births to mothers who meet the initial eligibility criteria are eligible for Study enrollment, including children born to surrogate mothers, those expected to be adopted or assigned to foster homes, and births to women who are on active duty in the military.

Women who are cognitively impaired or mentally ill are not eligible if they are not able to understand fully the Study requirements and grant informed consent.

6.3 Sampling Strategy

A number of study and sampling design options were considered for the NCS (see Sample Design Options and other related documents available at http://www.nationalchildrensstudy.gov/events/advisory_committee/other_work_062004.cfm). There are advantages and disadvantages to each of the candidate approaches, however, after careful consideration and upon the advice of the NCSAC, a national probability sample of all U.S. births was chosen as the design that best fulfills the following goals:

- Collection of high quality, objective data to minimize measurement biases
- Avoidance of selection biases and other biases that could lead to invalid inferences concerning exposure/outcome relations
- Ability to capture the diversity of the U.S. population such that both the range and diversity of exposures and outcomes are represented
- Ability to generalize results of the NCS to the U.S. population

The sample design for the NCS is a multistage probability sample of births in the United States where the births are identified from a sample of households. The design includes two or three stages of sampling.

The first stage of sampling was the selection of primary sampling units (PSUs), which correspond to single counties or groups of contiguous counties. The second stage is the selection of smaller geographic areas (segments) from within the primary sampling unit. In general, these segments comprise city or suburban blocks or combinations of blocks and roughly correspond to neighborhoods. The third stage, which applies only to very densely populated segments, involves the selection of groups of households from within the segments. Each stage is detailed below.

6.3.1 Selecting Study Locations

The process for selection of Study locations was based on the need to achieve representative coverage of the United States with respect to geographic areas, metropolitan/nonmetropolitan areas, and demography. All decisions on sample design options considered costs, coverage, statistical reliability, and practical concerns of the protocol. Cost models and logistical aspects of the NCS data collection led to the design decision to use 105 study locations.

The probability of a county being selected as a PSU is based on the number of births to residents of that county. Because the number of births in a county at a future date cannot be known, data on resident births (births based on the mother's residency at the time of birth) from four recent years (1999-2002, the most recent four-year period available at the time) were used as an estimated measure of size for sampling the PSUs.

The 3,141 U.S. counties were categorized into 18 large strata defined by metropolitan status (metro, nonmetro) and geography (nine census divisions). Within each of the 18 large strata, the total number of births determined the initial number of smaller strata. Based on their number of births, 13 counties were large enough to be designated as self-representing units (also referred to as certainty units). For three of these counties, the number of births was so large that each county was assigned multiple PSUs. Los Angeles County was assigned four PSUs, Cook County, IL, (containing Chicago) was

assigned two, and Harris County, TX, (containing Houston) was assigned two. These are units that were "certain" to be selected into the probability sample based on their large number of births. Thus, the design contains 13 locations but 18 PSUs that are considered self-representing.

The remaining 3,128 counties were placed into smaller strata. Within each of the 18 large strata, these smaller strata were formed to be of roughly equal size. The smaller strata were defined in terms of the size of county or the percent of births with specific characteristics. The characteristics used to define the smaller strata were percent of births to Native American women, percent births to Asian women, percent births to Hispanic women, percent births to Black women, and percent low birth weight. After all strata had been formed, one PSU per strata was selected with a probability proportional to size (i.e., number of births).

A minimum measure of size for a PSU was established as 2,000 births during a 4-year period (or an average of 500 births per year). If a county was selected that had fewer than 500 births per year, geographically adjacent counties in the same stratum were added until the PSU met the minimum measure of size. In a few cases, that criterion could not be achieved. For such cases, an additional PSU was selected.

The final first stage sample comprised 110 PSUs in 105 locations: 26 locations are non-self-representing PSUs from nonmetropolitan strata; 66 locations are non-self-representing PSUs from metropolitan strata; and 13 locations with 18 PSUs are from self-representing metropolitan strata. While this design is generally consistent with an equal probability sample design, differences in the sizes of the strata relative to the PSU probability of selection results in some variation. See Appendix B for a map of study locations.

6.3.2 Sampling within Locations (PSUs)

To meet the analytic needs of the Study, a total sample size of 1,000 enrolled live births is the target for each sampled PSU. With an enrollment period of 4 years, a sample size of 250 enrolled live births per year in each PSU is needed. (The Vanguard Centers have an additional year of enrollment and thus have 1,250 targeted births.) Because each selected PSU has greater than 250 births expected per year, a sample of births within each PSU must be designed and selected. This leads to the second stage of selection for the NCS. It is not feasible to take a simple random sample of births within each PSU. The second stage of the NCS design consists of forming small geographic units within a PSU called segments (or secondary sampling units) and then selecting a sample of those segments for inclusion into the Study.

6.3.3 Segment Sampling

To increase the operational efficiency, reduce costs, and provide for more useful representation of neighborhood-level characteristics, the segments within the PSUs are "clusters" of households. A geographic classification used by the U.S. Census Bureau (blocks nested with block groups, block groups nested within census tracts) is used to form segments. An advantage of using census geography is that data from other sources for these units can be linked to the sampled segments.

Prior to the formation of segments in a PSU, a target number of sampled segments is established. This number is primarily based on operational considerations and varies between PSUs. For most PSUs, it is expected that the number of sampled segments will be between 10 and 15. In general, a smaller number of segments are targeted in more rural, less densely populated PSUs that cover large areas; in more densely populated PSUs with larger numbers of births, the number of sampled segments

may be larger. The segments are constructed to be as uniform in size as possible within a PSU, but slight departures from the target segment size are expected.

As was done for the selection of PSUs, segments will be stratified to improve the precision of estimates and to ensure the sample is representative with respect to the stratum definitions. The NCS segments will be formed by combining a number of census blocks or block groups. Stratification can be done either before or after segments are formed. When stratification is done beforehand, the characteristics of the block groups can be used to form strata and only block groups in the same strata are then combined to form segments. These segments are homogenous with respect to the stratification variables but may not be geographically contiguous, thus increasing data collection costs. When stratification is done afterward, contiguous block groups can first be clustered to form segments and then "similar" segments are grouped to form strata.

It is expected that the segment stratification scheme will vary from PSU to PSU, with a goal of achieving locally defined neighborhoods as segments. (It is hoped that using locally defined neighborhoods will increase study participation rates and facility data collections at the community level.) Within most PSUs, geographic stratification will be used either as the sole stratifying variable or in combination with other variables. Geographic stratification is useful because many of the characteristics that differentiate subpopulations (such as income, race/ethnicity, educational attainment, and environmental measures) tend to be geographically clustered.

The strata are formed as equal in size as possible so that with approximately equal-sized segments, an approximately equal probability sample of segments is obtained. In some cases, it is desirable to allow for some variations in stratum sizes within a PSU to construct more homogenous strata than an equal-sized-strata scheme would permit. If the strata vary in size within a given PSU, the segments also vary in size across strata to equalize the sampling fraction within each stratum. For example, if one stratum is twice as large as another stratum within a given PSU, the segments within the first stratum are constructed to be twice as large as the segments within the second stratum.

In some cases, the strata are not geographically contiguous. This is typically the case when variables other than geography are used for segment stratification. In these cases it is necessary that each disjointed part of a stratum be large enough to form complete segments with minimal variation in segment size.

One challenge in having PSUs that have different sizes (number of births) is the large variation in the number of possible segments across PSUs. For example, among the Vanguard Centers, the smallest PSU has only 11 segments whereas the largest has approximately 1,800. A large number of segments causes difficulties in both forming and reviewing segments. In order to use resources more efficiently, a three-stage sampling protocol is used for large PSUs (typically those with more than 500 segments).

In large PSUs, geographic units are formed within strata and these geographic units, which vary in the total number of estimated births, are sampled with the probability of selection proportionate to the size of the geographic unit. Within each stratum, exactly one geographic unit is selected. Segments are then formed within the sampled geographic unit to be equal in size. Across strata, the segments are made equal in size if the strata are equal sized, or vary in size proportionate to the variation in stratum sizes if the strata are not equal sized. Within each sampled geographic unit, exactly one segment is randomly selected.

6.3.4 Listing and Enrollment

In selected segments, household screening is attempted in all households (dwelling units [DUs]) in the segment. The exception is a very large segment, which cannot be subdivided during segment formation. In such segments, DUs are subsampled. If one of these large segments is selected, the segment is divided into "chunks" and then a chunk is randomly sampled for listing and enrollment. For example, suppose a given segment is twice as large as the target segment size and consists of two very large apartment buildings that contain approximately equal numbers of DUs. In that case, each apartment building is a chunk, and one of the two is randomly selected to be retained in the sample. Other approaches for chunking (depending on the situation) include using floors of apartment buildings or block faces as chunks.

Household screening is attempted in each sampled DU, and all eligible women are enrolled. The scheduled monitoring of eligible women is dependent on each woman's likelihood of becoming pregnant. Women more likely to become pregnant are contacted more frequently (see Section 6.4.2). In some instances, the composition of the household will change or the DU will have new occupants. To enroll births from mothers in these situations, all DUs will be contacted at least once a year. This contact will be used to update the status of enrolled women's likelihood of pregnancy and thus her schedule for follow-up visits.

6.3.5 Rollout of PSUs

A sample of seven PSUs was selected to serve as the Vanguard Centers. These seven Vanguard Centers will serve as a platform to develop methodologies and procedures that will be refined and implemented throughout the Study. The remaining 98 PSUs will be introduced in three waves. The specific plan for the subsampling of the PSUs into the waves is currently under consideration. Pilot data collection is planned to begin in the Vanguard Centers in mid-2008, data collection in the first wave of additional PSUs is planned to begin in mid-2009 with the second wave two years later and the final wave two years after that.

The 98 PSUs not covered by the Vanguard Centers will be covered in the subsequent waves by the addition of Study Centers. Each Study Center will oversee participant recruitment and data collection at one to three geographically proximal study locations. The Vanguard Centers and Study Centers will work with the NCS Coordinating Center and the NCS Program Office to ensure effective development and implementation of study procedures.

6.3.6 Subsamples

In addition to the core set of measurements collected from all study participants, a number of data collections are being considered that involve collection of survey information, samples, or biological specimens from a subset of the total population or only at the community level. One example would be to reduce the proportion of samples obtained with nonmeasurable concentrations of an environmental substance. Questionnaire information on recent pesticide applications could be used to determine what homes will have air samples collected for nonpersistent pesticides since the air concentrations of these chemicals tend to decrease over time. Pesticide measurements in drinking water are currently being planned only in rural areas for homes using private wells since municipal water system information would be available for other locations and pesticide concentrations in drinking water in urban areas are often below detection limits. In some cases, environmental samples will be collected but not analyzed (e.g., metals in dust) unless biomarker concentrations (e.g., blood levels) indicate higher exposures have

occurred, and there is a need to determine the media or sources contributing to this exposure. Additionally, the large sample size of the National Children's Study affords the opportunity for more in-depth studies of subsamples within the framework of the longitudinal cohort study. A mechanism for adjunct study proposals is described in Chapter 16. Finally, to optimize the study's ability to incorporate state-of-the-art measurements, including some too costly or too burdensome for implementation in a sample of 100,000, the use of a validation sampling approach might be considered for certain measures. In this approach, a simple or less costly assessment is paired with the more costly or burdensome approach in a planned subsample of the population. For example, personal monitoring may be the best way to measure direct exposure to air pollutants or pesticides, but the cost and intrusiveness of this monitoring make this impractical to use on the entire cohort. The relation between the two assessments of the same domain is used to characterize and adjust for "measurement error" in the analysis of exposure-outcome relations for the entire cohort, although the majority of the study participants receive only the simpler, less expensive assessment. Similarly, a matrix approach for other applications (e.g. varying times of assessment) is also being considered.

6.4 Participant Recruitment

6.4.1 Recruitment Goals

The goal of recruitment is to obtain the highest response rate possible to reduce the potential for nonresponse bias. The minimum goal for combined response and coverage in each location will be between 65-75 percent. Study locations with traditionally lower survey participation rates will have lower targets. For example, in highly urban areas response rates for surveys are often considerably lower than in other settings.

To assess the impact of nonresponse bias, studies will be undertaken to assess the differences between responders and nonresponders. Lower response rates are acceptable only if it can be demonstrated that the nonrespondents are missing at random, or if a nonresponse assessment provides an adequate statistical procedure to adjust NCS estimates for nonrandom missingness. This combination of rigorously conducting the Study to obtain response rates as high as feasible along with studying the characteristics of nonrespondents is consistent with new standards and guidelines developed and distributed by the Office of Management and Budget.

6.4.2 Enumeration of Households

Within selected segments, all households will be enumerated to identify women of child-bearing age living in the household. This enumeration will be conducted in person by trained interviewers using computer-assisted personal interviewing techniques. An adult household reporter (age 18 or older) will be asked to answer questions about the number of household members, the number of males and females, and for females, their ages and their relationships to the household reporter. To ensure coverage of all dwelling units within each structure, questions will also be asked about other dwelling units that may not be easily visible or obvious, and therefore may have been missed during the listing process.

Two groups of age-eligible women (18-44) are targeted for enrollment: women who are in their first trimester or pregnancy, and women who are at some probability of becoming pregnant during the four-year enrollment period. After the age-eligible women are identified from the household enumeration, a separate pregnancy screener will be completed with each woman to determine her status. This will be done using a standardized set of questions related to her age, history of prior births, contraceptive use, and sexual activity. To ensure privacy these questions the pregnancy screener will be

administered in-person using computer-assisted self-interviewing techniques, which allow the woman to enter her responses directly into the computer. An audio feature of this will be included to read the questions to the woman to further ensure privacy and to circumvent possible literacy issues.

Women who are not currently pregnant, and who are not actively trying to become pregnant, or who are trying to become pregnant but based on the pregnancy screening have a relatively low probability of becoming pregnant, will be categorized as either "low probability" or "moderate probability." These groups will receive periodic phone contacts to determine if they have either become pregnant or, based on a limited set of screening questions, have moved to the group at higher probability of pregnancy. Women who are at high probability of becoming pregnant will be enrolled in the preconception cohort and actively followed for four menstrual cycles following enrollment. It is estimated that 55.2 percent of women in this group will become pregnant during this timeframe.

There will be periodic rescreening of households in selected segments to monitor for "move-ins" and other changes in the composition of the household living at each address. This periodic rescreening will take place only for those households where no eligible women are identified (estimated to be approximately 70 percent of all households). For those households with women being followed as part of the Study, scheduled contacts will be used to update information about household membership. This will be an important mechanism for monitoring changes in household composition as well as for identifying young women who "age in" (i.e., turn 18) during the four-year enrollment period.

6.4.3 Recruitment through Prenatal Care and Other Mechanisms

The primary mechanism for recruiting women for the Study is by contacting them in their households and encouraging them to participate in all phases of the Study. Some women, however, will move into sampled segments after the segments have been screened (and prior to the recontacts discussed above). Since children born to women living in the sampled segments are eligible, other mechanisms are needed to identify and recruit these women.

A supplemental mechanism to recruit eligible women (those living in the sampled segments) is through providers of prenatal care, birthing centers, and hospitals. All of the requirements of those sampled in households must be satisfied by these women, so this is simply another technique for identifying and recruiting eligible women from sampled households. In addition to increasing the Study's ability to cover the mobile population that otherwise would be missed, this supplemental recruitment also provides another opportunity to encourage participation from women who previously chose not to participate in the Study when contacted in the household screening. While this method is useful in reducing nonresponse and undercoverage, it does not provide full data from the pre-pregnancy and early pregnancy data collections and is thus viewed as a supplemental approach.

6.5 Community Outreach and Engagement

The NCS values community engagement, but it will not follow a strict community-based participatory research model. Community-based participatory research is defined as a collaborative research approach designed to ensure and organize participation in all aspects of the research process and action, emphasizing participation by the communities affected by the issue being studied, by representatives of organizations, and by researchers. Because the protocol includes data collection from multiple study sites to answer specific study questions that require a national sample, it was not possible to define the core study questions and initial protocol development through input of local communities or to account for their varied needs. However, principles of community-based research will be applied when

feasible and appropriate. A partnership with each community will be formed to ensure mutual respect and the establishment of an enduring relationship. Genuine community engagement offers the hope of enhancing recruitment, retention, and participant satisfaction.

Since the beginning of planning, the NCS has undertaken a range of community engagement activities to lay the groundwork for Study Center activities. Between 2000 and 2005, the NCS conducted many focus groups to obtain community perspectives on informing communities about the NCS, gaining the support of communities, recruiting and retaining participants, and NCS sampling and visits. Additionally, the establishment of working groups, the Study Assembly, and the Federal Advisory Committee allowed ongoing community input into the Study plans. The Vanguard Centers are working within local communities to prepare for recruitment. Study Centers will continually share experiences with and learn from each other in implementing community engagement plans.

Ideally, Study Centers will be able to build upon prior local community networks and relationships. However, the unique sampling strategy, data collection intensity, and length of the NCS necessitate different approaches to working with communities than previous studies or projects. To build trust, enhance the credibility of the Study, and ensure community engagement on the local level, during the first year of the Study the investigators from the Centers will conduct community needs assessments to identify children's environmental health issues in the target community. These assessments will focus on community concerns regarding the core NCS protocol and additional concerns (e.g., health issues) that may be considered for inclusion in the core protocol at all sites or as a specific sub-study focus in the particular site. Community activities will include identification of community representatives and resources and recruitment of community partners to facilitate engagement. Examples include advance contact with community leaders to gather information about the community, town meetings, and listening sessions. Key community members will be recruited and engaged in support of the Study in activities such as acting as a spokesperson for the Study, providing insight into local issues to enhance the relevance of the NCS for their community's health, and serving on community advisory boards. Reliance on secondary data sources like environmental and geographic data can actually enhance these activities. Previous studies have shown the importance of involving community members, either in the actual data collection for the study or as liaisons to special populations such as the medically underserved. These approaches will be utilized at the Study Centers to the extent possible.

Prior to the enrollment period, each Study Center will increase the awareness of the Study among community residents. Building on the community engagement efforts and involvement of community members described above, a variety of strategies will be used to announce the NCS enrollment period. Examples include press releases, appearances on local television and radio shows, and other methods to increase community excitement and interest. Wherever possible, these activities will involve joint participation of study staff and community members. These press and public relations activities will have the technical support of the Coordinating Center and the NCS Program Office, with the approval of the NCS Project Officer.

Throughout the Study, the Study Centers will involve and solicit input from the community. Examples of ongoing activities include establishing a community advisory board, partnering with other organizations to host events or forums, incorporating community leaders into the Study Center structure, and building referral networks between the Study and organizations. Steps for community engagement will vary depending on the characteristics and experiences of the communities and the Centers, and it is expected that the most effective approaches will vary. Once data collection begins, communities will be interested in learning about Study findings. Aggregate findings will be shared with individual participants and communities through newsletters, publications, and other means. The community perspective can inform NCS researchers on ways to be sensitive to unique cultural and political issues and to concerns

within each community when communicating results. Because the NCS is a long-term research effort, attention to sustaining community relationships will be very important.

6.6 Data Collection Schedule

The following section provides an overview of the data collection schedule at each contact until the child reaches age 1. For details about the measurements (e.g. content of questionnaires, targeted analytes in biological or environmental samples, or specifics of physical assessments) and their relation to hypotheses, see Appendices E through I.

The data collection schedule for the NCS includes a variety of data collection modalities at each participant contact. A comprehensive schedule of in-person visits in the home or a clinical setting, contacts by telephone, contacts through self-administered forms, and other contact methods has been carefully constructed to minimize respondent burden while enabling measurement of key exposures and outcomes at critical points from before pregnancy through the postnatal period and beyond. Although a framework of anticipated contacts with the study participants is provided through age 21, details of the data collections are specified only for the visits occurring before pregnancy, during pregnancy, at and around birth, and during the first 24 months of the child's life, with the most detailed information through 12 months. Less detail is presented for the preschool period, and provisional details only are presented for subsequent data collections. As technology advances new tools should become available to measure key constructs, and specifying measurement strategies too far in advance might serve to limit the use of cutting-edge advances. Thus, in developing the Study's protocol, maximum flexibility has, and will continue to be, retained with respect to specifying the timing and location of participant contacts for the later years of the Study.

Table 6-1. Current Schedule and Site of In-Person Contacts with Study Participants

Prior to pregnancy*: home	3 years: clinic
First trimester: home	5 years***: to be decided
Second trimester: clinic**, ultrasound only	7 years: to be decided
Second trimester: clinic, ultrasound only	9 years: to be decided
Third trimester: clinic, full visit and ultrasound	12 years: to be decided
Birth: delivery location	16 years: to be decided
6 months: home	20 years: to be decided
12 months: home	

* For women enrolled in the pre-pregnancy cohort (see Section 6.4.2)

** Only if the woman has not had early clinical ultrasound for gestational age dating

***Timing and location of visits from 5 years onward is provisional

6.6.1 Prior to Pregnancy

As described in Section 6.4.2, women who are determined to be at "high probability of pregnancy" will be invited to enroll in the Study's pre-pregnancy cohort. The first data collection for this group will be in the home prior to pregnancy and will include an interview with the enrolled woman, collection of biological specimens and environmental samples, and a brief physical examination. At this visit, women will also be given dietary questionnaires to complete and return to the Study Center. Multiple pregnancy test kits also will be provided and the women will be instructed to use them around the time of their expected menses to enable identification of pregnancy as early as possible. As soon as a woman learns she is pregnant, she will be asked to obtain a self-collected urine sample for assessment of

transient environmental exposures and to contact her local Study Center. For a woman who is not reporting a positive pregnancy test, a series of telephone contacts will occur beginning one month after the initial home visit to ascertain if she has become pregnant and to update contact and environmental exposure information. If after four months there is no pregnancy, the woman will be moved to a lower probability of pregnancy group (either low probability or moderate probability, as defined in Section 6.4.2).

After the initial screening visit, women who are determined to have a low or moderate probability of pregnancy will be asked to contact the Study if their intent to become pregnant changes or if they become pregnant. Both groups will be contacted by telephone by Study Staff every six months for the group with a moderate probability of pregnancy and yearly for the low probability group. The phone contacts will be used to confirm that there has been no change in residence, that the female is still eligible for the Study, and that there has been no change in their probability of pregnancy. If a woman in either the low or moderate probability group became pregnant during the four-year enrollment period, she would be invited to participate in the Study beginning with the appropriate pregnancy visit. Women at low or moderate risk of pregnancy at the initial screening who later move to the higher probability group (e.g., women using reliable birth control who, on rescreening, are no longer using birth control and are actively trying to become pregnant) will be invited to participate in the preconception cohort.

Summary of preconception visits for women with a high probability of pregnancy

- Initial preconception visit (home)
- One month following initial visit (phone)
- Two months following initial visit (phone)
- Four months following initial visit (phone)

6.6.2 Pregnancy

6.6.2.1 Pregnant Women

Two face-to-face visits, one visit for a fetal ultrasound, one more comprehensive clinical visit (including an ultrasound and other assessments), and several phone contacts are planned during pregnancy. The first visit is an in-person contact that will occur as early as possible during pregnancy and will be conducted in the home to allow collection of exposure data during this critical period of early development. In addition to environmental samples taken from the home, the visit will include collection of interview data, biospecimens, and a brief physical examination. Women will be given instructions for completing several self-administered questionnaires, which they will be asked to complete and to mail back after the visit. They will also be provided with a diary to record targeted exposures (e.g., fever) that might be subject to recall bias if ascertained only at planned contacts. Finally, the women will be provided with a health visit log to document visits to clinical providers as well as targeted data items (e.g., blood pressure) (Tang, Ash, Bates, Overhage, & Sands, 2006). Women will be contacted by telephone at approximately 16-17 weeks of gestation to update pregnancy information and environmental exposures. In the mid to late second trimester (approximately 22-24 weeks), women will be invited to receive an NCS-sponsored fetal ultrasound to assess fetal growth. The second core face-to-face data collection will occur in a clinical setting in the early third trimester (approximately 28-30 weeks). The clinical setting was chosen because it can help facilitate the collection of a second standardized

assessment of fetal growth by ultrasound and the collection of other biological specimens and physical assessments. There will also be a brief interview, and women will be given instructions for obtaining easily collected environmental samples from the home that will be mailed back to the Study Center. A telephone contact will again be made at about 36 weeks gestation to update delivery information (i.e., due date, hospital).

6.6.2.2 Early Dating Ultrasound

The Study recognizes the importance of obtaining an early ultrasound to date the pregnancy, to pinpoint the timing of exposures with respect to gestational age, and to assess targeted outcomes accurately, such as preterm birth or fetal and infant growth. Preliminary data suggest that between 40-70 percent of pregnant women from the initial NCS Vanguard Sites will receive a first trimester ultrasound. Thus, at the first Study visit during pregnancy, women will be asked if they already had an ultrasound or if they are scheduled for an early ultrasound. If the answer to either is yes, they will be asked to provide the name of the provider and the needed permissions (e.g., consent and Health Insurance Portability and Accountability Act [HIPAA]) for the Study to obtain results of that ultrasound from the provider. For the women who did not receive an early ultrasound as part of routine care, an ultrasound will be scheduled through the Study. This process was chosen both to decrease the mother's burden and the Study's cost.

6.6.2.3 Biological Fathers

Biological fathers will be invited to participate in the Study. During pregnancy, the primary data collection from fathers is at the time of the first trimester home visit. Targeted data collections include biological specimens, interview data, and a brief physical examination. If an enrolled woman does not want to reveal the identity of the biological father or does not want the Study to contact the biological father, the Study will not contact him. In these instances, the pregnant woman (and her child) would still be eligible for participation in the Study. The father does not necessarily need to live in the same home as the mother for initial inclusion in the Study, however, biological fathers or biological mothers who have no contact with the child following birth will not be followed.

Summary of pregnancy visits

- Early first trimester: (home: mother and biological father)
- First trimester (clinic: ultrasound for women without an early clinical ultrasound)
- 16-17 weeks (phone contact: mother)
- 22-24 weeks (clinical visit, ultrasound only: mother)
- 28-30 weeks (clinical visit with ultrasound: mother)
- 36 weeks (phone: mother)

6.6.3 Following Pregnancy

A number of data collections central to the Study occur at the birth location around the time of delivery. These include a brief maternal interview; the collection of biological specimens (e.g., cord blood, placental tissue, and meconium); information about the delivery and the hospital course of the infant as ascertained through abstraction of obstetric and neonatal hospital records; and a baseline neonatal physical and neurodevelopmental assessment. These collections should require at least two visits by Study staff to the place of delivery - one around the time of delivery and a second prior to the infant's discharge. Although the goal is to complete a physical and neurodevelopmental assessment of the child before discharge from the hospital, it is recognized that this will not always be feasible. Thus, if time does not permit assessment in the hospital, a home visit will be made at approximately 1 month after birth.

Following birth, alternating phone and in-person contacts are scheduled every 3 months through age 1 (3-month phone, 6-month in-home visit, 9-month phone, and 1 year in-home visit). After age 1, contacts are every 6 months through age 3 (18, 24 and 30 month phone contacts, and 3-year clinic visit). All contacts include interviews with the primary caregiver to assess both exposures and outcomes of interest. At the 6- and 12-month visits, the primary caregiver and the alternate caregiver (as identified by the primary caregiver) will be interviewed. During each in-person visit, the child will be assessed directly for growth and development and child-parent interactions will be observed. At the home visits, both environmental samples and observational data will be collected. Biological samples will be collected from the child primarily at the 12-month and 3-year visits, although urine will be collected more frequently for measurements of transient environmental exposures. The 3-year clinic visit provides the first opportunity for the measurement of physiologic and physical outcomes (e.g., lung function and body composition) that require larger equipment more easily operated and standardized in a clinical setting. The only biological samples obtained from parents following the birth of the child are salivary samples to measure cortisol as a biomarker of stress, because parental stress is anticipated to have a direct effect on parenting behaviors and child outcomes.

A number of self-administered data collection tools, primarily mail-in questionnaires, will be utilized for more in-depth assessment of some topics than is feasible during the home or clinic visits. Finally, comparable to the data collections during pregnancy, a health visit log for the child will be provided for collection of basic information about clinical visits, including date of visit, type of visit (well child vs. acute), diagnosis, immunizations, etc. Strategies and formats to make the health visit log most valuable to (and thus most utilized by) the participant will be explored during the pilot phase of the Study.

Summary of birth/postnatal visits through 24 months

- Visits around the time of delivery at the place of delivery
- Three months (phone)
- Six months (home)
- Nine months (phone)
- Twelve months (home)
- Eighteen months (phone)
- Twenty-four months (phone)

6.7 Overview of Data Collection for Participant Contacts through 24 Months

This section consists of three tables outlining the contacts between the NCS and Study participants from before pregnancy through the 24-month phone contact. The relations between each participant contact, the relevant data collection modalities for that contact, and the broad domains assessed during that contact are illustrated. Table 6-2 shows the pre-pregnancy and pregnancy contacts for the mother, Table 6-3 outlines the maternal and child contacts from birth through 24 months, and Table 6-4 shows partner contacts.

The appendices include more detailed text and tabular descriptions of the NCS data collection activities. Appendix D describes each of the data collection modalities, and Appendices E through I describe specific exposure and outcome measures as well as potential confounders that are being assessed.

Table 6-2. Prepregnancy and Pregnancy: Maternal Contacts

Visit	Questionnaire and Diary	Biologic Samples	Clinical/Developmental Examination	Environmental Samples
Prepregnancy home visit	Maternal interview Demographics Household composition Medication use Health behaviors Housing characteristics Chemical exposures Product use Occupational exposures Diet	Blood Urine Saliva Vaginal swabs Hair	Anthropometrics Blood pressure	Indoor air House dust
Prepregnancy phone follow-up	Maternal phone interview Diet Chemical exposures	------	-------	-----
First trimester home visit	Maternal interview Demographics* Household composition* Medication use* Health behaviors* Housing characteristics* Chemical exposures* Product use* Occupational exposures* Diet* Medical history Stress and social support Depression	Blood Urine Saliva Vaginal swabs Hair	Anthropometrics Blood pressure Fetal ultrasound (from medical report or clinic visit)	Indoor air House dust Drinking water Soil
Second trimester phone follow-up	Maternal phone interview Major life events Mental health update Medical update Chemical exposures update Housing update	-----	-----	-----
Third trimester clinic visit	Maternal interview Updates on: Demographics Household composition Medication use Health behaviors Housing characteristics Chemical exposures Product use Occupational exposures Diet Medical history Stress and social support Prenatal life events Depression	Blood Urine Saliva Vaginal swabs Hair	Anthropometrics Blood pressure Fetal ultrasound	Indoor air House dust (self-collected and mailed in)

* Updates if in prepregnancy cohort

Table 6-3. Birth through 24 months: Maternal (M) and Child (C) Contacts

Visit	Questionnaire and Diary	Biologic Samples	Clinical/Developmental Examination	Environmental Samples
Birth: At delivery, hospital	Maternal interview Health behaviors (M) Diet (M) Chemical exposures (M) Plans for infant feeding, sleeping, etc.	Blood (M) Urine (M) Cord blood Placenta and cord samples Heel stick (C)	Anthropometrics (C) Dysmorphology and neurologic exam (C) Digital photographs of face and anomalies (C) Chart abstraction (M, C)	-----
3-month phone call	Maternal phone interview Child care Medical update (C)	Breast milk (mailed in at 4-6 weeks)	-------	-----
6-month home visit	Maternal interview Stress and social support Family process and parenting practices Health behaviors (M) Depression and cognition (M) Diet (C) Medical update (C) Medication use (C) Media exposure (C) Child care Chemical exposures Temperament (C)	Urine (C) Hair (C) Saliva (M) Breast milk	Anthropometrics (C) Dysmorphology exam and photos (C) Dermatologic exam (C) Social development observation (M, C)	Indoor air House dust Drinking water Soil Visual assessment of house and neighborhood
9-month phone call	Maternal phone interview Child care Medical update (C) Housing update Chemical and occupational exposures (M, C)	-----	-----	-----

Table 6-3. Birth through 24 months: Maternal (M) and Child (C) Contacts (continued)

Visit	Questionnaire and Diary	Biologic Samples	Clinical/Developmental Examination	Environmental Samples
12-month home visit	Maternal interview Household composition update Family process and parenting practices Health behaviors (M) Diet (C) Medical update (C) Medication use (C) Media exposure (C) Child care Housing update Chemical and occupational exposures (M, C) Language acquisition and social interaction (C)	Blood (C) Urine (C) Hair (C) Saliva (C) Breast milk	Anthropometrics Blood pressure Dermatologic exam Cognitive exam Motor and language assessments Social development observation (child and father, if available)	Indoor air House dust Drinking water Soil Visual assessment of house and neighborhood Noise survey
18-month phone call	Maternal interview Child care Medical update (C) Diet (C) Housing update Chemical and occupational exposures (M, C)	-----	-----	-----
24-month phone call	Maternal interview Child care Medical update (C) Housing update Chemical and occupational exposures (M, C) Life events (M)	-----	-----	Indoor air House dust (self-collected and mailed in)

Table 6-4. Paternal or Partner Contacts

Visit	Questionnaire	Biologic Samples	Clinical/Developmental Examination
First trimester home visit	Partner interview Demographics Household composition Tobacco use Medical history Cognition	Blood Urine Hair	Anthropometrics Blood pressure
6-month home visit	Partner interview Family process and parenting practice Tobacco use Mental health	Saliva	-----
12-month home visit	Partner interview Family process and parenting practice Tobacco use Cognition (if not assessed at first trimester visit)	-----	Social development observation with child