# 12. HUMAN SUBJECTS PROTECTIONS

The National Children's Study is primarily observational in nature and will have both a low level of subject risk and a reasonable subject burden. However, the longitudinal nature of the research, the size and scope of the Study, and the diversity of the participants, make the human subjects protection issues significant. The NCS' commitment to collecting biologic, environmental, social, and behavioral measures and creating enduring data as well as biologic and environmental sample repositories with the potential for future studies not yet conceived, make the human subjects protections somewhat complex.

## 12.1 Study Population

The NCS will employ a national probability sample (see Chapter 6) with no exclusions based on gender, race, or ethnicity. Women, children, and men of all of the racial and ethnic groups and economic strata represented in the United States will be subjects. The rationale for this approach is to accrue and follow a population of children that captures the range and diversity of exposures and outcomes experienced by children in the United States.

Because a primary focus of the Study includes assessing the impact of exposures that occur early in pregnancy, three groups will be enrolled and followed: pregnant women of any age and their husbands/partners; adult women planning pregnancy; and adult women not planning pregnancy but with some likelihood of becoming pregnant. All births to mothers who meet the eligibility criteria will be included.

Women who are cognitively impaired or mentally ill are not eligible if they are not able to understand fully the Study's requirements and to grant informed consent. Only women with the capacity to consent will be enrolled.

At the time when a pregnant woman is enrolled in the Study, the biological father will also be invited to participate. If an enrolled woman does not want to identify or does not want the Study to contact the biological father, the Study will not contact the father. In these instances, the pregnant woman and her child would still be eligible for participation. The father does not need to live in the same home as the mother for initial inclusion in the Study, however, there are no plans to follow biological fathers or biological mothers who have no contact with the child.

Families that move will be followed to minimize the number of participants who are lost to follow-up. Because all births to mothers who meet the eligibility criteria are eligible for the Study, there will be children in the Study born to surrogate mothers, children who will be adopted, children who will be assigned to foster homes, and children whose mothers are on active duty in the military. In addition to children whose families move, foster children, adopted children, military children, and children whose parents divorce, may change households after birth. Because the children are the primary participants, they will be followed if they move or otherwise change households. The Study will use information collected from participants, as well as publicly available data, to track and locate families and children in the Study who change households.

### 12.1.1 Strategies/Procedures for Recruitment

Strategies for recruitment are outlined in detail in Chapter 6. The primary approach involves screening and recruitment from households located in neighborhoods targeted for inclusion in the Study

and through providers of prenatal care. A variety of materials and strategies, including, but not limited to, media outreach and distribution of brochures and newsletters, will be utilized to increase public awareness of the Study and aid with recruitment of Study subjects.

### 12.1.2 Special Classes of Research Participants

#### 12.1.2.1 Pregnant Women and Fetuses

The NCS will recruit and follow women prior to and during pregnancy. The NCS fulfills the requirements for research involving pregnant women and fetuses as described in section §45 CFR 46.204 of the Code of Federal Regulations, subpart B. The purpose of the NCS is to develop important biomedical and psychosocial knowledge about the impact of biologic, environmental, social, and behavioral exposures prior to and around the time of conception, during pregnancy, and as the child ages, on the future health and development of children. This information cannot be obtained by other means. Risks to the women and fetuses are not greater than minimal, and the research will in no way affect medical decisions about pregnancy management and outcome. Provisions in this section of the regulations also state that consent from the father of the fetus is not necessary when the research imposes only minimal risks to the fetus.

#### 12.1.2.2 Pregnant Adolescents

The NCS will enroll pregnant adolescents who are identified during the household screening or through sites of prenatal care, and who are otherwise eligible for participation in the Study (e.g., first trimester of pregnancy). Women younger than age 18 will not be eligible for inclusion in the preconception cohort. Laws regarding the legal status of pregnant adolescents vary by state. In some jurisdictions, pregnant adolescents are considered "emancipated" from their families and can be treated as adults for the purposes of obtaining informed consent for this research project. Additionally, in many jurisdictions pregnant adolescents may legally seek medical care for pregnancy without involving their parents. In these jurisdictions, Institutional Review Boards (IRBs) may permit pregnant teens to consent to participation in research in studies such as the NCS without parental involvement. Finally, even in jurisdictions where pregnant adolescents are not considered emancipated or able to consent for their medical treatment, IRBs may waive involvement of parents in the informed consent process under certain conditions [Section §45 CFR 46.408(c)]. Local centers, in consultation with their IRBs, will determine whether parental permission is required in addition to the consent of the pregnant adolescent under the age of majority.

#### 12.1.2.3 Children and Adolescents

Investigating the effects of environmental exposures and gene-environment interactions on the outcome of pregnancy and on the growth and development of children is the primary aim of the NCS. Thus, children from newborn to adulthood will be the subjects of this longitudinal Study. Each child's parent or guardian will be asked to grant permission for participation in the Study. It is the expectation that children, as young as toddlers and continuing through adolescence, will be informed about the Study and its goals in developmentally appropriate language, using creative methods such as newsletters, comic books, Web sites and DVDs. IRBs will receive all informational materials for review and approval prior to implementation. Issues related to consent and assent are described below.

#### 12.1.2.4 Economically or Educationally Disadvantaged Individuals

It is anticipated that some of the participant families in the NCS will be economically or educationally disadvantaged. Section §45 CFR 46.111(b) of the federal regulations requires the IRB to assure additional safeguards are provided in a study when some or all of the subjects are likely to be vulnerable to coercion or undue influence because of economic or educational disadvantage. The NCS will design additional safeguards into the recruitment and retention activities for all participants to encourage informed participation of all eligible subjects. Each Study Center will be required to develop meaningful and enduring partnerships with the communities from which participants will be recruited. These activities along with the informed consent process described below will result in no coercion or undue influence on potential participants.

#### 12.1.2.5 Foster Children and Wards of the State

Because of the subject matter of interest to the NCS and the probability-based sample design, it is important that every eligible child be enrolled and retained in the Study. Some children eligible for enrollment in the Study may be in foster care, may be wards of the state, or may transition into these arrangements at some time after enrollment in the Study. Permission for continued participation of the child in the Study will be sought from whatever administrative agency or institution is responsible for the care of the child and, in addition, from the foster parent. (See Section 12.6.6 for details on consent for participation of foster children and wards of the state).

### 12.2 Benefits

Although it is possible individuals may benefit from participation, the Study does not claim that participants will have the "prospect of direct benefit" from the Study. There are likely to be collateral benefits of participation, including information about individual examinations and tests performed during the course of the Study, health education, increased awareness of medical and social services available in the communities studied, and serendipitous findings of clinical relevance or of predictive value to participants and their families.

The potential for NCS to benefit society and children in general is extraordinary. The hypotheses being addressed and the data being amassed for future analyses are likely to impact the health and development of children for decades to come.

### 12.3 Potential Risks

Each of the procedures, measurements, and assessments in NCS is designed to fulfill the definition of "minimal risk" in the federal regulations [§45 CFR 46.102(i)] and to be reviewed by IRBs under §45 CFR 46.404 "Research not involving greater than minimal risk." Minimal risk as defined in the federal regulations means "that the probability and magnitude of harm or discomfort anticipated in the research are not greater, in and of themselves, than those ordinarily encountered in daily life or during the performance of routine physical or psychological examinations or tests." In addition, the NCS staff is committed to minimizing risks even when the risks are minimal. Well-trained and competent individuals who have experience with pregnant women and children of the appropriate age will perform each procedure that might include discomfort or pain, such as a blood stick. Settings in which tests will be performed or information will be obtained from women and children will be woman- or child-friendly and respectful of the participants' needs and privacy. Questionnaires will be structured to avoid creating

discomfort for the women or children; and participants will be reminded at each data collection encounter that their participation is voluntary, they have the right to withdraw from the Study at any time, and they may refuse to answer or may skip any question.

There are additional issues associated with the Study related to testing and storage of biologic specimens and environmental samples; reporting concerns regarding possible child abuse or neglect; possible breaches of confidentiality; and informing participants of Study findings (which potentially could result in psychological effects, such as anxiety, or could have a financial impact, such as costs for additional testing). Each of these has been considered by the Study, and plans are in place to protect the welfare of participants and families involved in the Study.

The NCS staff is cognizant that while research staff is in and around the homes of participants, they may observe or learn about environmental hazards or behaviors that place a child in imminent danger, and investigators may be legally required to report such observations or information to specific authorities in some jurisdictions. The NCS staff feels morally obligated to respond to protect the interests of children when they are found to be in serious imminent danger, even if there are no reporting laws. Thus, the informed consent process will inform participants that if a data collector observes a child is in imminent danger of serious harm or the subject of child abuse, the information will be reported to the proper authorities to obtain help for the child. Study procedure manuals and interviewer training will describe the process that will be invoked to report such observations to the principal investigator or his/her designee at each site. Primary data gatherers will be trained to note such dangers to participants and inform their supervisors immediately for evaluation as to the proper course of action. It will not be the sole responsibility of the data gatherers to report the observations to authorities; rather it will be the responsibility of the professional staff under the supervision of the principal investigator to assure reporting is performed in an appropriate and timely manner. Study Centers will each have knowledge of local resources including social service providers for referral purposes. Each Study Center will develop a local mechanism for this reporting and referral process.

Primary data gatherers will also be trained to respond to observations of adults in danger, such as domestic violence between adults or suicidal tendencies. The NCS staff has a moral responsibility to assist adults in dangerous situations, but these situations will be dealt with differently. The adult victims will be involved in the process, and no reports will be filed with any authorities without the involvement and approval of the adult victims, unless required by law. Names of social service referral agencies will be provided upon request to adult victims of domestic violence.

## 12.4 Adjunct Studies

It is anticipated that in addition to the core protocol for the NCS, there will be adjunct studies proposed and conducted by investigators associated with the NCS. Such studies will involve a subset of the NCS cohort, at one or more Study Centers, on all or a portion of the local participants or their data. To protect the quality and integrity of the NCS, adjunct studies will be reviewed and approved through a defined process involving formal review and approval (see Chapter 16 for details).

Since Study participants may be asked to participate in these adjunct studies, the Study consent process will include a statement that participants may be contacted for other studies connected with NCS as a result of their participation in NCS, but they are not obligated to participate in any of these adjunct studies. All adjunct studies that involve additional interaction with human subjects will require IRB review and additional informed consent.

## 12.5 Incentives and Compensation

Recruitment and retention for the NCS will be a significant challenge in light of the respondent burden and the long-term commitment required of participants. It is expected that reasonable incentives will be part of the strategy for recruitment and retention of participants.

Compensation for participation will include reimbursement for expenses incurred in research participation such as travel to and from the research centers, parking, etc., and reasonable payment for time spent in participation in the research (approximately $25 to $50 per visit or exam, depending on the amount of time and effort involved). Adult participants and older children will be compensated for time spent completing questionnaires, for providing biologic specimens, and for other Study activities.

Small "gifts of appreciation" for continued participation will be provided to participants periodically. These may include token items such as T-shirts, tote bags, toiletries, books, and CDs. Gifts will not have sufficient monetary value as to unduly affect the voluntariness of consent to participate or of continued participation in the Study.

## 12.6 Consent and Assent Processes

The informed consent process will begin when potential participants are first notified about the Study and will vary depending upon the ages and types of participants and the pregnancy status of women. The first step in the process will involve advance mailings of Study material to potential participants. These materials will include a letter describing the Study. The next step will be enumerating household members. Then, pregnancy screening will be performed with all eligible females. Pregnancy screening will involve a script and a computer-assisted self-administered interview and will only include what is needed to determine Study eligibility. The Study will ask IRBs to accept oral consent for this process, because the eligibility screening will only involve questions about criteria used to determine the eligibility status of potential participants and about age in order to determine which consent process to administer. If a participant is found to be eligible and is willing to participate, only then will the full informed consent process commence.

The informed consent plan for the Study takes into account the types of participants and is tailored to address specific issues pertaining to each type. Women will provide informed consent during pregnancy for themselves and their child. There will not be a new consent process specifically for the baby at the time of birth.

The types of participants providing informed consent, or in the case of young children, assent will include:

- Adult women at risk of becoming pregnant (preconception women)
- Pregnant women (adult and adolescent)
- Biological fathers
- Other caregivers
- Children (through the phases: young children, adolescents, young adults)

The consent plan recognizes there will be transitions for some participants between types, and these transitions will affect the consent process. For example, preconception women might become pregnant and will need to provide additional consent for their own full participation in the Study and for the participation of their children. The assent/consent process for children will also change as the children grow from young children, to adolescents, to the age of majority.

The informed consent materials anticipate low literacy, they are culturally sensitive, and they reflect the diversity of potential participants. As part of the informed consent process, there is a method, described below, to ascertain if the participant understands key elements of the Study and what is involved in participation.

All consent materials will be available in English and Spanish, and other translations will be available as needed. Interpreters will be available for additional languages. A copy of the informed consent document will be made available to the participants electronically and as a paper copy.

### 12.6.1 Electronic Audio/Video Consent Tool Pilot

A video approach to informed consent is being developed to address some of the challenges with the traditional method for obtaining informed consent, as well as to provide a means for assuring consistency in the informed consent procedures across multiple sites of implementation. The primary goal of the tools is to enhance prospective participants' understanding of the purpose of the Study and all of the essential elements of informed consent. The videos take into account the diversity of potential participants and the reality that some eligible participants may have low literacy. They also accommodate the hearing impaired through closed captioning. There are separate versions of the tool for each of the different types of participants (preconception [nonpregnant] women, pregnant women, and biological fathers). During the Study's pilot phase, a computer-based interactive video informed consent tool will be compared to traditional written informed consent. The two methods of obtaining informed consent will be compared both in terms of understanding of the Study requirements (content of the consent) and Study enrollment.

This audio-visual presentation will be shown on the data collector's laptop or tablet computer. Study staff will be present during the entire informed consent process to assist with the computer presentation and answer participants' questions. The presentation includes embedded questions that assess the participant's understanding of what they have seen and heard to help ensure they understand the key elements of the Study and what their participation will involve. If the participant does not answer a question correctly, the presentation provides additional information and chances until the participant selects the correct answer. In that way, participants will not be excluded if they fail to answer some of the questions correctly. To consent, they will be required to keep trying until they understand which answer is correct, and the presentation will explain why the answer is correct to reiterate the information. The participant's written signature will be obtained electronically at the end of the presentation. A written copy of the material described in the informed consent video will be left with each participant.

### 12.6.2 Women Age 18 and Older

The NCS will initially recruit women ages 18 and older prior to and during pregnancy. Potential participants will be told that they can share the consent materials and discuss participation with family, friends, and, if they choose, their physician before deciding whether to enroll. Local research staff will be available in person to answer any questions and clarify any aspects of the NCS.

### 12.6.3 Women Less Than 18 Years of Age

Women younger than 18 who are pregnant will be eligible for the pregnancy portions of the Study. Special procedures will be used for women younger than 18 to ensure that encouragement to participate will not be undue or interpreted as pressure. There will be age-related differences in monitoring women for pregnancy. The Study will not enroll those younger than 18 who are not pregnant, and these young women will not be asked whether they are planning to get pregnant.

The consent process for pregnant women under the age of majority will be consistent with the laws of the local jurisdiction. Generally, federal regulations permit pregnant women of any age to consent for minimal risk research for themselves and their children. If the pregnant young woman is between 15 and 18, she will be encouraged to consult with her family prior to providing informed consent for herself and her child. If the pregnant young woman is younger than 15, then the Study protocol will require the consent of her parent or legal guardian. The young women will be asked to enroll and to provide informed consent for themselves and for their children.

### 12.6.4 Assent of Children

Consistent with §45 CFR 46.408(a), it is the intention of the NCS to obtain assent for participation in the Study from children beginning at approximately age 7 if they are developmentally and cognitively able. Each child who is developmentally and cognitively able to assent to continued participation in the Study will be approached. The process for obtaining and documenting "child assent" will be presented to each participating IRB at least one year before the first subjects of the Study will become 7 years old. The description of this process will include the methods that will be used to determine if a child is developmentally and cognitively competent to be approached for assent.

All children enrolled in the Study will receive continual updates on the progress of the Study through developmentally appropriate newsletters, Web sites, and other communications. They will be encouraged to continue to participate in the Study, answer questionnaires, and attend scheduled follow-up visits.

An "adolescent assent" process will be developed to obtain the affirmative agreement of each teen to continue participation in the Study. This process will be initiated at approximately age 14. A description of this process and the methods to obtain and document assent from developmentally and cognitively capable teens will be provided to each participating IRB at least one year before any of the subjects turn 14. The description of this process will include the methods that will be used to determine if an individual adolescent is developmentally and cognitively competent to be approached for assent.

### 12.6.5 Consent of Adolescents (When Child Participants Reach Age of Majority)

As adolescent participants in the NCS reach the legal age of majority in each jurisdiction (generally age 18), a fully informed consent will be obtained from each participant for continued participation in the Study and for continued use of stored samples for analysis. A consent process for these adult subjects will be developed and submitted to the IRB at least one year before participants turn 18.

### 12.6.6 Foster Children

Foster children who are wards of the state are permitted to participate in research without any additional procedural safeguards when study risks are minimal (§45 CFR 46.409). Only when the research involves greater than minimal risk and no prospect of direct benefit is there a requirement for the IRB to provide additional procedural safeguards through the appointment of an advocate. Because the NCS is primarily an observational study with a minimal level of risk, no such procedural safeguards should be required. Because knowledge about the child's living environment is essential to the Study, in addition to obtaining consent from the agency responsible for the child, a foster parent will be approached to give permission for their participation and the child's continued participation in the Study. The foster parent will be fully informed about the purposes and procedures involved in the Study, and informed consent will be obtained for their participation (as caregiver), and for continued participation of the child.

## 12.7 Revealing Findings to Participants, Families, and Communities

Revealing some of the Study data findings to individual participants is seen as an ethical obligation but may also be an important recruitment and retention strategy. Revealing local aggregate findings to the communities is seen as an important strategy to maintain community engagement.

### 12.7.1 Revealing Individual Findings to Participants and Families

Some routine physical and laboratory test results will be revealed periodically as an incentive to participation. For example, results of routine physical measurements (e.g., height, weight, and blood pressure) and routine laboratory tests performed on biologic samples (e.g., hematocrit) will be provided to participants on a regular and recurring basis. These results will be presented in a context that allows the participant to compare their individual results with normative data when appropriate (e.g., growth curves, normal range of hematocrit for age).

Unless clinically relevant and actionable, NCS generally will not provide genetic information and other medical information to participants or family members. Much of the data collected in the NCS will be of uncertain relevance to the health or well-being of individual participants, and relevant for research purposes only. Participants will be informed of this during the consent process.

If clinically relevant and actionable medical information that may impact the health of the participants is found, they will be advised of that information. Participants may opt out of any measurement, test, biological specimen collection, or environmental sample collection. However, if a test, measurement, or collection is performed, and the results indicate a known health effect or risk to the participant that is clinically relevant and actionable, the Study is obligated to reveal the finding to the participant.

If clinically relevant and actionable genetic information is found in the future, participants will be informed that such information exists and may be obtained upon request. If participants request the information, NCS staff will explain to the participants the consequences of learning such information, and if the participants still desire the information, NCS staff will inform the participants in a sensitive and knowledgeable manner.

Results of environmental sample analysis will only be revealed to participants if there is a known and generally accepted risk relation between the exposure and a significant negative health outcome. This includes the following situations:

- There are state requirements to disclose (e.g., elevated blood lead or mercury concentration).
- Federal or state standards or guidelines exist.
- Appropriate risk assessment that has been conducted and published is applicable to the community in which the samples were collected (e.g., lead levels in dust or soil).

Environmental sample results provided to participants will be accompanied by an explanation and context for the result, basic information about the sources and risks of the chemical/agent, and guidance on where to find more information.

### 12.7.2 Revealing Aggregate Findings to Participants and Communities

The NCS is also committed to informing participants about aggregate data on a periodic basis as Study findings unfold. Because environmental findings may reveal local problems that could impact property values, etc., there may be potential risks to individuals, (participants and nonparticipants) and to the entire community, of revealing information found in the Study. Therefore, revealing information to communities must be done thoughtfully and with some level of preparation. The NCS will always inform individual participants living in a community of any personal findings of concern before informing communities of the findings.

To help keep participants engaged in the Study, all participants enrolled in the Study, adult and child, will receive periodic national updates on the progress of the Study through newsletters, Web sites, and other media. Web sites will be developed for the adults and for children and adolescents of various ages. This continual process will include updates on the progress of the Study, health information appropriate for all participants, some insights into how large studies such as NCS analyze findings to make inferences about how an exposure might be related to an outcome, and serially, information about the Study's findings.

Each site will also integrate a local process into this national process to reveal some of the aggregate findings to the local community, to maintain contact with participants, to give site-specific information to communities and participants, and to help maintain community engagement.

## 12.8 Biobanking and Environmental Sample Banking

Biologic specimens will be collected from women during the preconception period, during pregnancy, and after birth. Specimens will also be collected from biological fathers (during the pregnancy period) and from the child serially after birth. At the time of birth, collection of cord blood and placental material is planned. HIV testing is not currently planned for NCS.

The NCS plans to obtain biologic specimens from participants including blood, urine, saliva, breast milk, and small samples of hair. These specimens will be used to measure various physiologic parameters (e.g., hematocrit, iron stores) and environmental exposures (e.g., lead, chemicals), and to provide genetic information about each participant. Sample volumes will be kept minimal and all child

blood samples will be less than 5 milliliters per kilogram body weight. Specimens will be analyzed and/or stored in one or more repositories for future studies.

Periodically, the NCS will also collect environmental samples of air, dust, water, and soil from the homes of participants and other places where the child spends more than 30 hours per week. These samples will be analyzed to determine and measure environmental exposures and/or will be stored in one or more repositories for future studies.

Effects of environmental exposures on gene expression are among the most important interests of the NCS. Therefore, biologic specimens for DNA analysis will be obtained from participants. The NCS is cognizant that human genomic data are private, intimate, sensitive, and create special concerns about the potential for discrimination, stigmatization, and impact on future employment or insurance. The informed consent process will include reference to the reasons and importance of obtaining genetic information on each participant.

To protect the confidentiality of participants, only unique identification numbers without personal identifiers will be used for all biologic specimens collected and all information derived from those specimens. Data that can be used to link the specimens to personal identifiers and to other data obtained from individual subjects during this longitudinal study will be maintained separately, securely, and confidentially. To further protect participant confidentiality, the NCS will obtain a federal Certificate of Confidentiality through the National Institute of Child Health and Human Development from the U.S. Department of Health and Human Services. The Certificate of Confidentiality will protect the data from forced release through a court subpoena.