

***National Children's Study
Vanguard Study***

***Schema for the
Alternate Recruitment Strategy Substudy
May 25, 2010***

DOCUMENT HISTORY

DATE	VERSION	SUMMARY OF CHANGE
4/23/2010	20100423	FORMATTING, OMB COMMENTS FROM 4/20/2010 CALL
4/26/2010	20100426	Comments from SCs, NCSAC UPDATE ALIGNMENT
4/29/2010	20100429	Comments from 4/28/10 PO Senior Staff Meeting
4/30/2010	20100430	Comments from Graber, Balsam, Haugen
5/06/2010	20100506	Comments from Brenner
5/06/2010	20100506a	Comments from Keim
5/06/2010	20100506b	Preliminary adjudication by J. Park (some comments remain)
5/07/2010	20100507	Comments from Hirschfeld

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A. BACKGROUND AND INTRODUCTION

1. NCS PROGRAM

The National Children’s Study (NCS) is a prospective, national longitudinal study of the effects of environment and genetics on child health, growth and development. The NCS Main Study will follow a sample of 100,000 children, born to women recruited from about 105 Study Locations (generally corresponding to counties) within the US, from before birth to age 21 years. The Study defines “environment” broadly, such as air, water, soil, noise, stress and exposure to natural and manufactured products. By studying children through different phases of growth and development, researchers may be better able to understand the role these factors have on health and disease.

2. VANGUARD STUDY

To conduct the detailed preparation needed for a study of this size and complexity, the NCS was designed to include a preliminary pilot study known as the Vanguard Study. The purpose of the Vanguard Study is to assess the feasibility (technical performance and reliability), acceptability (impact on study participants and study infrastructure), and cost (level of effort, personnel, resources, and money) of the recruitment strategy, study logistics and operations, and study visit assessments that are to be used in the NCS Main Study. The Vanguard Study begins prior to the NCS Main Study and will run in parallel with the Main Study. At every phase of the NCS, the multiple methodological studies conducted during the Vanguard phase will inform the implementation and analysis plan for the Main Study.

Before birth and throughout the children’s lives, the Study will collect health-related information, administer health questionnaires, collect biological and environmental samples and make other assessments identifying children’s chemical, physical, psychosocial, and biological exposures, as well as their genetics. However, of primary interest to the Vanguard Study are operational and performance data; analytic data acquisition for exposure response relationship evaluation is the goal of the Main Study.

The initial Vanguard Study protocol was designed to enroll approximately 1,750 pregnant women through seven Study Locations after 12 months of data collection. Two of the locations began recruitment in January 2009 and the remaining 5 in April 2009. As of April 2010, however, approximately 800 pregnant women have been enrolled, leading to questions about the assumptions underlying the Initial Vanguard Study recruitment model. The seven currently enrolled sites use a household enumeration and screening strategy to identify eligible women for recruitment into the study. Although household enumeration is often considered a gold standard for reducing sampling bias, in that all dwelling units are given an equal probability for selection into the Study, for the NCS Vanguard Study this method has not yielded the target number of births in the time frame projected from initial models.

3. RECRUITMENT SUBSTUDY

Accordingly, we propose a Recruitment Substudy to the Initial Vanguard Study to evaluate the feasibility, acceptability, and cost of three separate recruitment strategies for enrollment of pregnant women into the NCS: 1) provider-based recruitment; 2) enhanced household based recruitment; and 3) two-tiered “high-low” intensity approach. Each recruitment approach would occur in 10 Study Locations, for a total of 30 Study Locations.

Study Locations, already currently under contract to the NCS, were selected to participate in an alternate recruitment strategy based on study center interest and expertise. Accordingly, results from recruitment approaches may be seen as “best case scenarios” in some circumstances and will be evaluated accordingly. Consideration also was given to geographic and demographic diversity of the locations in assigning Study Locations to an alternate recruitment strategy.

Although no attempt was made, for the purposes of the Vanguard Study, to select Study Locations that would permit generalizations to the U.S. target population as whole, sources of potential bias will be systematically examined. Each recruitment strategy will be approximately equally resourced, and will be associated with a specific communications theme appropriate for its mode of participant enrollment (see details below).

B. RESEARCH GOAL

The guiding research goal for the Recruitment Substudy is characterization of recruitment strategies, and components of recruitment strategies, that are effective in identifying, recruiting, and enrolling eligible participants into a population-based cohort study. We will measure progress toward this goal by examining the feasibility, acceptability, and cost of each recruitment strategy.

1. FEASIBILITY

The primary outcome measure of the Recruitment Substudy is feasibility. Feasibility will be measured by a description of recruitment and retention rates among the three proposed recruitment strategies.

Key rates associated with recruitment include:

- The number of women identified for contact by the study, per month
- The number of women successfully contacted by the study, per month
- The number of women determined to be eligible for the study, per month
- The number of women who have heard about the study, per month
- The number of eligible women consented into the study, per month

Key proportions associated with retention include:

- The proportion of age- and geographically-eligible women initially contacted when not pregnant who join the Study when subsequently becoming pregnant
- The proportion of consented women who participate in at least one data collection study visit
- The proportion of women consented during pregnancy, who participate in all data collection visits through the birth of a child
- The proportion of women who receive an ante-partum data collection visit who also receive a birth visit

2. ACCEPTABILITY

The secondary outcome measure of the Recruitment Substudy is acceptability. Acceptability will be measured by selection bias in characteristics of enrolled participants, enrollment burden, and the impact of enrollment methods on study infrastructure.

Key comparisons associated with selection bias in participant characteristics include:

- The distribution of women enrolled prior to pregnancy (preconception), during pregnancy, or peripartum
- For pregnant women, the distribution of gestational age at enrollment and at the first study visit
- The monthly enrollment rate of infants among consented women with due date within that month

Additionally, unit nonresponse will be examined, comparing the profile of recruited participants, retained participants, and those who declined participation, by recruitment strategy, will be compared to a reference population to inform understanding of potential sample bias. Comparisons may include:

- Race/Ethnicity

- Age (date of birth)
- Marital status
- Primary language of household
- Employment status and education level
- Urbanicity
- Study center organizational structure and types of partners
- Community engagement strategies employed

Key comparisons associated with respondent burden and study infrastructure include:

- The respondent burden realized to achieve enrollment for each recruitment strategy
- The impact each source of entry (such as provider referral, household enumeration, community outreach events, self-referral, and others) has on study infrastructure
- The impact each method of community engagement and outreach has on study infrastructure

Additionally, we will ask Study Centers to compile qualitative information about challenges to enumeration, recruitment and consent that are encountered during the conduct of the Study. These reports will be reviewed systematically to inform the Main Study.

3. COST

The third outcome measure of the Recruitment Substudy is cost. Cost will be measured empirically.

Examples of the type of data to be collected include:

- The cost of recruiting and enrolling a woman into the study, by timing of entry (for example, preconception, early pregnancy). Costs will be determined by tracking staff time, supplies and equipment.
- The cost of media and community outreach per recruited and enrolled woman by outreach methods employed particular to each of the three recruitment strategies. Cost will be determined by media invoices, staff time and materials.

C. INFORMATICS MODEL

1. CENTRALIZED MODEL

The Initial Vanguard Study utilized a Centralized Model of data management where NCS case management systems and data capture systems utilized the same approach throughout the Vanguard Study Centers. This centralized approach is common in large scale data collection, even in multi-center studies. In the Initial Vanguard Study experience, we learned that data capture systems and case management systems used successfully by other studies did not meet the particular needs of a study as complex and dynamic as the National Children’s Study. Therefore, a new solution was sought.

2. FACILITATED DECENTRALIZATION MODEL

The NCS Program Office proposes to use a Facilitated Decentralization Model to support informatics in the Recruitment Substudy. Like in the Initial Vanguard Study, the NCS Program Office will continue to develop evaluation questions and plans; data fields, tables and relationships; formatting and transmission standards; a central data archive; and specifications and guidelines for data security, participant confidentiality, and regulatory compliance. Distinct from the Centralized Model, however, the Facilitated Decentralization model allows Study Centers under contract with the NCS to select case management systems, data acquisition platforms, and as appropriate, data collection tools to acquire data whose content, format and security requirements have been established by the NCS Program Office. All data systems

are certified and accredited per the Federal Information Security Management Act of 2002 and related regulatory compliance. All data specifications are consistent with international standards (for example, CDISC and CaBIG).

The Facilitated Decentralization Model encourages the use of open-source, non-proprietary data capture and case management systems. It builds on local Study Center expertise with existing systems. In practice, we find that NCS Study Centers have proposed a short list of open-source systems, with collaboration in architecture and programming planned among Study Centers proposing like systems. It also allows a systematic evaluation of the feasibility, acceptability, and cost of various data capture and case management systems to inform the Main Study. Systematic comparison of data is possible due to the harmonization of data specifications and terminology established by the NCS Program Office, being also consistent with existing international standards.

D. INCLUSION AND EXCLUSION CRITERIA

Inclusion and exclusion criteria are comparable to those used in the initial Vanguard Cohort Study. Inclusion criteria include:

- Women aged 18–49 or pregnant residing in a selected NCS geographic segment at the time of enrollment
- Pregnant women aged younger than 18 at the time of enumeration who are considered to be emancipated minors per the laws of their jurisdiction or who obtain parental consent for participation
- Children born to enrolled women
- Biological fathers as identified by enrolled women
- Adult caregivers for enrolled children who have legal responsibility to authorize needed care for an enrolled child

Women must reside in a selected NCS geographic segment at the time of enrollment. From the Initial Vanguard Study experience, we have learned that some women eligible based on residency will move outside of a selected segment during pregnancy. Accordingly, we propose that enrolled women who move out of the selected segment to an area which is not a designated secondary sampling unit prior to the sample child's birth will be eligible for participation in the Vanguard Study. To remain geographically eligible, enrolled women must reside within 50 miles of the previous address that was initially located in the selected segment boundary. This will increase data available for methodological analysis without affecting generalizability of resulting data, because the Vanguard Study was not designed to yield representative data and, accordingly, sampling weights will not be created for Vanguard Study data. We expect this change in geographic eligibility to increase sample size by a very small amount while maintaining good will with study participants. Note that if enrolled women move farther than 50 miles from the participant's residence at the time of enrollment, participation in the NCS may be limited to phone and/or direct mail interviews.

If geographically eligible, women at any stage of pregnancy will be asked to enroll in the study (up to the end of the hospital stay associated with birth of the child). Pregnant women under 18 years of age at the time are eligible for enrollment into the Study either as emancipated minors or as minors (with parental permission) per the laws of the jurisdiction where they reside. Additionally, women between ages 18-49 who are not pregnant but, at the time of screening, are determined to be at a high probability of becoming pregnant will be invited to join the Study. The consent and assent processes for minors are described in greater detail in the initial Vanguard Study protocol.

We will also ask enrolled mothers to consent to enrolling their child in the Study upon birth through the first six months of age. Consent for child's continued participation for the duration of the Study will be solicited at the 6 month visit.

Biological fathers, as identified by participating women, will be invited to participate in the NCS Vanguard Study. Due to resource constraints, recruitment of biological fathers will start after the minimal data collection phase of the recruitment sub-study is completed. If an enrolled woman indicates that she does not want the NCS to contact the biological father, he will not be contacted and the woman will remain eligible for the Study.

Women not residing in selected segments at the time of enrollment are not eligible to participate in the Study. Women and men who are unable to understand NCS participation and grant informed consent will not be eligible to participate in the Study.

E. STUDY DESIGN AND METHODS

1. SAMPLING

The sampling frame proposed for the Recruitment Substudy is the same as the frame used for the Initial Vanguard Study, with one enhancement, as noted, for the Two-Tier, High-Low strategy.

i. PRIMARY SAMPLING UNITS

As in the Initial Vanguard Study, the sampling design for the Recruitment Substudy uses a multistage clustered approach. In the first stage, 105 locations (generally corresponding to single counties) were randomly selected from all U.S. counties. The process for selecting these Study Locations was based on the intent to achieve statistically and demographically valid coverage of the United States.

From these 105 Study Locations, or primary sampling units (PSUs), 30 were selected for implementation of this Recruitment Pilot. Each Recruitment Strategy will be employed in 10 Study Locations. As described above, Study Locations selected for each of the Recruitment Strategies counties are geographically and demographically diverse; however, they do not, and were not intended to, support generalizations to regions or the U.S. target population. See Tables 1-3 (below) for a listing of Study Locations (PSUs) by recruitment strategy and Study Center.

Table 1. Study Centers and Locations for Provider Based Recruitment

Study Center	Study Location
Arkansas Children’s Hospital Research Institute	Benton County, AR
Brown University	Providence County, RI
Children’s Hospital of Philadelphia	Schuylkill County, PA*
Michigan State University	Wayne County, MI ^
University of California, Davis	Sacramento County, CA
University of Mississippi	Hinds County, MS
University of North Carolina at Chapel Hill	Durham County, NC
University of Texas Health Science Center San Antonio	Bexar County, TX
University of Texas Southwestern Medical Center at Dallas	Lamar County, TX*
Yale University	New Haven County, CT

Table 2. Study Centers and Locations for Enhanced Household Based Recruitment

Study Center	Study Location
Saint Louis University	St Louis (city), MO
University of Washington	Grant, WA*
University of Iowa	Polk, IA
Maine Medical Center	Cumberland, ME*
University of Hawaii	Honolulu, HI
University of Arizona	Pinal, AZ
University of Miami	Baker, FL*
University of New Mexico	Valencia, NM

Table 3. Study Centers and Locations for Two-Tier High-Low Intensity Recruitment

Study Center	Study Location
Emory University	Baldwin County, GA*
Johns Hopkins University Bloomberg School of Public Health	Montgomery County, MD
Northwestern University	Cook County, IL ^
Tulane University School of Public Health	New Orleans Parish, LA
University of California at Los Angeles	Los Angeles County, CA ^
University of Colorado	Douglas County, CO
University of Minnesota	Ramsey County, MN
University of Pittsburgh	Westmoreland County, PA
University of Utah School of Medicine	Cache County, UT*
Vanderbilt University Medical Center	Davidson County, TN

NOTE: * Study Locations selected as non-metropolitan for sampling purposes. ^ Urban Locations selected with sampling certainty due population density.

ii. SECONDARY SAMPLING UNITS

As in the Initial Vanguard Study, geographic segments are formed within Study Locations during the second stage of sampling. These segments comprise census blocks, or clusters of households roughly corresponding to neighborhoods. As in the Initial Vanguard Study, approximately 10-15 of these segments will be selected within each Location based on density of the target population. As in the Initial Vanguard Study, these secondary sampling units, or SSUs, are selected to yield a predicted 250 births per year per Study Location based on vital record data.

Both the Provider-Based Recruitment strategy and the Enhanced Household Recruitment Strategy employ the same two-stage sampling design employed with the Initial Vanguard Study; primary sampling units and secondary sampling units will contribute in the same way to the sampling frame.

However, the Two-tier High-Low Intensity strategy employs a somewhat different secondary sampling unit and a tertiary sampling unit.

iii. TERTIARY SAMPLING UNITS

In the Two-Tier High-Low Intensity strategy, the tertiary sampling unit is equivalent in population density to the secondary sampling unit employed by the Provider-Based Recruitment strategy and the Enhanced Household Recruitment strategy (and the Initial Vanguard Study strategy). However, the secondary sampling unit in the Two-Tier High-Low Intensity strategy contains the tertiary sampling unit and at maximum 2 additional selected segments adjacent to the selected tertiary sampling unit. These “additional” segments contributing to the secondary sampling unit are selected by proximity to the tertiary sampling unit, population density, and relevant political and social neighborhood boundaries. See Table 4.

Table 4. Comparison of Sampling Frame Characteristics by Recruitment Strategy

Recruitment Strategy	Primary Sampling Unit	Secondary Sampling Unit	Tertiary Sampling Unit
Initial Vanguard Study	Counties (Study Locations)	Census Blocks (Segments)	NA

Provider-Based	Counties (Study Locations)	Census Blocks (Segments)	NA
Enhanced Household	Counties (Study Locations)	Census Blocks (Segments)	NA
Two-Tier High-Low Intensity	Counties (Study Locations)	Census Blocks (Segments)	Census Blocks (Segments)

NOTE: Shaded cells denote equivalence in population density.

The approaches proposed for the Provider-Based Recruitment and Enhanced Household Recruitment strategies do not require variation in the original sampling frame at the secondary sampling unit level. However, as described in detail below, the Two-Tier High-Low Intensity approach is proposed to inform the Main Study of the optimal size of the secondary sampling unit to yield sufficient numbers of Study-eligible pregnant women to meet NCS Program goals. Additionally, the Two-Tier High-Low Intensity approach to recruitment relies on a period of developing rapport with Study participants in a low intensity data collection experience prior to inviting participants to engage in a higher intensity data collection experience in sufficient numbers to support evaluation. Both objectives particular to the Two-Tier approach, therefore, require a comparatively larger secondary sampling unit (roughly three times the size of the secondary sampling unit selected for the other recruitment strategies).

2. GENERATION OF ADDRESS FRAMES

For each of the Recruitment strategies, a list of all known households in the selected segments will be compiled. These households represent the dwelling units from which eligible participants will be recruited and, as such, form the base for determining if a woman is potentially geographically eligible for the study. They also serve as the basis for evaluation of sample coverage as the study aims to recruit all eligible births to residents in these dwelling units.

There are two ways that Centers can compile household lists: United States Postal Service (USPS) Listings or 2) “Conventional Listing. In the first option, USPS address lists are purchased from approved vendors. To date, we have found acceptable coverage of addresses by USPS lists in urban and semi-urban areas in the Initial Vanguard Study Locations. However, we note that rural areas, and areas experiencing significant, recent housing growth, have much lower rates of coverage. The second approach, Conventional Listing, uses systematic, manual compilation of residential addresses in a given area. Trained field listers canvass selected segments, locate segment boundaries and then move systematically throughout the segment, compiling a list of all residential addresses. No contact with human subjects is necessary for listing. Conventional listing can be accomplished using either hard-copy or computer-based materials. Given the Initial Vanguard Study experience, we anticipate that Centers will make particular use of conventional listing methods in rural segments or segments experiencing rapid housing growth.

3. COMMUNITY OUTREACH AND ENGAGEMENT

Each Recruitment strategy will employ a community outreach and engagement plan that benefits from 1) core content generated centrally from the NCS Program Office; 2) themes reflecting Recruitment strategy enrollment approaches; and 3) conveyed in a way that best fits local interests and needs. This framework will allow systematic comparison of message themes across Recruitment strategies, and systematic comparison of locally-determined media use across all Recruitment Substudy Locations while maintaining consistency in core NCS content. See Table 5.

Core content, such as the purpose, goals, design, and management of the Study, will be consistent throughout outreach and engagement activities across Recruitment strategies. Message themes will be customized for each of the three

Recruitment strategies to emphasize aspects of enrollment most particular to a given Recruitment approach. Use of media and community activities will vary according to local interests to increase public awareness of the NCS and to aid with recruitment of Study participants. These methods will include but will not be limited to messages transmitted through local media (for example, newspapers, radio, and television), distribution of various NCS materials (for example, Study brochures, question and answer sheets, and newsletters), and secure use of electronic modes, such as Internet and social media.

Table 5. Community Outreach and Engagement Plan by Recruitment Strategy

Recruitment Strategy	Core Content	Message Theme	Conveyance
Initial Vanguard Study	NCS Program Office	General	Locally-determined*
Provider-Based	NCS Program Office	Relationship with Care Provider	Locally-determined*
Enhanced Household	NCS Program Office	Relationship with Community	Locally-determined*
Two-Tier High-Low Intensity	NCS Program Office	Self-Determination	Locally-determined*

NOTE: * Permits comparison of primary media use methods.

Costs and effectiveness of these approaches, particularly for minority engagement, will be evaluated systematically. For example, preliminary data from at least one Study Center in the Initial Vanguard Study suggest that current outreach and engagement practices may not be effective in reaching some age-eligible women of Asian ethnicity; this and other related findings will inform approaches used in the Recruitment Substudy. Other questions of interest include:

- How do local travel costs associated with outreach events vary across recruitment schema?
- What were the dates, costs, and geographic targeting of outreach and media campaigns?
- What is the cost per delivered message in media campaigns (exact or approximate)?
- What is the size of the targeted population of the media campaign?
- What is the yield of responses from particular media campaigns?
- What is the cost in time for community outreach efforts (both contractor and volunteer labor)?
- Does increased frequency of media messages result in increased response by interested individuals?
- Does varying the type of media message result in increased response by interested individuals?
- Are particular outreach efforts more or less successful with persons with particular demographic traits (race, ethnicity, age, marital status, primary language, employment, or education)?
- Are particular outreach efforts associated with more effective retention? For instance, participants encountered through a provider might be retained in the study better than participants recruited through a household visit.

4. RECRUITMENT

This Recruitment Substudy compares three different strategies to recruit eligible women into a longitudinal cohort study: Provider-Based, Enhanced Household Enumeration, and Two-Tiered High-Low Intensity strategies. Each is described below. The overarching goal of the Recruitment Substudy was presented above; objectives unique to specific recruitment strategies are included in the descriptions below.

i. PROVIDER-BASED STRATEGY

In the Provider-Based Recruitment strategy, potential participants will be personally introduced to the Study through the

existing health care system. First, prenatal care providers serving women living in selected segments will be identified by Study Centers. Care providers will include, but are not limited to, general practitioner offices, pediatrician offices, obstetrician/gynecological offices, and health clinics. Second, Study Centers will work to engage identified providers in the NCS as a means to provide information about the Study. Third, secure and HIPAA-compliant means will be used to identify potentially geographically eligible women through provider records or contacts. In the provider-based recruitment model, enrollment may occur in the provider setting or through referral off-site. In all cases, however, informed consent will be administered by Study staff (not providers). Health care providers will not be employees of the study nor engaged in the informed consent process or study data collection.

It is anticipated that the Provider-Based Recruitment strategy may more efficiently identify age and geographically eligible pregnant women through the strategy's connection with the health care system, which may be considered a familiar and trusted environment to Study participants. However, possible bias in participant demographic and pregnancy characteristics may be a potential issue. Therefore, in addition to recruitment evaluation questions applicable to all three Recruitment strategies, evaluation questions unique to the Provider-Based strategy include:

- What are the most efficient and effective ways to identify providers?
- What percentage of identified providers participate in the study?
- What techniques are most useful for engaging providers?
- Among participating providers, which strategies are most useful for identifying geographically- eligible women?
- How are provider strategies for identifying geographically eligible women related to rates of recruitment?

ii. ENHANCED HOUSEHOLD STRATEGY

In the Enhanced Household Recruitment strategy, potential participants will be personally introduced to the Study through an advance letter by direct mail, followed by household canvassing. First, potential participants will be approached at the household doorstep to share further information about the Study and enumerate a household. Second, Study staff will ask age-eligible women to take part in further eligibility (pregnancy) screening. Third, Study staff will invite eligible women to consent to participate in the study.

The Initial Vanguard Study used a household enumeration approach to identify age- and geographically-eligible pregnant women. The Enhanced Household Recruitment strategy will improve our ability to identify pregnant women by deploying staff trained in best practices to assist household enumeration and screening, among the most labor intensive aspects of the study. This strategy will utilize staff experienced in enumeration directly as enumerators, could also use the best of the enumerators to train new enumerators at study centers, or a combination of the two. The strategy will also benefit from optimized approaches based on the experience of the Initial Vanguard Centers as well as other best practices from other studies.

Although household enumeration may be least subject to respondent bias due to extensive canvassing, it is a particularly labor intensive approach. Therefore, in addition to recruitment evaluation questions applicable to all three recruitment strategies, examples of recruitment evaluation questions specific to the Enhanced Household Recruitment strategy include:

- What are the most efficient and effective ways to reach households in the selected segments?
- What techniques are most effective for engaging household members at the doorstep (enumeration, screening, and enrollment)?

iii. TWO-TIERED HIGH-LOW INTENSITY STRATEGY

In the Two-Tiered High-Low Intensity Recruitment strategy, a low intensity data collection effort will be implemented for age and geographically eligible women in a comparatively larger geographic area (secondary sampling unit) than those

selected for Provider-Based and Enhanced Household-Based Recruitment strategies. Then, after a period of time during which rapport has been developed between low intensity participants and the Study, a geographically-defined subsample of low intensity participants will be asked to engage in a higher intensity data collection effort. The higher intensity data collection effort will use the same instruments as those used in the Provider-Based and Enhanced Household-Based Recruitment strategies.

Specifically, the low intensity data collection effort will use marketing, direct mail, and other techniques to encourage self-referral and enrollment of the target population within the secondary sampling unit and the tertiary sampling unit (which is within the boundaries of the secondary sampling unit). These outreach methods will include, as appropriate to each Study Location, conventional marketing methods such as billboards, print advertising, web sites, bulk mail, direct mail, targeted electronic advertising and limited community outreach. The intensity and frequency of these media messages are planned to escalate over time to correspond with Study launch, and may be augmented as necessary with other methods, such as provider-mediated contacts and broad, directed community outreach efforts. The relative effectiveness of each of these methods will be evaluated in a systematic way.

To support direct mail marketing to potentially age-eligible households, listing information for potential participants may be augmented by commercial sources such as state departments of motor vehicles or InfoUSA™, an independent data source. Both data sources contain contact information and other associated demographic information on households across the U.S. To support direct mail marketing to stakeholders, some Study Centers may find it feasible to gather contact lists from community groups or other study partners.

After participants have joined the low intensity effort through self-referral and rapport with Study participants has been established, a geographic subset of low intensity participants will be invited to join the high intensity data collection effort. Low intensity participants also have the option of remaining in the low intensity effort, or, dropping out of the Study.

The major goals of the two-tier strategy include generating data to gauge the desired size of the secondary sampling units necessary to yield enrollment targets, and developing information needed to better estimate bias between women who chose to participate in the low intensity data collection and the high intensity data collection. Therefore, in addition to recruitment evaluation questions applicable to all three recruitment strategies, examples of recruitment evaluation questions specific to the Two-Tier High-Low Recruitment strategy include:

- What is the optimal size of the secondary sampling unit to identify sufficient numbers of age-eligible (pregnant) women to meet Study goals?
- What is the level of data collection intensity which optimizes the data collected at an acceptable response rate?
- If offered a high intensity effort and declined, what percentage of women will choose to remain in the low intensity effort (rather than dropping out altogether)?
- How do demographic and health characteristics of women who join the high intensity effort differ from those eligible but decline?

5. DATA COLLECTION

We plan a staged rollout of the Recruitment Substudy. This staged launch features minimal Study instruments initially to allow Recruitment Substudy Study Centers to gain familiarity with data collection operations and logistics. Subsequently, all Recruitment Substudy strategies will employ more robust (in length and complexity) and additional visit instruments that are anticipated to be commensurate with those used in the Initial Vanguard Study.

i. STAGE 1: MINIMAL DATA COLLECTION EFFORT

At our anticipated July Launch, we will limit data collection activities for all three Recruitment strategies in the number of instruments and the complexity of instrument. Specifically, for the Provider-Based, Enhanced Household, and Two-Tier High Intensity strategy, we will administer three prenatal interviews and one birth visit interview per participant: the Pre-Pregnancy Interview, the Initial Pregnancy Interview, the Second Pregnancy Interview, and the Birth Interview. The majority of items contained in these instruments were featured in the First Trimester Mother Instrument of the Initial Vanguard Study. Note that a Birth Visit, but not a Birth Interview is currently part of the Initial Vanguard Study. However, we would like to evaluate this as an option for the Main Study and therefore include the instrument in the Recruitment Substudy. We will also ask participants to complete a brief self-administered questionnaire evaluating the data collection experience. See Table 6.

Table 6. Study Instruments by Recruitment Strategy, Stage 1

Initial Vanguard Study	Provider-Based	Enhanced Household	Two-Tier High-Low Intensity	
			Low	High
Household Enumeration	<i>forthcoming</i>	Household Enumeration	<i>forthcoming</i>	<i>forthcoming</i>
Pregnancy Screener	Pregnancy Screener	Pregnancy Screener	Pregnancy Screener	Pregnancy Screener
General Study Informed Consent Form**	Women’s Informed Consent Form	Women’s Informed Consent Form	Low Intensity Informed Consent Script	Women’s Informed Consent Form
Preconception (PI)	Pre-Pregnancy	Pre-Pregnancy	<i>forthcoming</i>	Pre-Pregnancy
First Trimester (T1)	Initial Pregnancy	Initial Pregnancy	<i>forthcoming</i>	Initial Pregnancy
Second Trimester (T2)	NA	NA	<i>forthcoming</i>	NA
Third Trimester (T3)	Second Pregnancy	Second Pregnancy	<i>forthcoming</i>	Second Pregnancy
Birth Visit (B1)	Birth Instrument	Birth Instrument	<i>forthcoming</i>	Birth Instrument
3-month	<i>forthcoming</i>	<i>forthcoming</i>	<i>forthcoming</i>	<i>forthcoming</i>
6-month	<i>forthcoming</i>	<i>forthcoming</i>	<i>forthcoming</i>	<i>forthcoming</i>
9-month	<i>forthcoming</i>	<i>forthcoming</i>	<i>forthcoming</i>	<i>forthcoming</i>
12-month	<i>forthcoming</i>	<i>forthcoming</i>	<i>forthcoming</i>	<i>forthcoming</i>
18-month	<i>forthcoming</i>	<i>forthcoming</i>	<i>forthcoming</i>	<i>forthcoming</i>
24-month	<i>forthcoming</i>	<i>forthcoming</i>	<i>forthcoming</i>	<i>forthcoming</i>
36-month	<i>forthcoming</i>	<i>forthcoming</i>	<i>forthcoming</i>	<i>forthcoming</i>

NOTE: * A subset of items from the Household Enumeration Instrument may be administered to the Provider-Based Recruitment and the Two-Tier, High-Low Recruitment strategies as a mechanism for determining eligibility of a dwelling unit and identifying women that may be age-eligible to participate in the Study.

**As discussed below, we propose to administer the Women’s Informed Consent form to the Initial Vanguard Study participants subsequent to local IRB approval. This consent form has been approved by the NICHD IRB. The Women’s Informed Consent Form would replace the General Consent and the Biological and Environmental Sample Consent forms as a way to reduce the burden and redundancy associated with our current consent procedures that have emerged from our field experience. See *Human Subjects Protections*, below.

These instruments are much briefer than instruments used in the Initial Vanguard Study (approximately 30 minutes each compared to approximately 3 hours each). No physical measures, biologic specimens, or environmental samples will be collected. Reducing the length of the instruments for the July launch is possible given the goals of the Recruitment Substudy: a) evaluate Recruitment strategies and comparative effectiveness of those strategies; b) provide measures of study operations and logistics; c) evaluate item functioning of a small group of new measures that might inform Main Study instrumentation.

The interview instruments will be administered in person for Provider-Based Recruitment, Enhanced Household-Based Recruitment, and the high intensity tier of the Two-Tier High-Low Recruitment strategy. Alternate acceptable modes, such as telephone administration or secure web based administration, may be proposed in cases where participants are not available for in person interviews. However, with the exception of the Birth Visit Instrument, which is intended to be administered in a hospital setting, in-home administration is preferred for all other data collection events pertaining to the provider-based, enhanced household and high intensity recruitment strategies.

The low intensity tier of the Two-Tier High-Low Recruitment strategy will be administered by Computer Assisted Telephone Interviewing and self-administered questionnaire (either Paper and Pencil Administration or secure web administration). In particular, for the Low Intensity participants, consent administration will be conducted by telephone. We propose to allow Study Centers the option of submitting: 1) a secure and reliable method of obtaining informed consent through a website interface; and 2) a telephone or secure and reliable website-administered data collection instruments. Proposals for these modes of administration will require review by the NCS Program Office and the NICHD Chief Information Officer in addition to regulatory approval prior to use. See Table 7.

Table 7. Mode of Instrument Administration by Recruitment Strategy, Stage 1

Data Collection Event	Provider-Based and High Intensity	Enhanced Household	Low Intensity	
			Non-Pregnant	Pregnant
Household Enumeration	NA	In person	NA	
Pregnancy Screener	In person	In person	Telephone	
General Study Informed Consent Form	In person	In person	Telephone with direct mail information sheet*	
Pre-Pregnancy	In person	In person	Direct mail*	NA
Subsequent Pregnancy Screeners	Telephone	Telephone	Direct mail*	NA
Initial Pregnancy	In person	In person	NA	Direct mail*
Second Pregnancy	In person	In person	NA	Direct mail*
Birth Visit Instrument	In person ^	In person	NA	Direct mail*

NOTE: *Alternate acceptable modes may be proposed for approval. See *Minimal Data Collection Effort*. ^ In-hospital administration. Unless otherwise indicated, in-home administration is preferred for all other data collection events.

ii. STAGE 2: EXPANDED DATA COLLECTION EFFORT

Six months following initial data collection, or approximately January 2011 we will introduce somewhat more robust versions of the Pre-Pregnancy, Initial Pregnancy, Second Pregnancy, and Birth Visit instruments and begin the collection of physical, biological and environmental samples. In particular, items to be added to these pre-pregnancy and pregnancy instruments will include items whose methodological or logistical properties are not yet well known and would benefit from item functioning analysis. We will also administer additional visit instruments after appropriate IRB and OMB review and approval. As robust versions of the Pre-pregnancy, Initial Pregnancy, Second Pregnancy, and Birth Visit are launched and remaining study visits are added, we anticipate that data collection instruments for the Recruitment Substudy will be comparable (although somewhat briefer due to efficiencies gained from experience) to those currently in the Initial Vanguard Study protocol.

iii. OUTREACH DATA

Study Centers will be required to track the cost effectiveness of outreach campaigns. This information will be reported to the NCS Program Office for aggregate analysis. Specifically, for stationary outreach activities (such as community events, meetings, poster distributions, and billboards), Study Centers will track the geographic location of the outreach activity relative to the sampled segments. For ongoing outreach activities, Study Center media messages will include phone numbers, web addresses, or email addresses that are traceable to that media message (for example, separate phone numbers for television, mailed, and billboard messages) so the Center can track which message generated the response by the participant. In this way, costs associated with each campaign will be tracked on a per campaign basis, and where possible, costs per message delivery to a single recipient.

F. DATA ANALYSIS

The analytic aim of the new recruitment schema pilots is a quantitative description of the feasibility, acceptability, and cost of three discrete participant recruitment strategies. Overarching research questions, and research questions specific to particular Recruitment strategies, are presented above (see *Research Goals* and *Study Design and Methods, Recruitment*, respectively). The ways in which data will be collected are presented in *Informatics Model* and *Data Collection*. This section describes our decision rules that form the basis of our recruitment, participant bias, and retention evaluation plan.

1. EVALUATION OF FEASIBILITY

i. RECRUITMENT

Feasibility will be evaluated in terms of recruitment and retention of participants. Recruitment will not target a particular response rate or a particular number recruited. Instead, the outcome of interest is the defining the maximal rates and steady state rates for each of the Recruitment strategies in identifying eligible women, successfully gaining their consent, and successfully collecting data throughout pregnancy and including birth. Steady state rate is defined as 3 consecutive months of approximately the same rate.

Accordingly, outcomes that will be used to assess recruitment include:

- The rate at which the Study learns of potentially eligible women, which will occur through a variety of sources dependent on the recruitment schema.
- The rate at which the Study can successfully contact these potentially eligible women.
- The rate at which the Study determines the dwelling unit eligibility and the pregnancy screening eligibility of these women.
- The rate at which eligible women consent to entering the study after being contacted and screened for eligibility.

For the Main Study, a customized recruitment strategy may be required for different types of Study Locations. The Recruitment Substudy experience, along with other extant data and resources, will provide the guidance to define successful recruitment strategies for the Main Study. Should combinations of approaches be proposed on the basis of feasibility, acceptability and cost, special consideration will be given to estimated impact on the shared sampling frame and comparison of resulting data.

ii. RETENTION

The Main Study plans include health and developmental outcomes of Study subjects as they move through adolescence

and early adulthood. Thus, the retention of a sample of sufficient size in the Main Study is important to answer many of the central scientific questions posed for the Study. Determining expected rates of retention of participants through pregnancy to birth and beyond is a key part of the analytic plan for the Vanguard Study. Retention of Study participants from visit to visit will be carefully monitored.

Specifically, the NCS will monitor:

- The proportion of age-eligible women not pregnant at initial contact who consequently become pregnant and agree to join the Study.
- The proportion of consented women who participate in at least one data collection study visit.
- The proportion of women enrolled during pregnancy and participating in all data collection visits through the birth of a child that is enrolled into the Study.
- The proportion of women who receive a pre-birth data collection visit that also receive a successful birth visit.

Retention challenges and solution will likely vary by the nature of the visit, the length of time between visits, and the participant's stage in the Study cycle. For instance, women not planning to become pregnant are of interest to the Study, and yet identification with the Study may not appear salient to this group. Enrolled pregnant women are seen every few months, as are those women during the sample child's infancy. Past infancy, the periodicity of study visits and phone calls are more dispersed. This is also a time in the family's life cycle where moving may be more common, adding to difficulty tracing enrolled mothers and children over time. This may be somewhat compensated by the participant's commitment to the Study, which may increase over time of involvement. The NCS will monitor these aspects of retention carefully.

We also acknowledge that retention issues and solutions may vary by demographic and health characteristics. To the extent that we can measure variation in retention by these characteristics, and address them in the Recruitment Pilot, this will inform strategies adopted in the Main Study. Characteristics of planned comparison include race and ethnicity, age of women at enrollment, primary language of household, maternal education and occupation, parity and age of youngest child in the household. Health characteristics compared will include general health status, and medical conditions, that are of particular public health interest such as diabetes, obesity, hypertension, and asthma among others.

We note that two areas of retention are particularly important for generating recommendations for the Main Study's design. The NCS is distinct among longitudinal child cohort studies in that it aims to collect environmental exposure data prior to pregnancy and during pregnancy. It is because of these aims that the Study design does not draw from a birth certificate sampling frame, which is a simpler and less costly method of identifying women to enroll in a generalizable, large-scale study. In large part, then, the extent to which these recruitment schema successfully retain women pre-pregnancy and during their pregnancy in the Study will drive their recommendation for use in the Main Study.

2. EVALUATION OF ACCEPTABILITY

Acceptability will be evaluated in terms of selection bias and respondent burden. All recruitment strategies may introduce selection bias, and the Study will evaluate the selectivity inherent to each of the schema. The NCS is a study of the effects of the environment on children, and many relevant environmental exposures occur either before or during pregnancy. Thus, the Study is interested in identifying any bias in the stage of pregnancy when women enter the study and participate in their first data collection. The study will track the distribution of women who are enrolled before they are pregnant, during pregnancy, or at or around the birth event. The study will also record and examine the distribution of gestational age at the time of consent and at the time of first study visit for data collection, as these early data collections are important for understanding exposures during pregnancy.

The main NCS must be generalizable to the population of births in the United States, thus a broad range of enrollees must be recruited. Further, the receptiveness of particular women to particular recruitment strategies may be associated with demographic factors, such as: race, ethnicity, age, marital status, primary language, employment status, and level of education.

The study plans to examine the demographic and general medical characteristics of screened and recruited women and compare those characteristics among the three recruitment strategies, and, as measures permit, the cohort for the original seven Vanguard centers. Additionally, these distributions will be compared to population level data such as U.S Census or birth data for the geographic region.

As described above, respondent burden and impact on Study Center and Program Office infrastructure will be evaluated as well. All else being equal, methods that reduce respondent burden will be given priority over methods that reduce impact on study infrastructure.

3. EVALUATION OF COST

Evaluation of cost will consider level of effort, equipment and materials for data collection. Study Centers and the NCS Program Office will track these data; the NCS Program Office will evaluate the combined data. Evaluation will consider stationary or repeated costs, and investment in infrastructure that may reduce costs in the Main Study. Cost alone will not be the basis for retaining or rejecting a Recruitment strategy.

G. HUMAN SUBJECTS PROTECTION CONSIDERATIONS

1. INCENTIVES

In the beginning phase of the recruitment strategy Sub-study data collection for the pre-conception through birth visits will be limited to completion of a survey questionnaires which will take 30-60 minutes to complete. This is a smaller time and burden commitment than is expected in the Initial Vanguard Study. Participants will receive a remuneration equivalent to \$25 for completion of Study questionnaires. This is comparable to the amounts given to Initial Vanguard Study participants for completing self-administered questionnaires of comparable duration.

Once data collections activities are expanded for the Recruitment Substudy, compensation for participants in the in the Provider-Based Recruitment, the Enhanced Household-Based Recruitment, and the High Intensity effort of the Two-Tier High-Low Intensity Recruitment strategy, the incentive schedule will be re-assessed to make sure incentives are comparable to those received by participants in the Initial Vanguard Study in light of anticipated increased respondent burden. See Table 8.

Table 8. NCS Incentives, by Study Activity and Impact on Participants, Stage 1

Data Collection Activity Characteristics	Initial NCS Vanguard Study	NCS Recruitment Substudy
Time for encounter	3 hours	0.5 to 1 hour
Sensitivity of questions	Sensitive, including sexual activity	Few sensitive questions
Physical measures	Yes	No
Environmental specimens	Yes	No
Biospecimens	Yes	No
Participant observation	Yes	No
Monetary incentive, per visit	\$100*	\$25
Non-monetary incentives (tote bags,	In addition to the monetary	As an alternative to the monetary

post its, key chains, etc.)

incentive, non-monetary incentives valued at \$25 or less may be offered to participants

incentive, NCS logo gifts valued at \$25 or less may be offered to the participants in lieu of cash or local incentives not exceeding \$25 in value and deemed non-coercive by local IRBs

NOTE: *For Preconception, First Trimester Mother Interview, and Third Trimester Mother Interview Visits.

2. PRIVACY AND CONFIDENTIALITY

The recruitment evaluation will follow the same procedures and standards of confidentiality applicable to the NCS Pilot Phase. Study participants will be assured that the data collected will be safeguarded closely and that actions will be taken to protect confidentiality. Participants will be informed about the Certificate of Confidentiality granted to NCS to protect data from involuntary disclosure.

The Study Centers, under contract to conduct the NCS Vanguard Study, will have policies and procedures regarding confidentiality and protection of study data which will be reviewed by the NCS Project Office.

In addition to their own confidentiality procedures and policies, Study Centers will implement all federally required study-related confidentiality and data security procedures. All NCS Project Office staff, NCS Study Center staff, and other NCS contracting staff with access to NCS data must receive data confidentiality and security training provided by the NCS Program Office or its agent. These include completion of the NIH Computer Security Awareness Training, completion of a Human Subjects Protection Training, and signing an Assurance of Confidentiality or similar pledge that NCS data will only be used for the intended scientific purpose. All NCS Staff are required to complete security background checks consistent with Office of Personnel Management requirements. Only those cleared for Security Level D or higher will be eligible to request NCS data access.

To further assure confidentiality of participant data, the study will employ rigorous methods to provide security for personal identifying information. Each Study Center and the NCS Program Office Data Warehouse will be required to submit an NCS Security Plan and Assessment that is FISMA compliant. This Security Plan will include a) certification and accreditation of proposed data capture and case management software; b) configuration of those systems on Study equipment; c) full disk encryption and two-factor authentication of Study computers housing NCS data; and d) security assessment of the physical computing environment. After initial Study Center self-assessment of their Security Plans, the NICHD CIO will review all Study Center Security Plans to determine Study Center's Authority to Operate. Frequent and regular monitoring visits will assist in compliance with these terms.

Privacy Impact Assessments will be conducted prospectively and recurrently as needed.

Specific NCS data elements to be collected, disclosure review, and data access are described in detail in the Data Access and Confidentiality Committee Manual. Principles and policies are available at <http://www.nationalchildrensstudy.gov/about/organization/dacc/Pages/PolicyManualandDataUseAgreements.aspx>; the Manual is available upon request. Specifically, all NCS data files will undergo disclosure review personally identifiable information using procedures consistent with or exceeding those named in Working Paper 22 of the Federal Committee on Statistical Methodology, and steps will be taken to appropriately manage disclosure risk. For example, genome-wide scans conducted on NCS specimens will be considered personally identifiable information and treated as such. Some biologic analyses (e.g., HIV status, exposure to specific toxicants), results of some mental health screening tests, and reports of abuse are also considered sensitive.

3. DISCUSSION OF POTENTIAL RISKS AND BENEFITS

i. BENEFITS

There is no prospect of direct benefit to participants from the recruitment strategies evaluation. However, this Substudy will generate valuable information related to enhancing and maximizing recruitment and retention of participants in to the NCS and enable the Study to tailor the most effective and least burdensome methods of recruitment as the Study continues to expand to additional Study sites in the future.

ii. RISKS

The recruitment strategies evaluation does not increase participants' risk over and above the minimal risk entailed in participating in the NCS. Participants in the enhanced Household Based Recruitment, Provider Based Recruitment and the high intensity arm (Tier 2) of the two-tier approach will participate in approximately the same data collection activities as current Vanguard Study participants when the protocol is fully operational at the Study Centers conducting those strategies. The decreased data collection procedures, a subset of the current data collection procedure for each visit, that will be initially implemented at the Study sited will be even less burdensome and time-consuming than the full data collection procedures currently in place at the Initial Vanguard Study Centers.

Participants in the low intensity arm of the two-tier approach will participate by completing self-administered or telephone-based questionnaires containing only a subset of the assessments in the other arms. The potential risk to these participants is also minimal.

4. INFORMED CONSENT PROCEDURES

i. PROCEDURES FOR THE RECRUITMENT STRATEGIES (EXCEPT LOW INTENSITY)

The same consent process used in the original seven Vanguard centers will be used for participants in the Provider Based Recruitment, Enhanced Household Based Recruitment and the High Intensity Tier of the Two-Tier, High-Low Intensity Recruitment strategy. Participants in the in these Recruitment strategies will take part in the same data collection activities as participants in the current Vanguard Study after the initial six month minimal data collection phase.

Participants will be administered consent in the same manner and using the same Study informed consent form that have been approved by the NICHD IRB for administration at the seven Initial Vanguard Center sites (Appendix A). Additional Visit Information Sheets (tailored to the content of each visit and, on an as needed basis, other informational materials) will be developed for participants in each of these Recruitment strategies. These information sheets will inform participants that data collection activities will be enhanced throughout the course of their participation. However, enhancement of the data collection activities will not exceed the level of respondent burden of Initial Vanguard Study participants.

ii. PROCEDURES FOR THE LOW-INTENSITY ARM

A new consent form will be developed for participants in the Low Intensity effort of the Two-Tier High-Low Intensity Recruitment strategy as research participation in this effort will involve only completion of self-administered or telephone based questionnaires and will not involve face to face interviews and observations, physical measurements or

samples at any time throughout the recruitment Substudy. The consent form will be administered through mail, telephone, or via a secure internet site. The telephone consent script is included as Appendix A2.

The new consent form will describe to participants that they can expect to receive periodic questionnaires delivered through mail, telephone, or secure web instruments, that the study will follow children born to women participating in the Study for 21 years, and that the Study may at a later date invite geographically eligible participants to enroll in higher intensity data collections, for which they would go through an additional, separate informed consent process (that is, the same consent process described above for the Initial Vanguard, the Provider-Based, and the High Intensity Recruitment strategies).

We are asking the IRB for a waiver of documentation of informed consent for the low intensity tier participants. We believe that the consent evaluation meets the regulatory requirements for a waiver of documentation of informed consent as described in CFR §46.117 (c).

Only those women that live in the tertiary sampling unit will be offered the invitation to participate in the High Intensity data collection. This invitation will be offered by mail or by telephone. If women decline the invitation, they may still participate in Low Intensity data collections. If the women accept the invitation and give their consent for High Intensity data collections (using the same procedures), they will no longer be asked to participate in Low Intensity data collections (self-administered or telephone based questionnaires). Over time, participants may wish to cease participating in High Intensity data collections. If so, the study will offer them the opportunity to continue with the Study by receiving Low Intensity data collections, and notify them that they may return to High Intensity data collection as their preferences dictate. Participants may fully withdraw from the study at any time by giving verbal or written notification of their intent, and may decline any particular data collection event or component.