

1 ***Background***

2

3 Patterns of illness among children in the United States and other industrially
4 developed nations have changed substantially during the past 100 years [1].
5 Before and during the first half of the last century, infectious disease posed the
6 principal threat to children. In contrast, the major illnesses and disorders that
7 impair health, growth, and development today are chronic non-communicable
8 conditions stemming from the complex interaction of environmental exposures,
9 and genomic factors occurring before birth through adulthood (The Barker
10 Hypothesis).[2-4]. These conditions include premature births [5]; birth defects [6-
11 8]; cardiac defects and co-morbidities [9]; neurodevelopmental disorders, such
12 as learning disabilities, dyslexia, intellectual disability, attention
13 deficit/hyperactivity disorder, and autism [10-13]; asthma[14]; injuries [15]; obesity
14 and type 2 diabetes [16]; and childhood cancer [17]. Identifying the
15 antecedents to these conditions is the major challenge to public health
16 practitioners and pediatric researchers today, and is the pivotal frontier to be
17 crossed to advance science and improve the health and well being of children
18 in developed countries.

19

20 In 1999, the President's Task Force on Health Risks and Safety Risks to Children
21 concluded that a large study would be required to measure the effects of
22 environmental exposures on child health. Following the recommendation of that
23 Task Force, Congress passed the Children's Health Act of 2000. (Public Law 106-
24 310 Sec. 1004), which directed the National Institute of Child Health and Human
25 Development (NICHD) to conduct a national study. It was to be prospective,
26 longitudinal and focused on investigating the effects of environmental exposures
27 on child health and development with 'environment' broadly defined. The
28 Study was to comprise a diverse sample of children beginning in the prenatal
29 period and continuing to adulthood. The study was to be large enough to
30 investigate the impact of health disparities. Specifically, the Study is required to:

31

32 *(1) incorporate behavioral, emotional, educational, and contextual*
33 *consequences to enable a complete assessment of the physical, chemical,*
34 *biological, and psychosocial environmental influences on children's well-*
35 *being;*

36

37 *(2) Gather data on environmental influences and outcomes on diverse*
38 *populations of children, which may include the consideration of prenatal*
39 *exposures; and*

40

41 *(3) Consider health disparities among children, which may include the*
42 *consideration of prenatal exposures."*

43

44 The implementation of this program of research became the National Children's
45 Study (NCS).

46

47 ***Main Study Goals***

48 The overall goal of the NCS is to provide information that will ultimately lead to
49 improvements in the health, development, and well being of children.

50

51 The specific goals are to address the instructions in the Children's Health Act,
52 namely, to

53

- 54 1. *Incorporate behavioral, emotional, educational, and contextual*
55 *consequences to enable a complete assessment of the physical, chemical,*
56 *biological, and psychosocial environmental influences on children's well-*
57 *being;*
- 58 2. *Gather data on environmental influences including prenatal exposures and*
59 *outcomes on diverse populations of children*
- 60 3. *Gather data on health disparities among children including prenatal*
61 *exposures.*

62

63 The Study subscribes to the principle that both health and susceptibility to
64 disease are determined by dynamic processes that can occur at any time from
65 preconception through adult life. The Study recognizes that vulnerabilities to the
66 effects of environmental exposures vary by developmental stage and age. The
67 schedule and content of study assessments necessarily targets those areas
68 where current knowledge gaps are greatest, with frequent early evaluation to
69 identify factors that may be particularly influential in fetal and early infant
70 development. While many conditions and diseases of childhood have significant
71 effects on individuals and families, some also place a great burden on society as
72 a whole because of their prevalence, severity, or cost. The Study aims to
73 investigate the separate and combined effects of environmental exposures on
74 pregnancy outcomes, child health and development, and origins of adult
75 disease. Environmental exposures are broadly defined to include chemical,
76 biological, physical, psychosocial, and genomic factors. Also important is the
77 examination of predictors of health and well being to define mitigating factors
78 resulting in resilience as well as detrimental factors. Additionally the Study aims to
79 examine determinants of child, maternal and developmental health disparities,
80 such as prenatal exposures, geography, social status, race, ethnicity,
81 neighborhood characteristics, quality of social networks and the impact of
82 various disparities on health outcomes.

83

84 The NCS is to serve as a resource for current and future studies of child health
85 and development. The NCS will collect and archive high quality data,
86 biospecimens and environmental samples that can be used to address current
87 and future questions and hypotheses.

88

89 ***Relationship between the Vanguard Study and the Main Study***

90 The NCS is a system comprised of a Vanguard Study a Main Study
91 methodological substudies and formative research. The Vanguard Study is

DRAFT Concept of National Children's Study Main Study

July 20, 2011

92 designed to inform the Main Study by empirically testing the feasibility (scientific
93 robustness), acceptability (participant and infrastructure burden), and cost of
94 recruitment and retention, study visit measures, and study logistics.

95

96 The Vanguard Study precedes the Main Study, and follows a longitudinal sample
97 of children born to women recruited according to a geographic sampling
98 frame. Before birth and throughout the children's lives, the Vanguard Study tests
99 design, measurement, and logistic study components. Based on these results, the
100 Main Study design, protocol, and procedures will be selected.

101

102 Specifically, the Vanguard Study is testing four recruitment approaches: a
103 household enumeration-based approach: an enhanced household
104 enumeration approach; a provider-based approach; and direct outreach. All
105 four recruitment approaches used a sampling frame based on residence of
106 potential participants; that is, to be eligible, participants had to reside in selected
107 geographic locations, generally corresponding to neighborhoods. Each
108 recruitment approach is being implemented within a separate set of study
109 locations; each set includes urban and rural areas.

110

111 In the household-based approach, designated neighborhoods are canvassed
112 by field workers to identify eligible women and invite them to participate in the
113 Study. In the provider-based approach, potential participants first learn about
114 the Study through a healthcare provider. The providers share Study promotional
115 information and contact numbers or, with permission, provide the potential
116 participant's name and contact information to Study Center staff for follow-up.
117 In the direct outreach approach, direct mailings to geographically eligible
118 households are used to initiate contact. Women then contact the Study Center
119 directly to learn of their eligibility to enroll in the Study.

120

121 In addition to testing the four approaches for recruitment, the Vanguard Study is
122 also testing a provider based sampling approach which uses a sampling frame
123 of providers of prenatal care. In contrast to the provider based recruitment
124 approach, where eligibility is determined by the residence of the potential
125 participant, in provider based sampling, all or a sample of women receiving
126 prenatal care from a selected provider are eligible to participate in the Study.
127 This approach is potentially more efficient for identification and recruitment of
128 pregnant women.

129

130 Analyses of sampling and recruitment approaches used in the Vanguard Study
131 will examine variance in contact, eligibility, consent, retention, and cost by
132 recruitment and sampling approach. Efficiency of approach will be compared
133 according to urbanicity and other factors of interest. Preliminary results indicate
134 that there may be a need to recommend a combination of recruitment
135 strategies joined by a common primary sampling frame to produce national
136 estimates. Extent of coverage and sampling bias will also inform Main Study
137 design.

138

DRAFT Concept of National Children's Study Main Study

July 20, 2011

139 Overall, analyses of recruitment approaches tested in the Vanguard Study
140 indicate that initial estimates of the rate of identification, recruitment and
141 retention of eligible and pregnant women were optimistic. Recruitment
142 approach(es) selected for the NCS will need to target a larger initial population
143 from which to recruit and to be large enough to account for anticipated attrition
144 over the 21 years to achieve a target cohort of 100,000

145

146 After final sampling frame and recruitment approaches have been identified for
147 the Main Study, the Vanguard Study will continue to inform Main Study protocol
148 and procedures as children age. The remainder of this document describes the
149 Main Study.

150

151 *Main Study*

152 **Study Design**

153

154 The NCS is an observational longitudinal birth cohort study that will enroll and
155 follow pregnant women, fathers or partners, and their children. Women will be
156 enrolled prior to delivery (and for a subset, prior to conception) and their children
157 will be followed through 21 years of age. The study employs a national
158 probability sampling approach. In the first stage of sampling, Study Locations
159 are selected as the locations in which to conduct the study. A Study Location
160 generally corresponds to a single U.S. county; however, in counties that are
161 sparsely populated, counties are combined to form a single Study Location.
162 Based on input from survey statisticians and sampling experts, it is estimated that
163 the final study sample will need to include 150-225 Study Locations.

164

165 Two approaches will be implemented in the second stage of sampling,
166 depending on demographic features of the county. The first approach involves
167 dividing the primary sampling unit (the Study Location) into smaller geographic
168 areas, generally conforming to neighborhoods, based on expected birth rates
169 from U.S. Census data. Using a probabilistic approach, a sample of these
170 neighborhoods is to be selected as secondary sampling units. Eligible women
171 must reside within selected secondary sampling units at the time of enrollment. A
172 second approach involves sampling of providers. In this approach a sampling
173 frame of all providers of prenatal care in the Study Location is constructed. A
174 probability sample of providers is selected. Women who have their first prenatal
175 care visit with a selected provider are potentially eligible to participate in the
176 study.

177

178 **Sample Size and Recruitment Period**

179

180 The general recruitment goal of the study is to enroll and retain a sufficient
181 number of women such that there are 100,000 children enrolled in the study after
182 21 years. This target is based on the need to evaluate important, but relatively
183 rare exposures and/or outcomes that have a prevalence of less than 5% of the
184 general population. Assuming an optimistic 2-3% yearly attrition rate, about

DRAFT Concept of National Children's Study Main Study

July 20, 2011

185 150,000-200,000 infants would need to be enrolled initially to have about 100,000
186 participants at the end of 21 years. Additionally it is likely that not all respondents
187 will answer all questions or complete all components of the study at a given visit
188 (item non-response) and that some participants may miss entire visits but later
189 return for subsequent visits (unit non-response). Factoring in unit non response
190 and item non response will also decrease the effective sample size with the
191 magnitude of the effect being dependent on the analytic question being asked.
192 Based on our initial experience in the NCS Vanguard Study, it is expected that, of
193 women enrolled in the study during pregnancy, 80% will remain in the study
194 through the birth of the child and beyond. Thus to enroll 150,000-200,000 infants
195 in the study, we may need to enroll up to 190,000 - 250,000 pregnant women.

196
197 Approximately 1000-2000 infants will be enrolled in each of the Primary Sampling
198 Units over a two year recruitment period. (The exact number of infants per PSU is
199 dependent on the number of primary sampling units that are included in the final
200 sample.) Not all Study Locations will begin data collection simultaneously.
201 Initiation of data collection at the various locations will be rolled out over a two
202 year period for a rate of approximately 2 new Study Locations per week. In
203 combination, from the start of enrollment in the first Study Location to completion
204 of enrollment in the last Study Location, our recruitment period will span four
205 years.

206

Approach

208

209 The Main Study will consist of a series of study visits where assessments will be
210 administered to the mother, father, and child. Study visits will be conducted in
211 the home or clinic or by telephone interview. Collections include physical
212 measures, biospecimens, environmental samples, and information about health
213 status, health care access, occupation, cultural characteristics, lifestyle,
214 psychosocial and neighborhood characteristics. Study visits will be conducted at
215 intervals of child growth and development stages such that visits will be
216 structured prior to pregnancy, during pregnancy, at birth and at periodic
217 intervals thereafter. The NCS Main Study is envisioned to serve as a data platform
218 where rare health outcomes can be studied over time prenatally through
219 adulthood.

220

Eligibility

222

223 The Study will enroll 1) pregnant women (including emancipated minors and
224 minors); 2) and possibly non-pregnant adult women at some probability of
225 becoming pregnant during the two year enrollment timeframe; 3) children born
226 to enrolled women; 4) fathers of enrolled children (including emancipated
227 minors and minors); and 5) new adult caregivers of enrolled children. The
228 eligibility criteria described below assume a geographic sampling approach in
229 both the primary and secondary stages of sampling.

230

231

DRAFT Concept of National Children's Study Main Study

July 20, 2011

232 *Participant Inclusion Criteria*

233 1. Pregnant Women

234 1a. Pregnant Adult Women

- 235 • Pregnant adult^{1*} women residing in a selected NCS geographic segment
- 236 at the time of enrollment.

237

238 1b. Pregnant Emancipated Minors and Minors

- 239 • Pregnant women who are considered to be emancipated minors per the
- 240 laws of their jurisdiction residing in a selected NCS geographic segment at
- 241 the time of enrollment; or
- 242 • Pregnant women age 14 or older who are not considered emancipated
- 243 minors: 1) whose legally authorized representative provides written
- 244 permission for enrollment into the Study and 2) who reside in a selected
- 245 NCS geographic segment at the time of enrollment?

246

247 2. Non-pregnant adult women

- 248 • Adult women 49 years of age or younger at the time of screening
- 249 • Residency in a selected NCS geographic segment at the time of
- 250 enrollment; and
- 251 • Completion of NCS pregnancy screener resulting in determination of
- 252 "high pregnancy probability group."

253

254 3. Children

- 255 • Children born to enrolled women.

256

257 4. Fathers

- 258 • Fathers of enrolled children as identified by enrolled women.

259

260 5. New Adults

- 261 • Primary adult caregivers or adult guardians of enrolled children (in cases
- 262 where a parent may not be able to participate in the Study).

263

264 Participant Exclusion Criteria

- 265 • For women: Surgically or genetically infertile
- 266 • For all participants: Unable to understand NCS participation and grant
- 267 informed consent.

268

269 Surrogate mothers, mothers whose babies are expected to be adopted or
270 assigned as foster children and women who are on active duty in the military will
271 be eligible provided they meet all other eligibility criteria. At the time of
272 enrollment, participants or their legally authorized representatives will be asked
273 to provide written informed consent for participation in the Study.

274

¹ Adult is defined as meeting the local jurisdiction's defined age of majority. This age varies from 16-21 years of age among NCS Study locations.

DRAFT Concept of National Children's Study Main Study

July 20, 2011

275 **Data Collection**

276

277 The Main Study will focus on data collection related to the interaction of
278 genomic factors and environment on the health of children. Data collection will
279 be timed at periods of vulnerability during growth and development in the
280 embryo, fetus, infant, young child and developing adolescent in order to
281 capture exposures during key periods of development.

282

283 Data collection will take place at study visits in the home or the clinic to optimize
284 efficiency and economy and to minimize cost and participant burden. Data
285 collection will utilize diaries, interviews, select medical record abstractions,
286 observations, and self administered questionnaires to capture information about
287 behavior, cultural characteristics and lifestyle as well as data regarding medical
288 events and interactions with the healthcare system. Physical measurements,
289 photographs and videos will also be used to assess development and behavior.
290 Biological specimens including blood, urine, saliva, vaginal swabs, cord blood,
291 umbilical cord samples, placental tissue, and breast milk, will be collected to
292 assess health status and evidence of environmental exposures. Environmental
293 samples including air, dust, soil, water and community environmental data will
294 be collected to characterize the environment. The table below describes the
295 time of collection of data from participants.

296

297 Table1. Data Collection Schedule

298

Age of child	Location of visit
1st trimester	Home
2nd trimester	Clinic or Home
3rd trimester	Clinic or Home
Birth	Place of delivery
2 months	Phone
4 months	Phone
6 months	Home
9 months	Phone
12 months	Clinic or Home
18 months	Phone
24 months	Clinic
30 months	Phone
36 months	Clinic or Home
42 months	Phone
48 months	Clinic
54 months	Phone
60 months	Clinic or Home

299

300

301 Data collection may employ matrix sampling approaches for some measures for
302 efficiency and flexibility. In these instances a small number of participants would
303 receive detailed data collections and a larger number of participants would

DRAFT Concept of National Children’s Study Main Study

July 20, 2011

304 receive less intensive data collections in a manner that can relate results to the
305 entire cohort.

306

307 DATA AND SAFETY MONITORING PLAN

308

309 The NCS Main Study is an observational study with risk level characterized as
310 minimal as defined by 45 CFR § 46.102(h)(i). Specific risks associated with Study
311 procedures are detailed in the Study informed consent materials.

312 *Safety Monitoring Plan*

313 A chartered independent Study Monitoring and Oversight Committee (iSMOC,)
314 that reports to the NICHD Director, will meet regularly over the course of the
315 Study to 1) monitor human subject safety through review and evaluation of
316 accumulated Study data, 2) review Study conduct and progress, and 3) make
317 recommendations concerning continuation or modification of the Study. The
318 iSMOC will review accumulated Study data on unanticipated problems and
319 adverse events to determine whether the research places subjects or others at a
320 greater risk of harm (including physical, psychological, economic, or social harm)
321 than was previously known or recognized. The operations of the iSMOC are
322 detailed in the Official Charter of the Independent Study Monitoring and
323 Oversight Committee (iSMOC) for the National Children’s Study, Version 1.93, 28
324 April 2009.

325

326 The NCS has developed a centralized Incident Response Mechanism, to support
327 the timely reporting, accounting, and self-auditing of incidents, unanticipated
328 problems (including data loss), and adverse events that occur in relation to the
329 NCS in a manner compliant with NIH policy, OHRP guidance, and DHHS
330 regulations for the protection of human research subjects (45 CFR § 46).
331 Additionally, the Study will comply with requirements of the Federal Information
332 Security Management Act of 2002 and DHHS and NIH information security policy
333 with regard to protection of Study information and reporting of suspected or
334 actual breaches of information security.

335 *Site Monitoring Plan*

336 Individual Study sites are responsible for developing a site monitoring plan in
337 compliance with institutional policy, state and federal regulations and DHHS and
338 NIH policy. The site monitoring plan should be submitted to the Institutional
339 Review Board of record. In addition the NCS Program Office will conduct routine
340 audits and site visits to assure data integrity and compliance with all relevant
341 policies and regulations.

342

343 OUTCOMES AND PLANNED ANALYSES

344

345 Priority outcomes in the NCS include pregnancy outcomes such as premature
346 birth, stillbirth and birth defects and assessments of child health and well being.

DRAFT Concept of National Children's Study Main Study

July 20, 2011

347 The NCS Vanguard Study is currently developing a suite of objective assessments
348 using multiple modalities to determine child health at different developmental
349 stages.

350

351 Additional outcomes are descriptions of symptoms and history of conditions that
352 affect children or may be early signs of adult chronic disease such as but not
353 limited to asthma, obesity, neurodevelopmental and behavioral outcomes such
354 as autism and attention deficit disorder, schizophrenia, inflammatory conditions,
355 growth disorders, childhood malignancies and childhood injuries. Further
356 outcomes are descriptions of social networks, access to services and support
357 such as but not limited to educational opportunities, age appropriate and
358 nutritious diet, routine and subspecialty health care, and social and
359 psychological support.

360

361 Initial analyses will focus on the efficiency of recruitment with event driven interim
362 analyses at enrollment numbers such as 5 000, 15 000, 25 000, 50 000 and 100 000
363 participants to make any potential adjustments in the implementation of
364 recruitment strategies.

365

366 All interim analyses will be reviewed by the Independent Study Monitoring and
367 Oversight Committee and the recruitment adjustments will be prospectively
368 identified with specific triggers for implementation.

369

370 While many other analyses will be deferred and conducted as nested case
371 control studies after the outcomes have occurred, some proportion of real time
372 analyses of biological specimens and environmental samples are also being
373 explored to enable early reporting of important findings. Furthermore our data
374 collection efforts are being constructed in a manner that complements and
375 augments other national databases, such that data are maximally compatible.

376

377 The Study's prospective longitudinal design will permit an in-depth examination
378 of both the episodic and cumulative effects of environmental exposures as they
379 unfold over time. This will include an unprecedented, process-oriented
380 opportunity to understand how exposures at particular points in development
381 lead to both short and long-term consequences for children, and what
382 circumstances, characteristics, or genomic predispositions mediate or moderate
383 the relationships between exposure and outcome.

384

385 The size and probabilistic nature of the sample will permit both valid inferences
386 about the U.S. population as a whole and exploration of subgroup-specific
387 patterns of adaptation and maladaptation.

388

389 Public use and restricted use datasets will be established as soon as feasible on
390 an ongoing basis consistent with current NCS Data Access and Confidentiality
391 policies. All potential users will be eligible to apply for access concurrently.

392

393

DRAFT Concept of National Children's Study Main Study

July 20, 2011

394 **REFERENCES**

395

396 1. Bloom B, Cohen RA, Freeman G. Summary health statistics for U.S. children:
397 National Health Interview Survey, 2009. National Center for Health Statistics.
398 *Vital Health Stat* 10(247). 2010

399

400 2. Barker DJ, Winter PD, Osmond C, Margetts B, Simmonds SJ. Weight in infancy
401 and death from ischaemic heart disease. *Lancet*.1989;2:577-580.

402

403 3. Bateson P, Barker DJP, Clutton-Brock T, Deb D, D'Udine B, Foley RA, Gluckman
404 P, Godfrey K, Kirkwood T, Lahr MM, McNamara J, Metcalfe NB, Monaghan P,
405 Spencer HG, Sultan SE. Developmental plasticity and human health. *Nature*.
406 2004;420:410-21.

407

408 4. Gluckman P, Hanson M, Cooper C, Thornburg KL. Effect of in utero and early-
409 life conditions on adult health and disease. *NEJM*. 2008;359:61-73.

410

411 5. Ananth CV, Joseph KS, Oyelese Y, Demissie K, Vintzileos AM. Trends in
412 preterm birth and perinatal mortality among singletons: United States, 1989
413 through 2000. *Obstet Gynecol*. 2005;105 (5 Pt 1):1084-91.

414

415 6. Centers for Disease Control and Prevention. Hospital stays, hospital charges,
416 and in-hospital deaths among infants with selected birth defects—United
417 States, 2003. *Morbidity & Mortality Weekly Report*. 2007;56:25-29.

418

419 7. Wang Y, Hu J, Druschel C. A Retrospective Cohort Study of Mortality Among
420 Children with Birth Defects in New York State, 1983-2006. *Birth Defects Res A*
421 *Clin Mol Teratol*. 2010;88:1023-1031.

422

423 8. Correa A, Cragan JD, Kucik JE, Alverson CJ, Gilboa SM, Balakrishnan R,
424 Strickland MJ, Duke CW, O'Leary LA, Riehle-Colarusso T, Siffel C, Gambrell D,
425 Thompson D, Atkinson M, Chitra J. Reporting birth defects surveillance data
426 1968-2003. *Birth Defects Res A Clin Mol Teratol*. 2007;79,65-186.

427

428 9. Reller MD, Strickland MJ, Riehle-Colarusso T, Mahle WT, Correa A. Prevalence
429 of congenital heart defects in Atlanta, 1998-2005. *J Pediatrics*. 2008;153,807-
430 813.

431

432 10. Van Naarden Braun K, Yeargin-Allsopp M. Epidemiology of intellectual
433 disabilities. In: Levene MI, Chervenak FA, editors. *Fetal and Neonatal*
434 *Neurology and Neurosurgery*. London: Elsevier; 2008. p. 876-897.

435

436 11. Newschaffer CJ, Falb MD, Gurney JG. National autism prevalence trends
437 from United States special education data. *Pediatrics*. 2005;115,277-282.

438

DRAFT Concept of National Children's Study Main Study

July 20, 2011

- 439 12. Centers for Disease Control and Prevention. Increasing Prevalence of Parent-
440 Reported Attention-Deficit/Hyperactivity Disorder Among Children - United
441 States, 2003 and 2007. *Morbidity & Mortality Weekly Report*.2010;59:1439-1443.
442
- 443 13. Handler M, Fierson M. Joint Technical Report—Learning Disabilities, Dyslexia,
444 and Vision. *Pediatrics* 2011;127:e818–e856.
445
- 446 14. Akinbami L, Moorman J, Liu X. Asthma Prevalence, Health Care Use, and
447 Mortality: United States, 2005–2009. *Natl Health Stat Report* 2011;32:1-14.
448
- 449 15. Thornton TN, Craft CA, Dahlberg LL, Lynch B S, Baer K. *Best practices of youth*
450 *violence prevention, A sourcebook for community action (Rev.)*. Atlanta:
451 Centers for Disease Control and Prevention, National Center for Injury
452 Prevention and Control, 2002.
453
- 454 16. Nolan C, Damm P, Prentki M. Type 2 diabetes across generations: from
455 pathophysiology to prevention and management. *Lancet*. 2011;378:169–81.
456
- 457 17. Ross J, Spector L. *Cancer epidemiology and prevention*; 2006 Oxford
458 University Press, Schottenfeld D, Fraumeni J eds. Pg 1251-1268.