



Design and Ethical Considerations in Longitudinal Research Studies

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B · O · S · C HUMAN HEALTH PROGRAM REVIEW

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RESEARCH & DEVELOPMENT

LTG 3 Poster 04

Science Questions

- Which methods and models are appropriate for longitudinal research with children?
 - What design issues and approaches need to be considered in planning longitudinal research studies?
- What are the ethical considerations for longitudinal research studies during the design, implementation, and analysis phases?

Research Goals

- Develop approaches, protocols, methods, models, and other resources that support the design and implementation of longitudinal research studies
 - Identify and evaluate design issues
 - Develop methods, protocols, models, and other tools
 - Provide ORD research and expertise to National Children's Study (NCS), especially for:
 - Recruitment and retention of participants
 - Participant burden
 - Community linkages
 - Sampling design options
 - Exposure assessment and classification
 - Utilize the lessons learned from the research conducted by the EPA/NIEHS Children's Environmental Health Centers
- Identify ethical considerations and develop approaches to address ethical issues in the design and implementation of longitudinal studies
 - Develop the document *Scientific and Ethical Approaches for Observational Exposure Studies (SEAOES)*
 - Explore ethical issues in subject recruitment among children, minority and vulnerable populations
 - Develop education materials for participants as part of the consent process

- The planning of BeFirstNC provided to the NCS study planners valuable tools (e.g., questionnaires), strategies (e.g., sample selection), protocols and procedures
- Many different design issues for the NCS were explored by ORD scientists such as exposure assessment, validation sampling, recruitment and retention of participants, recruiting pre-conception cohort



BeFirstNC Pilot Study

BeFirstNC was a planned pilot study for the National Children's Study (NCS) to test study designs, subject burdens, recruitment and retention, and to follow children from birth to 18 months of age

- Given uncertain future of NCS in 2006, OMB declined approval of BeFirstNC for Paperwork Reduction Act and thus EPA decided to withdraw application
- However all materials (questionnaires, sampling strategy, recruitment retention strategies, biologic and environmental sampling, etc.) have been transferred and utilized by NCS study planners

Sample selection, and community engagement explored

- Census tracts vs. school catchment areas
- Household enumeration
- Commercially available mailing lists vs. counting and listing
- Differing strategies needed for rural areas and urban areas
- Achieving the cooperation of local medical facilities
- Potential reasons for participating or withdrawing from a longitudinal study

Recruitment protocols were set up for the following eligible study participants

- Women likely to become pregnant (high, moderate, low)
- Women who are pregnant
- Women who have recently given birth, and are still at the hospital for the delivery

Developed 30 different data collection instruments

Protocols developed for collection of the following:

Biologic Samples	Environmental Samples
Blood	Surface and floor dust
Breast milk	Soil
Hair and nails	Water
Urine	Physical Exam
Vaginal swab	Anthropometrics
Semen	Blood pressure and pulse
Cord blood and cord sample	Ultrasounds
Placenta and photo	Community Measures
Saliva/buccal cells	Routine monitoring
Meconium	Groceries
	Administrative data

Incorporating a Pre-Conception Cohort

(Selevan et al. 2006 Paediatr Perinat Epidemiol 20: Suppl 1:64)

Workshop conducted to examine the possibility of recruiting a pre-conception cohort as part of the NCS

Four key issues discussed when considering to recruit a pre-conception cohort:

- Differences between pregnancy 'planners' and 'nonplanners'
- A tiered approach to preconception data collection
- Data gaps in preconception studies
- Assessment of early pregnancy in subsequent pregnancies for women/couples with a child already in the study

Findings and Conclusions

As highlighted from the EPA/NIEHS Children's Environmental Health Centers, community advisory boards for environmental health studies take time to establish, but provide a great benefit toward the longitudinal study. The key is to establish this process early in the design and implementation of the study.

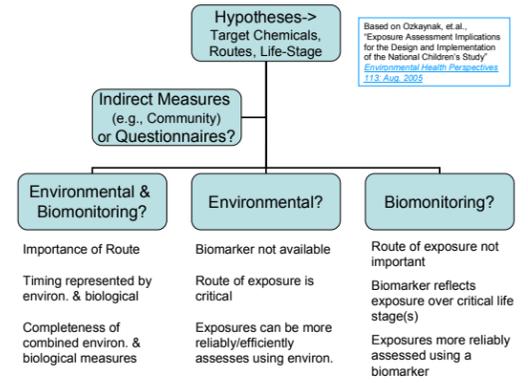
SEAOES is a valuable new resource supported by these peer review comments:

From the HSRB Final Report (Mar. 6, 2008) – "The Board concurred that the document is extremely well-written, presents information accurately and clearly, and will be extremely useful...The document received nearly universal praise from the Board for the clarity of its writing and its thoughtful consideration of the many issues involved in observational studies of toxicant exposure in human subjects."

From the American Academy of Pediatrics (Nov. 14, 2007) – "Protection of and respect for human subjects is paramount in research, and this report will serve as [an] invaluable resource to investigators in designing ethically and scientifically sound observational exposure studies. Again, the AAP applauds you in this effort to ensure research integrity."

Methods/Approach

Exposure Assessment Approaches and Considerations for the NCS



Lessons Learned from EPA/NIEHS Children's Centers for the NCS (Kimmel CA et al., 2005 EHP 113: 1414-1418)

- Important to identify population with a wide range of exposure concentrations
- Establishing study procedures for recruitment and retention - necessary to allow for population differences in literacy, language, and culture
- Assessment tools need to balance measures both broad and narrow in scope
- Questionnaires, neurodevelopmental instruments, and the like should include a core set to evaluate the entire cohort and additional segments for selected populations that may be unique based on their exposure or other attributes
- Exposure assessment should include a combination of environmental and personal measurements as well as data derived from questionnaires and from observational and ecologic data
- Procedures for monitoring the quality and accuracy of data collection must be established and maintained not only for the collection and analysis of biologic or environmental specimens, but also for the assessment of questionnaire, developmental testing, and other health outcome data
- ethical issues in a longitudinal birth cohort study are likely to become increasingly more complex in the changing medical and legal environment and must be carefully considered in designing research protocols and following the cohort.
- Communication of risk to participants and the community and translation of research findings into interventions and policies are of utmost importance and should be part of the research plan and cost consideration.
- Establishing some form of community advisory board advantageous for study - need to have commitment to this process

Design Considerations for Exposure Assessment in the NCS: Validation Sampling

- A validation sample is a small sample that is designed to provide information related to the bias or error introduced by using surrogate (less detailed) measures of exposure.
- The information gathered from the validation sample is designed to allow for appropriate statistical adjustments to the data collected in the larger cohort to address bias and error.

Example Uses of Validation Samples Within the NCS

Larger cohort	Collect exposure information using low-cost, low-burden methods across the cohort	Use questionnaires or community-measures for most respondents
Sub-samples	Conduct detailed exposure assessment	Residential and personal exposure monitoring

- When reasonable lower cost, less detailed surrogate measures of exposure are available, it may not be necessary to collect the "ideal" exposure information for the entire cohort
- This efficiency results in reduced costs and reduced subject burden.

Scientific and Ethical Approaches for Observational Exposure Studies (SEAOES)

- Identifies important scientific and ethical issues for consideration during the design and implementation of observational studies
- Compiles state-of-the-science information on scientific and ethical approaches
- Provides references and information sources on ethical issues
- Serves as a resource of information for researchers designing and performing observational exposure studies
- Ensures that science is of the highest quality and ethical standards are understood and upheld at the highest possible level

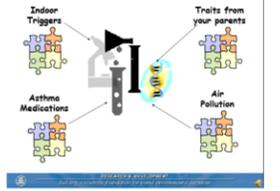
Educational Module Created for Use in the Informed Consent Process - Mechanistic Indicators of Childhood Asthma (MICA)



Thank you for taking the time to participate in this study. This slide show will provide some additional information we would like you to know.



For this study, we have 5 different stations. We are going to ask you to provide different things at each station that will help us learn more about asthma.



We know that many things can play a part in your asthma. Figuring out how all these things fit together is like putting together a puzzle. Some of the puzzle pieces we are looking at are indoor triggers, the train you are born with which we call DNA, the influence of your medications, and air pollution. We hope that this study will help us put more pieces of the "asthma puzzle" together.



We thank you for the chance to look at these many factors. With your help, we are hopeful that we can better understand how all the asthma pieces of the puzzle fit together.

Impact and Outcomes

- Much ORD research supporting the NCS posted at <http://www.nationalchildrensstudy.gov/research/methodspilot/Pages/default.aspx> and <http://www.nationalchildrensstudy.gov/research/reviewsreports/Pages/default.aspx>.
- Extensive use of ORD's research in development of the NCS Research Plan
 - national probability-based household sample
 - pre-pregnancy enrollment
 - exposure assessment designs and methods
- National Academies' review of the NCS Research Plan
 - considered sampling design a major strength of NCS - ORD research
 - recommended use of personal exposure monitoring in subsamples - ORD research provided statistical framework and tools for designing sub-studies
- BeFirstNC materials adapted for NCS Pilot Study protocols (Vanguard Centers); recently approved by OMB and NICHD IRB
- EPA/NIEHS Children's Environmental Health Centers provided valuable "lessons learned" for the NCS
 - approaches for assessing exposures and outcomes over time
 - incorporating community input at all levels of study decision making
- Ensuring highest ethical standards and improving scientific quality - ORD has developed tools, methods, and resources for longitudinal studies conducted by EPA and other organizations. Examples:
 - SEAOES available as a resource for researchers, both within and outside of the Agency
 - educational module created for use in the informed consent process for MICA to improve study comprehension for participants

Future Directions

- ORD will continue to develop protocols, approaches, and methods that will support the design and implementation of longitudinal studies.
- Lessons learned from research conducted at the EPA/NIEHS Children's Environmental Health Centers that are applicable to the NCS and other longitudinal studies will continue to be identified, evaluated, and published.
- EPA researchers will continue to serve as sources of information to the NCS, particularly on design issues as the cohort gets older.

Contributors

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Susceptible Populations

This poster does not necessarily reflect EPA policy. Mention of trade names or commercial products does not constitute endorsement or recommendation for use.