Maternal and Child Health
RESEARCH PROGRAM

Active Projects
FY 2000 AND FY 2001
Maternal and Child Health
RESEARCH PROGRAM

Active Projects FY 2000 and FY 2001

Supported by
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Preface

This publication presents information for each of the 50 research projects active under the support of the Maternal and Child Bureau (MCHB) Research Program in FY 2000 and FY 2001. The variety of research topics and the diversity of research traditions represented by these projects mirror the broad mandate of the MCHB Research Program as well as the multidisciplinary approaches historically used by MCHB to carry out its mission. An underlying characteristic of the projects, as a group, is the applied nature of the research. This is consistent with the mandate authorized in an amendment to Title V of the Social Security Act, which established the MCHB Research Program in the early 1960s.

Projects are arranged alphabetically according to name. The projects are indexed by subject at the back of this publication.

This edition also features a classification system for quick identification of abstracts. Each study is classified according to the Healthy People 2010 objectives addressed, study design, time design, care emphasis, population focus, and racial/ethnic focus. In addition, the MCH Research Program Priority Needs are identified for those projects which address these priorities.

The content of the abstracts is similar. The specific items in the summaries represent requests and suggestions from users of this information, both within and outside the Federal Government. Many of the intended users are concerned with the production of discipline-specific knowledge and with the overall technical aspects of conducting research and interpreting research findings; thus, the publication presents detailed descriptions of the research plan, particularly as it refers to the research study design, measurement approaches, sample size, and data analysis plan.

The information in the pre-award evaluation contains the written comments of the assigned reviewers as well as notes taken during the discussion that precedes the collective recommendation of the MCHB Research Grants Review Committee. This information is made available for several reasons. First, it attests to the significance of the research questions and the technical quality of the research plan, as judged by a panel of peers who are guided by a set of procedures designed to minimize bias and promote fairness and objectivity during the review process. Second, the pre-award evaluation indicates the strengths as well as the weaknesses of the proposal. This approach gives a more balanced view of the nature of funded research and emphasizes that, for the most part, it is less than perfect. Third, the pre-award information also attests to the contribution of the peer review process in improving the research that is ultimately funded. While the reviewers’ recommendations for improvement are not binding on the investigators (unless issued as conditions of the awards), the recommendations are usually adopted before the research is begun. Fourth, the pre-award evaluation is instructive for those who practice or plan to practice the research crafts, particularly for graduate students and new doctoral-level professionals seeking to establish themselves in an extremely competitive field.

Kishena Wadhwani, Ph.D.
Acting Branch Chief, Maternal and Child Health Bureau Research Program
April 2002
Maternal and Child Health Bureau
Research Grants Review Committee

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Each project in this book is classified according to the Healthy People 2010 objectives addressed, study design, time design, care emphasis, racial/ethnic focus (if applicable), and population focus. In addition, the MCH Research Program Priority Needs are identified for those projects which address these priorities. These categories are described below.

**Healthy People 2010 Objectives**

This category lists the Healthy People 2000 objective(s) addressed by the project. The number of the objective(s) is listed for each abstract and a complete listing of the objectives corresponding to these numbers is provided in the appendices of this book.

**Study Design**

The study designs are divided into three subcategories: (1) Experimental, which includes randomized clinical control trials; (2) quasi-experimental, which includes case/matched control, case/unmatched control, case/historical control, and interrupted time-series studies; and (3) observational, which includes studies that are purely descriptive or seek to elucidate cause and effect associations without the investigator actually seeking to control the situations under which these associations unfold or take place.

**Time Design**

This category includes three components: (1) Cross-sectional, (2) longitudinal, and (3) mixed. Cross-sectional studies describe or examine cause and effect relationships through measurements taken at one point in time. Longitudinal studies, however, seek to ascertain through serial measurements how cause and effect associations change or do not change over time. Mixed studies are those that include both longitudinal and cross-sectional components.

**Care Emphasis**

This category distinguishes between interventional and noninterventional studies. In interventional studies, the investigator, through a particular effort, treatment, or program, seeks to purposively influence the outcome(s) in an individual or a group. In noninterventional studies, the investigator merely observes, measures, and describes a situation without purposively manipulating or seeking to alter in any way the ensuing outcomes.

**Population Focus**

This category describes the investigation’s primary population, including age, gender, family role, and pregnancy status dimensions or characteristics. The particular dimensions and subdivisions within these stated dimensions or characteristics (i.e., neonates, preschool children, pregnant women, etc.) are specific to maternal and child health program issues and concerns.

**Race/Ethnic Focus**

This classification sorts projects according to whether they are able to describe or elucidate issues related to race and/or ethnicity status, using either a within-group or a between-group study format. Studies that do not fall under this definition are classified as having no racial/ethnic focus.
MCH Research Program Priority Needs

This category lists the MCH Research Program Priority Need(s) addressed by the project. The number of the priority is listed for each project which addresses these priorities. A complete listing of the priorities corresponding to these numbers is provided in the appendices of this book.
Adolescent Attitudes About Pregnancy

Grantee
University of Colorado Health Sciences Center

Investigator
Catherine Stevens-Simon, M.D.
4200 East Ninth Avenue
Denver, CO 80262
(303) 861-6133

Project Number R40MC00112

Project Period 10/1/1998-9/30/2001

Costs

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Summary

Statement of the Problem

Primary health care providers are inadequately equipped to identify the factors that put their adolescent patients at risk for pregnancy. Efforts to predict which young women will conceive during adolescence have been largely unsuccessful because the similarities between socioeconomically disadvantaged adolescents who become parents and their peers who do not typically outweigh the differences. Thus, despite repeated attempts at intervention, the adolescent pregnancy rate in the United States remains one of the highest in the western world. Although the consensus is that a major reshaping of our approach to this problem is needed, empirical data provide little guidance about what additional programs and services might be required to prevent adolescent pregnancy. The goal of this research is to develop a screening tool that will enable clinicians with variable levels of training in adolescent medicine to formulate a differential diagnosis when they are confronted by the perplexing diagnostic dilemma posed by the nonconceiving, sexually active adolescent. Scientific knowledge about the consequences of adolescent pregnancy greatly exceeds knowledge of its antecedents. Indeed, the antecedents of adolescent childbearing attitudes have not been studied directly. We hypothesize that they arise from the simultaneous consideration of the effect that a baby would have on the various aspects or domains of life. This research tests this hypothesis by examining various sources of strongly positive, ambivalent, and strongly negative feelings about childbearing; the ways in which these feelings about the probable effect of childbearing on the various life domains influence intended pregnancy status and the capacity to use contraceptives; and the ways in which these intentions and capacities...
influence the actual use of contraceptives and risk of conception among adolescents during the 4 months following a negative pregnancy test. The inclusion of ambivalence in the model is novel and, theoretically, extremely important because it implies that both the direction and the strength of the anticipated effects of childbearing on the various life domains contribute to the formation of attitudes and intentions about pregnancy and contraception.

We will use this information to accomplish the following: (1) Profile the characteristics, attitudes, and behaviors that antedate conception in a racially and ethnically diverse group of low-income, inner-city adolescents whose history of having just had a negative pregnancy test puts them at particularly high risk for conception; and (2) develop a preconception risk assessment questionnaire, "The Preconceptional Risk Assessment Battery," that will be appropriate for screening adolescent patients in primary health care settings. (In subsequent studies, we plan to use this questionnaire prospectively to guide the selection of interventions that are apt to be most helpful to individual adolescents in primary health care settings.)

**Research Questions or Hypotheses**

Pursuant to developing a brief screening questionnaire that will enable clinicians to determine which of their adolescent patients are at risk for pregnancy, we have formulated the following five research questions and a prediction or hypothesis about the probable answer to each:

**Question 1.** What is the relative prevalence of strongly positive, ambivalent, and strongly negative feelings about the probable effect of having a baby on the various life domains among adolescents following a negative pregnancy test?

**Hypothesis 1.** Following a negative pregnancy test, the majority of adolescents will express ambivalent feelings about the effect of having a baby soon; that is, most will not be certain that a baby will have a clearly positive (or negative) effect on their relations with parents, peers, and partners; feelings of self-worth; and future goals.

**Question 2.** How do the anticipated effects of having a baby on the various life domains shape intended pregnancy status among adolescents following a negative pregnancy test?

**Hypothesis 2.** Following a negative pregnancy test, the intent of adolescents to become pregnant is directly related to the number of aspects of their lives in which they anticipate a baby will be a positive influence. Adolescents who have positive feelings about babies, anticipate that a baby will improve their relationships with their family members, and anticipate that a baby will make it easier for them to socialize in their peer group will express a stronger desire to be pregnant than adolescents who anticipate that a baby will strain their relationships with their family members and/or make it difficult for them to socialize with their peers.

**Question 3.** How do the anticipated effects of having a baby on the various life domains affect the capacity of adolescents to use contraceptives following a negative pregnancy test?

**Hypothesis 3.** Following a negative pregnancy test, the capacity of adolescents to use contraceptives is inversely related to the number of aspects of their lives in which they anticipate a baby will be a positive influence. Adolescents who have positive feelings about babies, anticipate that a baby will improve their relationships with their family members, and anticipate that a baby will make it easier for them to socialize in their peer group will express more attitudes that make them incapable of using contraceptives than adolescents who anticipate that a baby will strain their relationships with their family members and/or make it difficult for them to socialize with their peers.

**Question 4.** How does intended pregnancy status affect the capacity of adolescents to use contraceptives following a negative pregnancy test?

**Hypothesis 4.** Following a negative pregnancy test, the capacity of adolescents to use contraceptives is directly related to the strength of their intention to remain nonpregnant; that is, adolescents who express a strong desire to remain nonpregnant will identify and encounter fewer obstacles to contraceptive use than adolescents who do not mind or who want to be pregnant.

**Question 5.** How do intended pregnancy status and the capacity to use contraceptives affect the consistency of adolescent contraceptive use and their exposure to the risk of conception following a negative pregnancy test?

**Hypothesis 5a.** Following a negative pregnancy test, the consistency with which adolescents use contraceptives is inversely related to their intended pregnancy status and directly related to their capacity to use contraceptives. Adolescents who desire pregnancy and have attitudes that make them incapable of using contraceptives will be less likely to use contraceptives consistently than adolescents who do not want to be pregnant and have attitudes that make them capable of using contraceptives.

**Hypothesis 5b.** Following a negative pregnancy test, exposure to the risk of conception is inversely related to the intended pregnancy status and directly related to the capacity to use contraceptives. Adolescents who desire pregnancy and have attitudes that make them incapable of using contraceptives will be more likely to expose themselves to the risk of conception.
than adolescents who do not want to be pregnant and have attitudes that make them capable of using contraceptives when they are sexually active.

**Study Design and Methods**

This study uses a prospective, repeat-measures design to assess the relationship between the ways in which nulliparous adolescent girls anticipate that childbearing will affect the various domains of their lives at the time of a negative pregnancy test and the consistency with which they use contraceptives during the subsequent 4 months. Specifically, we plan to establish the validity of "The Preconceptional Risk Assessment Battery" as a predictor of both the adolescents' initial choice of contraceptives (e.g., at the close of the negative pregnancy test clinic visit) and the consistency with which they use the contraceptive methods they have chosen during the subsequent 4 months. We have chosen to study adolescents who have had negative pregnancy tests because they are easy to identify and are at extremely high risk for conception; we have chosen a 4-month observation period because studies of oral contraceptive users indicate that the discontinuation rate is maximal during the first 3–4 months of use, and because it will give those who choose to use oral contraceptives or DepoProvera time to demonstrate their willingness to obtain a second prescription or injection.

**Population and Sampling Plan**

This research is being conducted at three adolescent clinics in the Denver metropolitan area. All nulliparous females under 19 years of age who reside in the Denver metropolitan area and are not using a reliable form of contraception consistently are asked to participate in the study when they obtain a negative pregnancy test. Eligible, consenting adolescents are enrolled consecutively. The majority of adolescents who patronize these three adolescent clinics come from low-income families. Race and ethnicity varies among the clinics, but we anticipate that the study population will ultimately be composed of approximately 130 non-Hispanic, white adolescents; 130 Hispanic adolescents; 120 African American adolescents; and 20 adolescents of other races. We are targeting this racially and ethnically diverse population of low-income adolescents because the results of our preliminary studies indicate that 68 percent of the adolescents who have negative pregnancy tests at these clinics become pregnant within 18 months.

**Analysis Plan**

To obtain a basic understanding of the data, frequencies and correlations among key variables will be examined. Analysis of variance will be used to measure differences in the consistency of contraceptive use related to each of the intervening variables. Those variables that are statistically significant predictors of contraceptive use will be included in the multivariate analyses used to test the study hypotheses.

Next, the psychometric properties (e.g., the internal consistency and reliability) of "The Preconception Risk Assessment Battery" will be evaluated. To that end, exploratory and confirmatory factor analyses will be used to determine precisely which combination of the life domains will be included in the model.

The five study hypotheses will be tested individually, at first, and then the overarching model will be tested in its entirety by employing Bentler's EQS structural equation program. This is a mediational model in that both the direction and the strength of the anticipated effect of childbearing on the various life domains are hypothesized to affect the following: (1) Intended pregnancy status (Hypothesis 2), (2) the capacity to use contraceptives (Hypothesis 3), and (3) the correlation between these two mediators (Hypothesis 4). Ultimately, we anticipate that the interaction between these two mediators will predict the consistency of contraceptive use (Hypothesis 5a) and the risk of pregnancy (Hypothesis 5b). Initially, for each of the study hypotheses, the direct association between the independent variable and the outcome of interest will be determined with Spearman rank correlations (when the dependent variable is treated as a continuous variable) and Wilcoxon rank tests (when the dependent variable is treated as a categorical variable). The results of these initial correlational analyses will also be used to inform the path analysis models to be examined.

After establishing the predictive validity of "The Preconceptional Risk Assessment Battery" for the consistency of contraceptive use by adolescents following a negative pregnancy test, we will modify this lengthy battery of questionnaires into a briefer, less cumbersome, and easier-to-use screening questionnaire; this briefer questionnaire will enable primary health care providers with variable levels of training in adolescent medicine to not only systematically identify their adolescent patients who are at highest risk for conception following a negative pregnancy test, but also determine why each of them is at such high risk. To this end, factor analyses will be performed to determine if the number of variables can be
reduced to a smaller number of psychometrically sound predictors.

**Pre-Award Evaluation**

**Evaluator 1**

**Originality and Importance**
This study is based upon a conceptual model that extends our understanding of the possible groups of teens that do and do not become pregnant. This is a major strength in that the simple pregnant/not pregnant dichotomy usually used to study this problem has always seemed insufficient. The range of reasons underlying why a particular teen falls into one or the other group tends to get lumped into two big piles by the fact that they are either pregnant or not. Anticipating more variation in the phenomena of teen pregnancy and sexual behavior will allow for a more complex, yet clear look at the possible pathways towards a positive or negative pregnancy status.

**Regional and National Significance**
As stated in the introduction of the proposal, current policies have reduced the number of teens who have access to contraceptive information and methods, yet the teen pregnancy rate remains at an unacceptably high level. A better understanding of the factors related to avoidance of contraceptive behavior is greatly needed if we are to reduce the number of children born to young women who have not completed the requisite life preparation to insure a life beyond poverty.

**Scientific and Technical Merit**
The research questions and hypotheses stated are clearly linked to the literature and model presented. Moreover, the progression of preliminary studies conducted by the principle investigator seems to lead logically to the proposed project. The variables chosen for study are clearly delineated and span a range of issues which may converge to predict those most at risk for teen pregnancy. The scoring of the independent variable is a bit confusing. The effects of pregnancy on different life domains are measured by the individual's positive, ambivalent or negative endorsement of statements within each domain. The author states that a strongly positive attitude is the result of positive endorsement of all the statements, while a less strongly positive attitude is indicated by positive endorsement of statements about family, partner and peer relations but negative endorsement of future plans and sense of self. Aren't there some other possible combinations? A more elaborate explanation of how the scale is scored does not appear anywhere else in the proposal. The scale is described and the internal reliability is reported, but the scoring is not detailed. The description says that each sub-scale consists of four items. What if half are endorsed positively and the other two receive a negative and ambivalent response. How is this pattern scored? Percentage of a particular type of score is discussed, but the relationship between percentage and overall scores is unclear. The scoring of the remaining scales is clear.

While it seems reasonable that contraceptive use is the best dependent variable for the study, the possible effects of social desirability responses within a study such as this seems high. Asking such questions in a clinic setting where these young women have just received a second pregnancy test seems to be asking for socially desirable, or maybe more appropriately, denial responses. An alternative may be to complete the scale first and then have the pregnancy test, or to complete the questionnaire and the interview in a non-clinic setting and have the teen go from the interview to the clinic in order to take the test and receive the $15 compensation. It seems that the pressure of the test results and the environment of the clinic may influence how the young women respond to the self-report measure.

The study has good ethnic representation but the socioeconomic status is biased towards working class. It seems that economic status variation would add greatly to the type of information yielded from such a study.

There are no human subjects concerns and the personnel appear well suited to conduct the proposed project.

**Evaluator 2**
Originality and Importance
The proposed research seeks to develop a brief screening questionnaire, which will profile characteristics, attitudes, and behaviors that antedate conception in a racially and ethnically diverse group of poor, inner city teenagers who are at particularly high risk of pregnancy. A clear theoretical framework is given linking domains childbearing could affect with intended pregnancy status, capacity to use contraceptives, consistency of contraceptive use/pregnancy risk and traditional risk factors for teen pregnancy.

The investigators make an excellent argument for not categorizing adolescents based on their pregnancy status, i.e. those who become pregnant and those who do not. Some pregnancies may have been contraceptive failures while some non-pregnant individuals may have just lucky. They give good evidence for questioning the assumptions that a) women can control their fertility, b) all teenagers who become pregnant fail to use contraceptives consistently, and c) all teenagers who do not become pregnant either use contraception consistently or abstain. Much previous work has failed to acknowledge that pregnancy may have significant benefit to the adolescent and many do not actually wish to avoid pregnancy. They argue convincingly for the need for a more appropriate screening tool as the ones now available do not specify etiologic relationships between risk factors and outcomes.

Regional and National Significance
This is an extremely well written, well-justified application which proposes to investigate reasons for adolescent pregnancy. Problems resulting from adolescent pregnancy and the long-term implications for mother and child are well known. Most research on adolescent pregnancy has focused on the individual and societal costs to the mother and child. The proposed research approaches the reasons for pregnancy in this population from a less commonly studied angle and questions some of the widely held assumptions.

Scientific and Technical Merit
A detailed, clear review of the literature is provided briefly reviewing societal costs of teen pregnancy, but focusing on how previous research has blurred the reasons for the failure to impact the teen pregnancy rate and the benefits of pregnancy for an adolescent.

Four prior studies by the principle investigator are reviewed which directly relate to the research. She has found that in the population to be studied, 68% of adolescents conceived within 2 years after a negative pregnancy test, despite contraceptive counseling and prescription. Many were concerned about their fertility (22%) and half either wanted to be or wouldn't mind being pregnant. Teens who were concerned about their fertility were less likely to use contraceptives, as were those who were ambivalent about becoming pregnant. Finally, adolescent's concerns about contraceptive side effects increased as their ambivalence towards pregnancy increased. In other words, many teens look for reasons to stop contraceptives and allow pregnancy to occur. The principle investigator's previous work in this field is clearly a strength of the application.

Concepts of domains childbearing could affect intendedness of pregnancy status, capacity to use contraception, motivation to use contraception, consistency of contraceptive use and risk of conception are clearly defined.

Five research questions are posed and stated in 6 hypotheses. In addition, a brief screening questionnaire will be developed for clinical use. The independent variable is the anticipated effect of childbearing on domains of life. Intervening, mediating and dependent variable are given along with how they will be measured and the units of measurement for each. A few need specification, such as "older boyfriend" and "involvement in socially deviant behaviors". No information is collected from the questionnaires included with the proposal that might give information on socially deviant behaviors. What qualifies and how will the information be obtained?

The measurements to be used have been piloted on 22 adolescents drawn randomly from the target population. There are several strengths to the questionnaires: the pilot information showing their validity in this population, original development based on established instruments, the proven ability to detect ambivalence in this population and the close attention the investigators have paid to reliability of the information obtained. The investigators acknowledge the problem of relying on self-report in collecting this information, particularly information of contraceptive use, which may be thought of by the
adolescent to be socially desirable. They justify this by stating, "Although actual pregnancy status would be easier to document objectively, it is not an appropriate outcome measure for this study because during adolescence many conceptions are determined by chance variations in fecundity and contraceptive efficacy."

The study design is detailed in the text and summarized in a figure. A strength of the study is that background sociodemographic information and type of contraceptive chosen will be obtained on all eligible individuals seen in clinic, allowing the investigators to establish if the study population is representative of the clinic population as a whole. All subjects enrolled will be followed for 4 months, a time frame chosen because discontinuance of contraceptives is highest in the first 4 months after initiation. Many will not have returned for a second Depo-Provera injection, or to obtain a refill for oral contraceptives. Subjects not returning for their follow up research appointment will be contacted by phone. From previous experience, 75% of the enrolled individuals are expected to return to complete the second interview.

Good descriptive information is available for the three clinics that will enroll subjects. Adequate sample size is calculated to be 280, so the expected enrollment of 300 should be fine, even if attrition is somewhat higher than anticipated. Data will be analyzed by correlation between the key variables and analysis of variance in consistency of contraceptive use for each of the intervening variables. Variables significant at the .10 level will be included in the Bentler's structural equation model. Each hypothesis will be tested individually before testing the model.

Time line is given and seems appropriate. No other source of funding is sought. IRB approval has been obtained. A history of sexual abuse or symptoms of depression may be identified through the questionnaires. Will the nurse administering the questionnaires address these issues?

The budget is appropriate, requesting 30% time for the principle investigator, 100% time for a research assistant, 50 hours of consultation per year with a psychology consultant and a statistical consultant. Patient incentives (maximum of $25) are budgeted at $8500. The only unnecessary expenses are $900 for condoms and $400 for educational materials, which should be available already in the clinics. Medical directors of the three adolescent clinics have committed to the project with no request for funds.

The principle investigator is extremely well qualified to carry out this work having published extensively on the topic of adolescent health. She has 15% current support and 65% pending.
Alternatives for Developmental Screening in Primary Care

**Grantee**  
Medical and Health Research Association of New York City, Inc.

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**Project Number**  
R40MC00096

**Project Period**  
9/1/1997-12/31/2000

**Year 2010 Objectives**  
16.23

**Study Design**  
Experimental

**Time Design**  
Longitudinal

**Care Emphasis**  
Interventional

**Population Focus**  
Infants, Toddlers, Preschool-age children

**Race/Ethnic Focus**  
African Americans, Hispanics-Overall

**Priority Research Issues**

**Summary**

*Statement of the Problem*

Regular developmental screening of the 5 to 15 percent of the population of infants ages newborn to 3 years who are at risk for delay is widely promulgated but rarely achieved. This is increasingly true as primary care providers face cost-containment measures, including staffing reductions and higher patient volumes. Screening approaches that use parent-completed developmental questionnaires such as the Ages and Stages Questionnaire (ASQ) offer valid and reliable screening and opportunities for parent involvement, in addition to freeing staff to meet other professional duties. However, the use of these tools as reliable screening instruments needs to be assessed in low-income urban settings with high-risk families in unstable housing situations.

*Research Questions or Hypotheses*

The goal of this randomized, clinical controlled trial is to examine the feasibility of three different approaches to the periodic screening of at-risk children within the context of a public health agency/primary care clinic. Three approaches are to be compared: (1) The Denver Developmental Screening Test (Denver II), to be administered by a provider, plus an initial ASQ, which will be mailed to parents one time only; (2) the ASQ alone, which will be mailed to parents at certain stages of their...
Six hypotheses are proposed:

1. The percentage of initial screening by ASQ will be equal to or better than the rate of initial assessment by providers;
2. Patient retention will be equal or higher in groups 2 and 3 than in group 1.
3. The percentage of ongoing screening in group 3 will be greater than in group 2;
4. In a child who has been screened with both the Denver II and a one-time ASQ, there will be concordance on suspected delay.
5. With ongoing screening, cross-group comparisons will show that the rate of "suspected delay" screening in the ASQ groups (groups 2 and 3) will be equal to or greater than in group 1.
6. Certain subgroups (defined by demographic and/or risk factors) may respond better than others to an ASQ approach.

Study Design and Methods

This randomized clinical controlled trial seeks to compare three approaches to developmental screening within the context of a public health agency/primary care clinic. Study subjects are referred to the Infant-Child Health Assessment Program (ICHAP), which randomizes the subjects to one of three group formats for screening.

For subjects enrolled in group 1, the Denver II screening will be administered by the primary care provider when the child is 6, 12, 20–24, and 30 months of age. In addition, the ASQ will be mailed one time to the parents. Parents of children in group 2 will receive only the ASQ when their child is 4, 6, 8, 12, 16, 18, 20, 24, 30, and 36 months of age. The parents of children in group 3 will receive the ASQ with the same frequency as those in group 2, but will also receive a monthly newsletter plus a toy. For the latter two groups, ICHAP handles all subsequent outreach to the family, conducts the mailing and scoring of ASQs, and submits feedback to the pediatrician. For those in group 1, the pediatrician periodically administers the Denver II.

Population and Sampling Plan

The project will be implemented at two sites selected because of their large at-risk populations: One site has a predominantly black population, the other a predominantly Hispanic population.

Families with at-risk children ages 3–18 months who attend a pediatric primary care center and are eligible for ICHAP (New York’s P.L. 99–457, Part C, Child Find program) are offered enrollment by their pediatrician. Approximately 400 children will be enrolled, with an estimated 30 percent loss to followup.

Eligibility for the study is based on the following criteria: (1) The child has one or more risk factors, based on a list by ICHAP of New York; (2) the child has no known developmental delay; (3) the child is between 3 and 18 months of age; (4) the caregiver speaks English or Spanish; and (5) the caregiver can be contacted by telephone (either a personal phone or a friend's phone).

Analysis Plan

For each of the three groups, the project will examine the rates of initial and followup screenings obtained, the rate of positive screenings, and the percentage of at-risk children who remain engaged in care. Additionally, the degree to which income, maternal education, risk status, and other factors predict outcomes within the three groups will be analyzed. This project will also explore the feasibility of a public health/primary care/parent partnership that could lead to a cost-efficient model adaptable for wider use in Part C at-risk programs.

Preliminary data analysis will start 3 months after the beginning of enrollment and will continue through the followup period to monitor progress.
An Intervention for the Transition to Fatherhood

Grantee
University of Minnesota

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Project Number R40MC00141

Project Period 8/1/1999-7/31/2002

Costs

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Summary

Statement of the Problem

The issue of father involvement with children is receiving increasing attention in academic, applied, and policy settings. A clear consensus has emerged at many levels of society that children's well-being is enhanced by high levels of nurturing involvement by fathers combined with cooperative father-mother coparenting. Unfortunately, millions of children in single-mother families are being raised without meaningful involvement with their fathers, and even in two-parent families the degree of paternal involvement is less than optimal for today's two-earner families and the needs of children. This study addresses the transition to fatherhood, the time when father identity is formed and co-parenting practices are established. There appears to be no better time to forge strong father involvement with children, and mutually satisfactory co-parental relations, than at the birth of a first child. Although a number of studies have described the process of becoming a father, little research has been done on how to intervene in this process in order to promote active, responsible fathering and good mother-father cooperation.

Research Questions or Hypotheses

Year 2010 Objectives
7.7, 7.9

Study Design
Experimental

Time Design
Longitudinal

Care Emphasis
Interventional

Population Focus
Pregnant women (not otherwise identified as adolescents), Parents/Families/Mothers/Fathers

Race/Ethnic Focus
No Stated Race, Ethnic Focus

Priority Research Issues
The main research question is whether an educational intervention during the transition to parenthood can increase father involvement with children, enhance the quality of father-child relationships, promote co-parenting partnerships, and decrease parenting stress.

The second research question inquires about which factors are associated with successful outcomes of the intervention. Factors investigated here are prenatal attitudes towards fathering, prenatal relationship satisfaction, attitudes towards the pregnancy, family of origin experiences with fathering and co-parenting, and social support during pregnancy and after the birth.

Study Design and Methods

First time fathers and mothers in the second trimester of pregnancy are being recruited into the study. They must be married or cohabiting, and the child they are expecting must be the first one for both parents. Half of the couples are randomly assigned to an intervention group and half to a control group. The intervention group receives an eight-session educational intervention designed to promote father involvement, father skills, and co-parental cooperation, and to reduce parental stress. The first session is in home and the last seven are in group classes in an HMO clinic. A standard curriculum is being implemented by experienced parent educators, and sessions are being observed by graduate students who take detailed notes about the process for ethnographic analysis. Control group couples are followed without intervention. All couples in the study are assessed at the second trimester of pregnancy and again at six months and 12 months after the birth. A variety of father, mother, child, and parent-child assessment tools are used to determine which fathers will become more involved, the fathers’ level of skill with the baby, the quality of the mother-father relationship, the couples’ level of stress, and other factors.

Population and Sampling Plan

One-hundred seventy couples in the second trimester of their first pregnancy are being recruited from an HMO and through public media. They must be married or cohabiting, age 18 or over, and speak and read English. Couples are being recruited to reflect the demographic characteristics of the Minneapolis-St. Paul region. There are no primary plans to test specifically for racial or ethnic health issues, but these will be explored in secondary analyses of the data if feasible.

Analysis Plan

After preliminary analyses to establish the success of the randomization procedure to yield demographically equivalent groups, the primary test of the efficacy of the intervention will be conducted with 6 month and 12 month outcome data, using analysis of variance with repeated measures, with two factors: Group (experimental versus control) and Time (6 months and 12 months). Separate ANOVAs will be conducted for coparenting outcome scores, quality of father-child interaction outcome scores, and parenting stress outcome scores. For the three father involvement variables, a MANOVA will be conducted on father engagement scores, father accessibility scores, and father responsibility scores. Ethnographic field notes will be subjected to qualitative content analysis for emergent themes that characterize interactions in the classes.

Pre-Award Evaluation

Evaluator 1

Originality and Importance
This proposal addresses a number of issues that are central to MCHB priorities, primarily the focus on fathering and enhancing processes that might predict more positive parenting by fathers.

Regional and National Significance
No statement of regional and national significance.

Scientific and Technical Merit
This proposal is well written, and is impressive in many respects. The strengths include the conceptual model that drives the intervention plan and the proposed measurement scheme, the attention to the role of the mother and the nature of the co-parenting relationship, the study design that attends well to various important threats to validity, and the investigator’s care in noting that intervention implementation will be carefully monitored and assessed to assure comparability. Randomization plans are appropriate, sample size and power issues are addressed, and the assessment plans are comprehensive. The design also mixes basic quantitative approaches with qualitative approaches to data collection and analysis, a combination of methodologies that may prove intriguing in the findings it generates and the explanatory power offered. Finally, the investigative team is excellent.

Concerns about the lack of child measurement, particularly the lack of expected effect of the intervention on the child remain. The principle investigator has included a Bayley Scale measurement, as well as a number of behavioral indices coded from the father-child interactions. The principle investigator is to be commended for selecting the observed child behaviors during interaction. These should provide excellent indices with which to understand the impact of the quality of fathers’ involvement. The Bayley is a rather weak choice, in contrast. Such global cognitive measures are not very likely to be very sensitive to the interventions being planned; a fact that has been repeatedly documented in previous early intervention studies with like methodologies. Despite the inclusion of the measures, it is surprising to see that the investigator expects "no effects" of the intervention on children's behavior. Such expectations seem contrary to a vast parent-child interaction literature, as well as the rationale for this study overall. If one purports that early fathering interventions are needed to increase the quality and involvement of fathers in their children's lives, but then suggests that no differences between children in the intervention and control groups would be expected, then it raises the question of whether the interventions are really meaningful. The principle investigator makes the case that the effects are more likely long term than short term; yet most studies suggest that the most proximal relations are usually the strongest. Likewise, there is a huge literature on the nature of "reciprocal" effects in parent-child interactions; and the historical parent-effect model has proved to be not very useful in describing the actual nature of parent-child relationships. The likelihood of significant differences between groups of children on the behaviors of interest are great IF the intervention accomplishes what the principle investigator suggests it will.

One area in which the principle investigator has provided a strong rationale is that of whether there is sufficient descriptive data available to guide an intervention in the first place. The principle investigator notes that "the literature focusing on the transition to fatherhood is primarily small-scale, with non-representative samples, and is seldom guided by theory." Also, the principle investigator notes that "there is relatively little empirical research specifically dealing with the transition to fatherhood," and that "most studies of fathering deal with ongoing father-child relations with young children, not on the transition to fatherhood." Relatively little attention has been paid to how these bonds are forged during the transition to parenthood. The principle investigator attempts to make the case for the intervention focus in the introduction, noting that there have been three major longitudinal studies of the transition. Given the explicit conceptual model they present, they believe that more can be learned by trying to prevent and modify than by taking a descriptive approach "one more time." Yet, the "one more time" notion seems clearly at odds with the idea that there has been "little" work done in the area. There is some conceptual inconsistency here. The basic issue is whether there is sufficient data available to suggest that the specific transitional processes and parenting behaviors to be taught the fathers and mothers are the ones that are indeed (1) lacking, and (2) most related to child and family outcome. This is an issue open to interpretation within the literature.

One area in which the principle investigator has clearly given substantial attention is in the development and presentation of the intervention protocol. The principle investigator has gone to great lengths to include descriptive information about the intervention protocol and the underlying mechanisms of change involved with each aspect of the intervention.

The principle investigator wants to explore the combinatorial function of father and mother data after first testing the effects separately. Although there are those who suggest that two measurement sources for one construct will increase reliability and validity of measurements, this may not be the case when the data are basically subjective and the measurement sources may or may not share appropriate frames of reference. Is there any reason to assume that mothers and fathers reports of fathering behavior or attitudes are or should be correlated? Combining measurements that are unrelated may not offer more explanatory power; in fact, it may offer more confusion than enlightenment. This is, of course, an empirical question. Data analyses otherwise continue to appropriately address the questions raised.
This investigative team remains strong. The principle investigator has an excellent record of scholarly productivity. An expert on fathers of color will serve as a consultant. This team is very well qualified to conduct this research.

No concerns on human subjects are apparent.

Sub contracts are proposed with Georgia State University and with Health Partners, Inc. These seem appropriate to the scope of the work proposed.

The budget was judged to be rather high. Specifically, the consultant time is higher than the justification makes a case for. In addition, clarification of the subcontract would be appropriate.

**Evaluator 2**

*Originality and Importance*

The proposal requests four years of funding to implement and assess a randomized clinical trial of an intervention designed to increase fathers’ involvement and improve fathers’ relationships with their infants across the transition to fatherhood. The proposal is exceptional, building upon the extensive work of the principle investigator and his collaborators both within the State of Minnesota and at the University of Georgia. Moreover, the proposed project focuses on the MCHB priority of fathering, which as is noted in the literature review, is an area that has received far too little attention.

*Regional and National Significance*

There are a number of strengths to the proposed research. Conceptually, the principle investigator has presented a very strong conceptual rationale for conducting a clinical intervention as opposed to a descriptive, longitudinal study. Specifically, the principle investigator asserts that the latter would elaborate on the challenges that confront couples as they transition into the new roles of parenthood. Whereas, the clinical intervention allows the researchers to test the utility of a multidimensional conceptual framework by focusing on the transition to fatherhood and by attempting to influence how that transition occurs. Concurrently, this clinical intervention affords the researchers to focus on the co-parenting relationship, and to further understand this impact on child outcomes.

*Scientific and Technical Merit*

A major strength of this proposal is the scientific integrity of the design which addresses important threats to validity. The principle investigator and his colleagues should be commended for their scientific rigor.

There are, however, a few remaining questions that arise in relation to the proposal as well. The study will use a randomized clinical control trial design to recruit participants. Health Partners, a closed-panel HMO, and Regions Hospital will be the two main sources from which subjects will be identified. Health Partners is described to be comprised of primarily middle-class white-collar workers. Regions Hospital has been targeted to insure adequate ethnic and socioeconomic diversity in the sample. Herein, are some important issues the principle investigator has not adequately developed. What comprises an "adequate ethnic and socioeconomic" sample that is diverse? What are the parameters of ethnic diversity? And if multiple ethnic groups are recruited, what might be the contribution of ethnic ideologies to paternal involvement in the socialization of young infants? Granted that the principle investigator has clearly stated that all participants must speak English, does this mean functionally or as a second language? The principle investigator states, for example, that "Because the intervention and assessment will be conducted in English, they must be able to read and speak English." How will this be evaluated? No measures of verbal communicative competence or literacy competency have been incorporated into this study. And given that a diverse sample population is targeted, should there not be some measure of cultural ideology and beliefs? If these are mute points, then why is a consultant who has expertise on cultural competence built into the project?
Assessment of Enhanced Prenatal Care by Ethnically Diverse Women

Grantee
The Regents of the University of California

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Project Number R40MC00137


Costs

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Summary

Statement of the Problem
The general aims of the study are to determine whether enhanced prenatal services that include nutrition, psychosocial and health education services are associated with measurable benefits as perceived by women enrolled in Medicaid managed care plans, and whether those benefits differ for African-American, Hispanic and white (non-Hispanic women).

Research Questions or Hypotheses
The fundamental research questions are, 1) Whether quality prenatal psychosocial, health education and nutrition services delivered according to official guidelines are associated with better provider-patient interactions, patient satisfaction and behavioral adherence to advice according to the women; and 2) Whether these perceived benefits differ for African-American, Hispanic and white women.

Study Design and Methods
To answer these questions, a consumer survey instrument with measures for quality of prenatal care advice, quality of
interpersonal care, patient satisfaction, and behavioral compliance with prenatal care advice has been developed. The
reliability and validity of these measures for African-American, Hispanic and white low-income women will be determined.
The survey will be useful for measuring enhanced prenatal care quality and outcomes by Medicaid managed care plans and
others who want to evaluate the quality of the enhanced prenatal services.

Population and Sampling Plan

The populations of interest are African-American, Hispanic and (non-Hispanic) white pregnant women enrolled in public
Medicaid managed care plans in the four San Francisco Bay Area counties in California. Women surveyed will be between
the ages of 18 and 44, and their pregnancies will be between 24 and 32 weeks gestation. Each woman included must have
made at least two visits with a prenatal care provider in the plan but have not yet given birth. We seek a final sample of 300
eligible subjects per ethnic group (900 respondents in all).

Analysis Plan

Once the surveys are completed, the data will be cleaned, coded and missing data will be considered for possible imputation.
The variability of different measures will be examined and those with limited variability will be dropped. For multi-item
scales, multivariate regression Structural Equation Modeling (SEM) techniques will be used for factor analysis of appropriate
items to include in the scale for each latent variable. Reliability of the survey will be assessed, i.e. the extent to which
scales are free of random error and are thus reproducible will be examined. Since no gold standard exists for the measure of
process of care, the focus will be on construct validity.
SEM will be used to facilitate determination of the adequacy of hypothesized relationships between latent variables in this
study. The hypothesized relationships between main variables are tested in two stages. First, analyses are conducted
separately for each ethnic group to evaluate the fit of each model for each hypothesized relationship. A common model
(including potentially confounding variables) with adequate fit across all three groups for each hypothesis must be identified
prior to proceeding to the second step. Next, in a multiple group analysis, parameter estimates are constrained to be equal
across groups. The two models (separate parameter estimates in all groups and constrained parameter estimates) are
compared. If there is not a significant decrement in fit when the parameter estimates are constrained to be equal, the
hypothesis that the relationship in the three ethnic groups is different can be rejected, and the strength of the hypothesized
relationship can be tested across groups. If the models are significantly different, further investigation can be conducted to
identify which specific parameters are different across groups for inspecting the modification indices. These indices suggest
which parameters are most influential on the goodness-of-fit indices.

Pre-Award Evaluation

Evaluator 1

Originality and Importance
It is not clear exactly how these findings will have relevance to the national scene due to the very local aspects of the
managed care plan implementation, especially in the absence of collection of birth outcomes. Yet in the sense that California
is a nation unto itself, it might be argued that enough population is affected to make this an important project.

Regional and National Significance
No statement of regional and national significance.

Scientific and Technical Merit
Several concerns remain to be resolved. First, the telephone-sampling plan has problems. The principle investigator expects
to get a consent rate of about 50 percent, a rate they declare acceptable in hard to reach populations. Yet what matters is not
the absolute percentage of the eligible population that one samples; rather it is how representative the sample is that allows
one to draw strong inferences. The principle investigator attempts to address this issue of non-response by evaluating the
difference between the responders and non-responders on socio-demographic and health variables and adjusting accordingly.
Yet this assumes that non-response is related to some set of these variables. One wonders if it would be feasible to go out in the neighborhoods and draw a random sample from those who could not be contacted by telephone to better evaluate this assumption.

The role of the advisory board is not clear. The principle investigator proposes to seek out advice from a whole range of members drawn from both managed care plans and local communities to "advise on how to implement our research study, while being accountable to the constituencies involved." This obviously entails the strong possibility that the research plan, as proposed here, will not be the one implemented if the constituencies involved do not concur with the plan.

It is also clear that the measurement development will depend heavily on the outcomes of the focus group work and every attempt will be made to construct instruments that are culturally sensitive. While this is commendable, it also directly contradicts the data analytic strategy for assessing measurement invariance and the steps that will be taken if measurement invariance is not found. If one understands correctly, the principle investigator intends to modify the measurement model by deleting items that do not demonstrate invariance across ethnic groups via the equality of factor loading, thereby eliminating items which, empirically, demonstrate differential cultural sensitivity. If only invariant items remain, then such items are by definition culturally insensitive. Therefore, one must generally choose between the two alternative strategies in that they maximize different aspects of validity. It is not clear which emphasis the principle investigator prioritizes.

The strategy to investigate both measurement and structural invariance across the three ethnic groups presupposes that a common model can be found which fits well in all groups, before between-group structural differences are examined. This position makes the assumptions that the best-fitting model within each group is simply a nested version in some fashion to the models that fit in other groups. It is the intention of the principle investigator to restrict model searches for best-fitting models only to those that are common, thereby eliminating the potential that very different, non-nested models might fit best in each of three different groups?

How the principle investigator attempts to incorporate covariates into the SEM analysis is not clear. There are a number of different strategies for doing so (either explicit inclusion into the model or by analyzing partial-covariance matrices) each with their respective pluses and minuses. This principle investigator must address this issue.

There was no power calculated for the SEM analyses. When one looks at the MacCallums' Tables for assessing fit, it appears that the model given had sufficient power to detect a non-fitting model. Yet because the manner in which the principle investigator intends to handle covariates is not made clear, one is not sure if the power one has calculated is correct.

Finally, the principle investigator still intends to address reliability as assessed by an internal-consistency measure by splitting the scale items and computing alpha. One wishes again to assure the principle investigator that it is not necessary to split the items into subsets to compute alpha, since alpha is proportional to the average of all possible split-half reliabilities.

Evaluator 2

Originality and Importance
Twenty percent of the nation's children living in poverty live in California, and one fourth of the Hispanic births in the country are to women in California. Therefore, the results are applicable to a large enough group of women and children to merit funding.

Regional and National Significance
The information learned should be useful in providing services to women in Medicaid managed care in other areas of the country, or at least in developing research in those populations.

Scientific and Technical Merit
An initial issue of concern was how representative was the sample to be studied, or more importantly, the characteristics of
the unstudied women (i.e., whether they vary in demographic and health characteristics from the population that is actually
studied). Results of other studies showing no differences in responders and non-responders is given. More importantly, a
field interview company has been identified with experience in locating and interviewing hard to reach individuals. The
company will use the study interviews in teams with an interviewer from the company trained in working in these frequently
unsafe areas.

The advisory board's role is clear. They will be used only to help the investigators better understand the constituencies being
studied in a way that will make the proposed study more acceptable to the potential subjects.

The proposal will attempt to devise instrument questions that are culturally sensitive. Configural invariance and factorial
loading invariance are to be used to detect cultural sensitivity in the measurement models. Two additional levels of factorial
invariance, strong factorial invariance and strict factorial invariance will also be tested. It is clarified that the best fitting
model will be found for each group and differences in the models between the cultural groups will be reported.
Community-Based Violence Prevention for High-Risk Youth

Grantee
Children's National Medical Center

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Project Number R40MC00174

Project Period 1/1/2000-12/31/2003

Summary

Statement of the Problem

America's most precious resource is its youth, but that resource is increasingly threatened by violence. Recommendations for violence prevention have highlighted the need to focus on youth and to explore targeted interventions. Nowhere is the need greater than in our nation's capital where the intentional injury fatality rate for youth age 14-19 is higher than any of the 50 states. Building on the CDC-supported project "Adolescent Violence: A Community-Based Strategy" which instituted city-wide surveillance of injuries, this proposal extends our work to identify high risk individuals and develop and test interventions.

Research Questions or Hypotheses

1) To assess violence prevention services provided to assault victims in the emergency department (ED) and after discharge;
2) To assess the receptiveness of injured youth & their families presenting to the ED to violence prevention interventions; and
3) In a sample of high risk youth presenting to the ED with assault injuries, determine the feasibility and effectiveness of an
individualized home-based youth & family intervention with community involvement. Prior intentional injury is a significant risk factor for subsequent injury. Presentation to an ED for an injury may be a sentinel event and opportunity for prevention. We hypothesize, however, that among assault-injured youth age 10-14, many are involved in risky behavior and few are offered violence prevention services in the ED or after discharge. We also hypothesize that a high proportion are willing to participate in violence prevention interventions recommended by hospital personnel. Though many violence programs assume a uniform etiologic basis for youth violence and that the same behavioral intervention would be effective for all youth, we postulate that strategies for intervention differ depending on injury cause, circumstances, risk, protective factors, and community factors. Home visiting family-based education programs targeting high risk infants have been effective in preventing child abuse, neglect and future antisocial behavior. We test the feasibility and impact of an individualized home visiting intervention in a pre and early adolescent high risk population. Focusing on parental supervision and monitoring, youth social skills and self esteem, and community linkage, we target assault-injured youth presenting to the ED to reduce future violence and injury.

Study Design and Methods

This study is a randomized controlled trial of the feasibility and effectiveness of an individualized intervention. The intervention group receives a six session social skills and mentoring curriculum for youth implemented by community mentors. Their parents receive a three session parental monitoring curriculum from health educators visiting their home. Both intervention and control groups receive community referrals to needed services. Youth and parents from both groups are assessed through in-person and phone interviews at baseline, post-intervention (4-6 months), and 12 and 18 months after recruitment. Health educators and mentors also assess youth, parent, and neighborhood variables and their perceived impact of the intervention.

Population Description and Sampling Plan

A consecutive sample of youth age 10-14 years presenting to the emergency department for interpersonal assault injuries and their parents are recruited for the study. Child abuse and sexual abuse are excluded. Youth and parents with severe psychopathology or inability to comprehend the curriculum are excluded. Families are recruited in the hospital or by phone. We plan to recruit 98 families in the control group and 98 families in the intervention group.

Analysis Plan

Predictor variables (demographics, school functioning, stressful life events, exposure to violence, family communication, history of mental health disorders), impact outcome variables (attitudes, beliefs, self efficacy, parental monitoring), and terminal outcomes variables (aggression, fighting, and injury) are measured. Control and intervention groups will be analyzed together for baseline description of this population and will be compared longitudinally. Comparison of attitudes of the youth versus parent will also be assessed.

Pre-Award Evaluation

Evaluator 1

Originality and Importance

The AVS surveillance project has determined that for every death due to injury in youth, there were 8 hospitalizations and 102 ED visits. The investigators make a convincing argument that this is the next logical step - to target high-risk youths that have been injured and present to an ED and design and evaluate a community-based intervention program for preadolescents. This proposal addresses many of the "issues/questions" on the Maternal and Child Health Bureau Research Agenda including: 1) evaluation of emergency medical services, 2) the design of educational and health promoting interventions during formative years that help reduce risk of developing specific disease and conditions in adulthood, and 3) "conduct randomized clinical trials of interventions designed to reduce exposure to risk of injury in the environment."

Regional and National Significance
Homicide is the third leading cause of death for youth 10-14 years and the second leading cause of death for those 15-19 years. For African Americans, homicide is the leading cause of death for males and females ages 15-19 years. This proposal builds upon an injury surveillance system for youth violence in the District of Columbia, which has a higher intentional injury fatality rate for ages 15-19 than any of the fifty states.

**Scientific and Technical Merit**

This is a well-written, thoughtfully designed proposal. The PI offers an organized and literature based approach to targeting an intervention for youths at risk for intentional violence. The AVS project has defined the problem through surveillance and epidemiology. This is the next logical step. The study aims and hypotheses have been modified and are well defined. The study designs for Aims A and B (cross-sectional) and Aim C (prospective, randomized clinical trial) are appropriate and well justified. Working definitions and independent and dependent variables are clearly defined. Tests and measures used to assess the youths and their parents have been modified based on input from the MCH Review Committee and newly sought expert advice. Assessment of psycho pathological violence is now included. The PI has begun to pilot and modify these tools for this age group. Potential covariates or confounders are identified through past study and literature review and monitored. Quality assurance mechanisms will be included to train staff, form completion, patient enrollment and capture rates, random assignments, and range and consistency of data. The analysis plans have been expanded and include survival analysis for the real possibility of loss of participants. Sample size is calculated based on data from the AVS study and main outcome measures. Preliminary data is given that suggests that the PI has the experience to identify, design, and run this large ED and community based study.

There are some limitations and concerns. Aim A may suffer from the Hawthorne Effect. Since the EDs from which the high-risk youth are selected and enrolled have been part of AVS for many years and study personnel will be orienting and reminding personnel to identify these youth, there is a large bias toward finding a higher rate of referral than is part of routine practice. To determine whether EDs provide violence prevention services to youth and their families, a representative sample of EDs across the country would need to be surveyed. Aim A should probably be eliminated and the investigators provide descriptive data about baseline ED services from the randomized intervention trial.

Recall bias is a problem throughout the study. Many measures are based on youth or parental report. The inclusion of teacher surveys, chart review, and retest of a 10% random sample will help with this problem.

Although pilot studies indicate that there will be great interest in participating in this intervention by both parents and youth and sample size has allowed for some attrition, loss to follow-up and dropouts may be a real problem. The investigators indicate that this is also useful information and there will be a six month follow-up. The effect of the intervention will be assessed for all enrolled at 12 months, but further funding is needed for all to complete an 18-month follow-up. One hopes that the intervention, if effective, will be useful through the teenage years when they are most at risk, but this will not be assessed.

Finally, the intervention itself is costly and labor intensive making it less feasible to replicate in multiple setting and without funding. None-the-less, any attempt to provide services and evaluate interventions for a problem of this magnitude is worth exploring.

**Evaluator 2**

*Originality and Importance*

No statement of originality and importance.

*Regional and National Significance*

No statement of regional and national signifinance.

*Scientific and Technical Merit*

The PI has done a commendable job in the resubmission in addressing the committee's concerns. The proposal has been
streamlined, and a more narrow focus, based on a dual foundation of preliminary data analysis of a previous study and an emerging literature on violence prevention, should prove profitable. The study aims are more focused and likely to be obtainable, with the primary focus on the evaluation of the intervention effects. The addition of Thomas Dishion as a consultant adds expertise to the already strong research team in the area of family models for violence prevention. The intervention appears to address proposed causal mechanisms of violence more directly, rather than just markers of violent behavior.

Improved measures of psychopathology (an important marker for future violence) have been added, and the exclusion of those children with academic difficulties (retention) has been eliminated. The age range of the sample has shifted to 9-12 year olds, and with subsequent pilot work, the issue of using measures developed on older children has been somewhat ameliorated. Measures intended for broad surveys have been dropped (e.g. ADDHealth) and more refined measures have been added.

The mode of interviewing has been standardized for all participants, and the PI no longer proposes to develop a violence prediction profile on such a small sample, which would more than likely have very little cross-sample validity (using Darlington’s rough rule of 30 subjects per predictor).

Because of the thorough job the PI has done in responding to the concerns of the committee, few weaknesses remain. For this reviewer, only two concerns are worth mentioning for the Pls consideration: 1) the use of survival analysis on such a small sample may lead to a lack of power to detect differences in the timing of the re-commission of violent acts, and 2) the sheer number of measures may lead to a problem of compliance with the study protocol and/or increase attrition beyond what is expected.
Comprehensive Elementary School AIDS Education

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Yale University

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Project Number R40MC00109

Project Period 10/1/1998-9/30/2002

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Summary

Statement of the Problem

One of every four cases of sexually transmitted diseases and one of every four new infections with HIV occur in adolescents; every hour, approximately two adolescents in the United States become infected with HIV. Adolescents represent one of the fastest growing risk groups becoming infected with HIV. In many urban centers within the United States, significant numbers of children are already sexually active by the time they complete elementary school. Early onset of sexual activity is associated with unprotected sex and is more common among low-income and African-American and Latino adolescents. Research has shown that it is more effective to delay the age of initiation of sexual intercourse and/or to promote the initial adoption of safer sexual practices than to attempt to intervene once adolescents have already established patterns of high-risk sexual activity. For AIDS prevention efforts to be of maximal benefit, they will need to begin before the age when children and adolescents initiate high-risk behaviors that place them in jeopardy of acquiring HIV. Yet few school-based AIDS education efforts have involved young children, and those that have did not assess behavior change, which provides little empirical data about the characteristics and instructional content of effective programs for elementary school students.
This study will assess the efficacy of a 3-year elementary school AIDS education initiative involving AIDS prevention instruction in the fifth through seventh grades, embedded within a comprehensive social development program based on social cognitive and social influence theories. If successful, it will be the first demonstration of an effective AIDS prevention initiative at the elementary school level and will have practical implications for the prevention of the initiation of risky sexual behaviors in preadolescents and young adolescents.

**Research Questions or Hypotheses**

The major goal of the project is to evaluate the efficacy of a comprehensive elementary school AIDS education initiative to prevent the adoption of high-risk sexual behaviors as compared with a nonenhanced, standard social development curriculum with limited AIDS prevention content. The study will also investigate the impact of the intervention on key mediating variables (i.e., perceptions of vulnerability, fears about AIDS, peer sexual norms, and perceived self-efficacy for risk prevention measures).

The primary hypothesis is that students in the intervention group will have fewer self-reports of high-risk sexual behavior than students in the control group, as assessed at the end of the seventh grade upon the completion of the 3-year intervention. Specifically, significantly more students in the intervention group will remain abstinent through the seventh grade than those in the control group, and students in the intervention group who initiate sexual intercourse by the seventh grade will be more likely to use condoms than students in the control group. The intervention effect will persist after controlling for covariates (sociodemographic and academic variables and personal experience with AIDS).

Because the intervention effect may actually be more subtle and/or more widespread, we also propose hypotheses to test the impact of the intervention on key mediating variables. We hypothesize that students in the intervention group, as compared with students in the control group, will perceive themselves as less vulnerable to HIV disease and will have more realistic fears about AIDS, peer sexual norms that are more supportive of abstinence and condom usage, and greater perceived self-efficacy for risk-prevention measures.

**Study Design and Methods**

This project is designed to assess the efficacy of a 3-year elementary school AIDS education initiative involving AIDS prevention instruction embedded within a comprehensive social development program that is based on social cognitive and social influence theories. This integrated curriculum will be tested in a randomized, controlled trial involving all 1998–99 fifth graders (*n*=1,530) who will be followed through the seventh grade while attending regular education and bilingual classes within New Haven Public Schools, an urban school system within an AIDS epicenter. The intervention group, consisting of 13 schools, will receive an enhanced social development curriculum that includes the following: (1) Monthly teacher-inservice training, (2) ongoing facilitation and coinstruction by a social development facilitator, (3) additional AIDS prevention lessons, (4) a peer education program, and (5) involvement of community educators to assist with the training and support of peer educators. A cohort of 1998–99 seventh grade students (*n*=60–70) will serve as peer educators (over 3 years) to the fifth grade student cohort in the intervention group to accomplish the following: (1) Foster group norms that favor risk-reduction behavior, (2) model skills to resist peer pressure, and (3) provide a supportive network of older peers to assist with the transition to middle school. Students in the control group will receive a standard, limited curriculum on social development that includes only one lesson on AIDS education in the sixth grade. At the end of the sixth, seventh, and eighth grades, the rates of sexual abstinence and, for those who are sexually active, the proportions who adopt safer sexual practices (measured by reported use of condoms and the avoidance of drug or alcohol use and sex), will be measured in both groups using a confidential, self-administered survey (the Social and Health Assessment Survey (SAHA)) that is administered systemwide, independently of this project. The AIDS Survey for Kids (ASK), an individually administered, standardized, semistructured interview, will be given to a random sample of 280 students drawn from the intervention and control schools to measure factual knowledge, conceptual understanding, misconceptions, perceptions of personal vulnerability, and fears about AIDS.

**Population and Sampling Plan**

Because classroom instruction in social development (including AIDS education) is currently provided to all students within the school system who are participating in the project, and because the principal outcome measure (SAHA survey for determination of self-reports of sexual behavior) is administered districtwide, all students attending regular education fifth
grade classes, including bilingual classes, in 1998–99 will participate in the study except for those whose parents disapprove of their child's participation. There are 1,530 eligible students (57 percent black, 29 percent Hispanic, 12 percent white, 2 percent other, 52 percent female) in the 1998–99 fifth grade cohort. The SAHA survey will first be administered to this cohort in the spring of 2000; based on prior administrations, it is anticipated that less than 1 percent of parents will deny permission for participation in the survey.

A subsample (*n*=283) of randomly selected fifth graders who provided assent and written parental consent were interviewed during the first year of the study.

**Analysis Plan**

In order to test the primary hypothesis, both of the dichotomous outcome measures (i.e., "yes" or "no" to engaging in sexual intercourse and, if sexually active, "yes" or "no" to using a condom during the most recent incidence of intercourse) will be regressed against group assignment (i.e., intervention vs. control group). If a significant effect for the intervention is demonstrated, the following additional predictor variables will be entered into the logistic model to determine whether the effect remains: Covariates (sociodemographic and academic variables and personal experience with AIDS), elementary school attended, middle school attended, and an intervention dosage variable to control for the percentage of the curriculum received by the student. The mediating variables (social skills, AIDS factual knowledge and conceptual understanding for the subsample of children (n=283) who completed the ASK interview, perceptions of vulnerability, fears, sexual norms, and perceived self-efficacy) will also be added to the model to measure their contribution to the treatment effect. We will use the t test for comparing independent groups to determine the differences between the intervention and the control group on the following variables: Perceptions of vulnerability to HIV disease, fears about AIDS, peer sexual norms, and perceived self-efficacy for risk prevention measures.

We will have 80 percent power to detect an increase in the rate of abstinence at the end of the sixth grade from a baseline rate of 75–82 percent (alpha = 0.05). There will be sufficient power to detect a smaller increase at the end of the seventh and eighth grades.

**Pre-Award Evaluation**

**Evaluator 1**

*Originality and Importance*

The proposed project represents an excellent and quite timely idea. The proposed work indeed makes a strong case for the need for such work.

*Regional and National Significance*

The project addresses a variety of MCH research priorities. Providing an effective prevention intervention for high risk sexual behavior and AIDS is significant.

*Scientific and Technical Merit*

The strengths of this proposal: (1) the proposed work is intelligently developed, (2) the investigative team is strong, experienced, and already in place, (3) the investigators have worked already within the New Haven School system to establish relationships and develop the base for the AIDS education initiative, (4) preliminary work by the investigators has established some support for the model that underlies the intervention effort, and (5) the preventive model is developmental in its approach.

The investigators provide an in-depth discussion of the underlying social-cognitive framework for the study. The principle investigator goes to lengths to describe the basic underlying propositions within models of social-cognition and social influence and the mechanisms within each that would be likely to promote the intervention effect hypothesized to be found. This was a well-considered presentation that clearly articulated the concepts.

The principle investigator has made significant efforts to address detail. A description exists for the standard curriculum, the
specific enhancements to the standard curriculum for the intervention group, how classroom teachers and the social
development facilitator will be trained to implement aspects of the curriculum, the specific AIDS lessons that have been
added to the standard curriculum (6 sessions for 4th graders and 7 sessions for 8th graders), and the peer education aspects of
the intervention. From the greater detail, it is apparent that the variability in the curriculum is not problematic, and there is
support for the appropriateness of the level of intervention to produce the desired effect.

The principle investigator discusses strategies to document the integrity of treatment administration, treatment integrity
across teacher training and observational evaluation, as well as peer training and observational evaluation, and effect of the
use of peer education processes within each classroom. This represents thoughtfulness to process issues in the intervention
protocol.

The principle investigator proposes to assess a spectrum of related factors that would logically be affected by the intervention
as well as abstinence and condom use. Covariates such as academics and personal experience with AIDS will be included in
the analysis scheme, as will mediating variables such as social skills, AIDS factual knowledge, conceptual understanding of
AIDS, perceptions of vulnerability, fears, perceived self-efficacy, and sexual norms. Further, the analysis of treatment process
factors will add to the understanding of these more broadly based factors as well.

Evaluator 2

Originality and Importance
This proposal seeks four-years of funding to assess the efficacy of a three-year AIDS education initiative for elementary aged
children. The proposed curriculum will be piloted with 1,400 4th through 6th grade youth enrolled in bilingual and regular
education classes within the New Haven school district. The proposal has an array of strengths: It is being implemented in a
community where nearly twenty five percent of all children are sexually active, includes youth with limited-English
proficiency, involves multiple sectors of the New Haven community, and addresses an important public health problem
(AIDS and sexual activity).

Regional and National Significance
The proposed project addresses a host of AIDS education issues in a developmentally appropriate manner, while addressing a
targeted population where there has been a noted increase in AIDS.

Scientific and Technical Merit
The principle investigator has assembled a collaborative team that presents an array of unique talents that are complementary.
He has apparently identified several significant consultants who will contribute to the overall project in a meaningful and
facilitative manner. Taken together, the array of investigators and consultants provides a well-rounded, multidisciplinary
team of experts who contribute to the fulfillment of the investigative goals and objectives. Moreover, the extensive work that
several of the co-investigators have been involved in underscore the unique contributions of this collaborative effort.

One of the proposal strengths is the literature review. Although the literature is focused primarily upon adolescent issues, the
investigator effectively uses this focus to illustrate the dearth of programmatic and research that has been conducted with
elementary-aged children. Significant ties to literature related to the delay of sexual intercourse and the adoption of safer sex
practices underscore the theoretical and developmental approach that the investigator seeks to examine in this investigation.
This approach is particularly important given the earlier onset of sexual activity among urban minority youth as cited.

The evidence related to optimistic bias provides additional support related to the targeted population of this investigation.
Specifically, the authors note that "...perceived vulnerability to health problems increases between the ages of 8 and 13, and
then decreases during adolescence. The sixth grader therefore sits, unprepared, on the threshold of adolescence, a time when
the health and safety consequences of unrealistic optimism intensify as autonomy increases and risky behavior accelerates." There are, nonetheless, a series of shortcomings and questions that require elaboration.

With respect to the intervention, the utilization of multiple facilitators (peers, investigators, teachers, and members of the
community) provides an array of role models for young children. Such an array may facilitate the development of interpersonal relationships for young children. This in turn may contribute to the desired outcomes. Yet, it is curious that this is not part of the model. It should be noted that throughout the document the importance of role models and interpersonal relationships is stressed.

For example, the literature related to peer-educators and the reduction in risk behaviors is not fully developed. A discussion of the effectiveness of this approach within and across ethnic groups is nowhere found. Similarly, the potential differences that might occur across SES categories and ethnicity have not been addressed.

The process evaluation that has been described is adequate, but perhaps not the strongest type of evaluation that might be utilized. While this focus on documenting the implementation of the intervention is noteworthy, it does not allow for an examination of the extent to which the program's highest priority goals are and are not being achieved. Some of these goals may be cognitive (gains in knowledge or skills) or affective (e.g., ability to cope with peer pressure). Through the introduction of an outcome-based evaluation model, the investigators would be able to discern the impact that this intervention program has on the intended population. While it is acknowledged that this is the intent of part of the evaluation, there are an array of outcomes that could be focused upon to enhance the lessons learned during this investigation.

The plan for data analysis for the first hypothesis appears to be adequate. However, it is not clear why the children enrolled in bilingual classes will be excluded from the analysis. It is also stated in the plan for analysis that “initial analyses will be restricted to those students who remain within the same treatment condition throughout the three years of the study.” Based on this statement, it can be interpreted that youth who transition out of the bilingual education classroom settings will be treated as either missing data or as having terminated their participation. Why? Toward that end authors state that “a sample size of 270 assigned to each treatment condition is sufficient to detect a 10% difference between the control and intervention groups.” Does this imply that the bilingual population is sufficiently large?

The timeline that has been provided is clear, and reflects the feasibility of completing the study in the allocated time.

The budget for the proposed project, while reflective of the multiple stakeholders that will be involved, appears to be rather extensive. The second research associate, for example (TBH) will receive a salary that exceeds the current research associate. No institutional matches are offered for any of the investigators on the project. Moreover, the fees offered to the Institute for Community Research, Inc. seem to be somewhat inflated.
Does Education Limit Lead Burden?

**Grantee**
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**Project Number** R40MC00124

**Project Period** 1/1/1995-12/31/2000

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**Year 2010 Objectives**
7.11, 8.12

**Study Design**
Experimental

**Time Design**
Longitudinal

**Care Emphasis**
Interventional

**Population Focus**
Neonates, Infants, Toddlers, Preschool-age children, Adolescents, Parents/Families/Mothers/Fathers

**Race/Ethnic Focus**
African Americans, Asians-Overall, Hispanics-Overall, Native Americans

**Priority Research Issues**

**Summary**

**Statement of the Problem**

Lead abatement is a costly and disruptive secondary prevention procedure, whose effects benefit only those who live in the abated home. Primary prevention interventions—which may be less expensive and reach more people—are necessary. Establishing the efficacy and cost-effectiveness of such primary prevention strategies will affect policy decisions related to prevention and intervention strategies for lead burden.

**Research Questions or Hypotheses**

The purpose of this study is to assess the efficacy of a community-based, intensive, culturally specific educational intervention for the primary prevention of lead burden. The goal is to maintain lead levels below 10 µg/dl in offspring of mothers who receive the education. It is hypothesized that the lead levels of the children whose mothers receive the intensive education will remain lower than those of children whose mothers receive the basic education. It is hypothesized that mothers receiving the education intervention will perform better on knowledge-based tests than will mothers who do not receive the intervention.
Study Design and Methods

Two groups—one basic and one intensive—have received educational materials in this randomized trial. The basic educational materials consist of face-to-face advice given routinely to patients by health care providers as well as pamphlets (typically in English but occasionally translated into the participant's native language) commonly found in doctors' offices or distributed by the local health department. All participants have had access to this information throughout the study, regardless of their group assignment. In addition to the basic material, each mother in the intensive education group is receiving 20 intervention sessions, primarily during the first year of the child's life. The intervention is being conducted primarily in the mother's home and in her own language by a peer teacher from her own community and racial or ethnic group who has assisted in developing the form and content of the educational materials. Quarterly booster sessions that are tailored to the developmental stage of the child are conducted (following the first two sessions) for the remainder of the study.

The intensive educational phase and booster sessions have been tailored to the racial or ethnic background of the participant. Through participation in focus groups conducted by the research team, members of different racial or ethnic groups have expressed an interest in receiving more information through different media. Intensive interventions and booster sessions have focused on sanitation, hygiene, and nutritional guidelines for the prevention of lead burden. Prenatal exposure to lead has been measured by maternal and cord blood levels. Lead levels of the children are being assessed three times per year by analyzing 5 mL of venous blood with atomic absorption spectroscopy. At enrollment and whenever relocation, remodeling, or rehabilitation of the home has occurred, samples of paint, dust, water, and soil have been taken from each participant’s home. Dust samples have been collected once or twice per year throughout the study because changes in household sanitation resulting from participation in the intensive education intervention would be likely to affect only this source of lead contamination.

Population and Sampling Plan

Over 600 mothers from the Phillips neighborhood of Minneapolis and parts of adjacent neighborhoods have been recruited during the prenatal period or during their offspring's early infancy. They have been randomly assigned within racial or ethnic groups (African American, Native American, white, Southeast Asian, Hispanic) to an intensive or basic education group.

Analysis Plan

Lead levels of the offspring of mothers in the basic and intensive education groups will be compared to determine whether the levels for those in the intensive education group have remained significantly lower than for those in the basic education group. Data analyses will focus on two primary outcomes consisting of blood lead levels (prenatal and prospectively collected samples every 3 months) and knowledge base (including risks of lead burden, effects of lead burden, and preventive strategies).

Analyses of continuous variables for knowledge and blood lead will be done by general linear models for correlated data (SAS procedure MIXED). This approach will allow for repeated measures when there may be partial data. Dichotomous outcomes (i.e., blood lead levels >10 µg/dl) will be analyzed by applying the general linear model to distributions (SAS macro GLIMMIX). In addition, actuarial methods, including Kaplan-Meier nonparametric stratified survival analysis and Cox proportional hazards, will be used to assess time to an outcome.

Pre-Award Evaluation

Evaluator 1

Originality and Importance

This proposal makes an effective and convincing argument that home-by-home lead abatement will never adequately address the public health problem of lead exposure in millions of U.S. children. A simple but credible alternative is proposed: Use intensive, culturally appropriate educational interventions to alter household practices with known influences on the degree of exposure to lead in contaminated environments. The study is original because it offers a plausible alternative to current public health practices, and it is important because of the magnitude and potential consequences of lead burdens in the Nation’s children.
Regional and National Significance
The principal issue addressed in this application—the possible short-term and long-term developmental consequences of lead exposure in early life—is an important scientific and public health issue. Recent surveys suggest that environmental lead exposures affect 3 to 4 million U.S. children; of these, 1 in 6 children is younger than 6 years of age. While the neurologic and encephalopathic consequences of acute high-level lead exposures are recognized and well known, little is known about the more subtle behavioral and developmental effects of chronic low-level exposure. If widespread chronic lead exposure can result in deficits in attention and memory, these cognitive and behavioral obstacles to learning would constitute a far greater threat to public health than the occasional acute lead intoxication seen in urban medical centers. Thus, the national significance of the proposed research lies in the possibility that subtle but highly prevalent neurotoxic effects on learning may be present in millions of U.S. children.

Scientific and Technical Merit
The proposed study has several strengths. First, the investigators provide strong justification for a study of a primary prevention intervention to reduce lead burden in young children living in the inner city. The effects of elevated lead levels on the child are well documented as are the costs of lead abatement and its potentially disruptive effect on low-income families. The need for a primary prevention strategy to be implemented in the target community is also thoughtfully argued by the investigators.

Second, the intervention has been generated from the community and assessed for its cultural appropriateness by the investigators. Focus groups have been conducted among Asian Americans, Hispanic Americans, African Americans, and Anglo-Americans to determine the best educational approach for each group. The investigators were solicited by the community to conduct an evaluation of the intervention; the Phillips Neighborhood Lead Collaborative has been established and the investigators have become members. Preliminary studies have also been conducted to assess the relationship between lead levels of children in the Minneapolis inner city, some of whom reside in the Phillips neighborhood, and measures of their intellectual functioning.

Third, the plausibility of an intensive educational intervention is proposed by the investigators. They argue that one-on-one intensive education is more effective than less personal approaches. A well-defined conceptual framework is provided to examine how changes in parent knowledge will affect changes in behavior with regard to sanitation and hygiene and the nutritional status of the child. These changes, in turn, are expected to result in lower lead burdens among children whose mothers receive the intensive educational intervention.

Fourth, the measurements of lead levels, lead exposure in the environment, the mother’s knowledge base concerning lead exposure and its prevention, and assessment of the nutritional status of the child are well described in the study proposal. Stratification by race/ethnicity and clinic of origin in the selection of the sample will ensure that these two potential confounders will be adequately addressed in the design of the study. Moreover, the investigators are aware of the potential education contamination that may occur in the study because of the relatively tightly knit racial/ethnic groups within the community. They have weighed various alternatives to the current study design and have concluded that it offers the best approach, given the logistic, theoretical, and financial constraints.

Sixth, the research team appears to be capable of conducting the project. They have already done a good deal of work in preliminary studies and in reviewing the literature on previous work in the area. The principal investigator has amassed a study team that appears very knowledgeable in the field of environmental toxicology and childhood lead exposure. Despite the reasoned and articulate discussion of the conceptual and methodological components of the study, some omissions in the proposal may affect implementation of the study. First, recruitment of subjects and their assignment to study groups could have been more completely articulated. The exact clinics from which subjects will be recruited and the number expected from each site are not provided in the project narrative. Moreover, the random method that will be used to assign study subjects to the intensive and basic education groups is not specified. Assignment of these subjects in permuted blocks within racial/ethnic and clinic groups should be considered. Preterm and low birthweight infants as well as infants affected by excessive alcohol or cocaine exposure would be potentially excluded from the sample only if a companion grant on the effect of lead burden on development is funded. These exclusions would seem appropriate, regardless of whether the companion grants were funded.

Second, the educational intervention has not yet been fully developed. An outline of its overall objectives and the content to be covered during each session is presented, but the detailed content for each racial/ethnic group has not been completed. The timeline indicates that it will be completed prior to the start of the funding period.
The investigators state that the intervention they will design will be modeled after the Expanded Food and Nutrition Education Program (EFNEP) of the U.S. Department of Agriculture. This is a community health education program designed to assist low-income families in improving their diets. The authors cite a number of reports claiming important benefits of this program, though none has appeared in peer-reviewed, scholarly publications. The principal investigator notes that nutrition is important in preventing lead burden; beyond this connection, however, there is little explanation of the manner in which the proposed intervention will benefit from the EFNEP experience.

The proposal includes points where the investigators indicate that they will collect data if a given condition occurs; for example, lead exposure in the family’s environment will be assessed upon enrollment in the study and will be assessed again only if the family moves or their home undergoes lead abatement. It would be preferable to measure this exposure again during the study period, perhaps at the end of the first year, to ensure that exposure has not changed for a child whose family has not moved or whose home has not undergone abatement. There are other examples in the proposal where measurements for all children should be considered, not just those presenting with problems.

The major weakness of the proposal is the plan of analysis. It is well organized but brief and is not adequately linked to the conceptual framework. It also does not indicate how the repeated measures of dust samples will be analyzed. More importantly, the analysis plan does not include some of the newer statistical methods that permit the investigators to take full advantage of the richness of the repeated measures that are collected over time. This is particularly true with regard to the repeated quarterly venous blood lead levels and the knowledge levels of mothers at baseline. A final problem with the analysis plan is the lack of any discussion about how the data will be analyzed by racial/ethnic group. Moreover, the power to detect differences in lead burden for each racial/ethnic group is clearly limited by the small numbers expected for some groups and the fact that the sample is already at the lower limits of an acceptable size. It may be possible to compare mean lead levels between the intervention and control groups for each racial/ethnic group, but no discussion of this strategy is presented.

A total of 560 subjects eligible for the study will be recruited through local health clinics and facilities serving children and pregnant women. The eligibility criteria are somewhat unclear. One section of the proposal states that birthweight will not be a criterion unless the companion study is funded, while in another section it is suggested that only infants with birthweights > 2,500 grams will be included in the study. This discrepancy needs attention.

One minor problem is the use of Hollingshead’s measure of socioeconomic status (SES). This measure may not be useful with respect to several of the racial/ethnic groups included in the study sample. A more thoughtful assessment of measures of SES is necessary.

Although the quarterly sampling of blood from the children is desirable in many respects, the trauma involved may cause attrition of some subjects. A related issue concerns the benefits of keeping children enrolled in the study past their second birthday. There was no discussion of how many subjects will be available for group comparisons at ages 3 or 4 years, so it was impossible to evaluate power to detect modest effect sizes. Data collection might be scaled back after the children reach age 2 in order to save cost. Some discussion of this option should have been offered.

Although some effort will be made to characterize subjects who drop out of the study and those who refuse to participate, the proposal contained no discussion of how data from dropouts will be handled. In general, this data ought to be retained in the analysis.

A final problem with the proposal is the budget. The costs for year 1, for example, appear excessive, given the plans outlined in the proposal.

The proposed research was judged to have numerous strengths, particularly the involvement of the community. Questions were raised about the budget, process of randomization, potential exclusion of subjects, possible contamination of the control group, the use of the Hollingshead measure, the uncompleted content of the intervention, and the lack of connection between the data analysis plan and the conceptual framework driving the study. The recommendation was for approval following a site visit to clarify questions raised.
Does Lead Burden Alter Neuropsychological Development?

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Project Number  R40MC00046

Project Period  12/1/1995-8/31/2001

Costs

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Year 2010 Objectives
8.11, 19.12

Study Design
Observational

Time Design
Longitudinal

Care Emphasis
Noninterventional

Population Focus
Infants, Toddlers, Preschool-age children

Race/Ethnic Focus
African Americans, Asians-Overall, Hispanics-Overall, Native Americans

Priority Research Issues

Summary

Statement of the Problem

Prospective studies, as a whole, demonstrate that low levels of lead have an effect on intellectual development. While the effect (a decrease of 4 to 8 I.Q. points) may not make a profound difference on an individual level, it has been shown that a downward shift of 4 I.Q. points in the population places four times as many children within the lower tail of the distribution and results in a substantial loss within the gifted range as well.

The effects of lead on I.Q. have been demonstrated in several cross-sectional studies of older children and in prospective studies of global cognitive development in young children. However, controversy surrounds the validity of those findings, due to methodological difficulties. Effects of lead on specific neuropsychological functions have not been well documented and several questions remain unanswered.

First, could deficits in component neuropsychological functions, such as attention and memory, which are important to intelligence test performance, result from lead burden? Second, are there windows of time during which children are at greater risk for long-term or specific neuropsychological deficits due to the state of the maturing nervous system at the time the child was first burdened with lead? Third, are findings dependent on the method of measuring neuropsychological outcome? Fourth, have all confounding factors been accounted for, or might lead burden coexist with other factors that could influence neuropsychological development? Specifically, do the factors of nutrition and iron deficiency influence the
relationship between lead burden and attention and memory? Answers to these questions have implications for health care delivery and educational intervention for children affected by lead. Greater understanding of the contribution of other health risks to lead burden sequelae (such as nutrition and iron deficiency) has implications for delivery of primary care focusing on nutrition education for parents of children at high risk for lead burden. Greater understanding of the interaction of developmental factors and lead burden on attention and memory will help focus the diagnostic and intervention efforts of schools attempting to understand curriculum and special education needs of burdened children. In addition, should attention in lead-burdened children be found deficient, medical intervention (namely, administration of stimulant medication) may prove to be an effective method of addressing an important neuropsychological deficit in affected children.

Research Questions or Hypotheses

The purpose of this investigation is twofold: (1) Ascertain the effects of age when first burdened with lead, duration of lead burden, and magnitude of lead burden on children's development of attention and memory from 12 to 48 months of age; and (2) explore the relationships between lead and attention and memory as a function of the method of measuring these areas. The research will also address how early nutrition and iron status influence the relationships between lead and attention and memory.

Study Design and Methods

All children will receive a baseline developmental assessment at 8 months of age. Children will then be seen 11 times between 12 and 48 months of age to complete the Bayley Scales of Infant Development-II or the Wechsler Preschool and Primary Scales of Intelligence, neuropsychological and experimental measures of memory, or experimental measures of attention. Different measures will be administered at each testing session to achieve six time points for developmental status, attention, and memory domain assessments.

The neuropsychological and experimental measures will be administered by trained technicians indigenous to the community and representative of the ethnic makeup of the neighborhood. In addition, electrophysiological measures of attention and memory will be administered to a subgroup of lead-burdened children and controls (matched for age, race, sex, and an average of Bayley scores prior to lead burden) at approximately 8-month intervals from the time of initial lead burden. It is expected that 30 percent of the sample will be identified as having lead burden over the course of the study.

Population and Sampling Plan

Approximately 560 children from an ethnically diverse inner-city neighborhood of low socioeconomic status will comprise the study sample for this research.

Analysis Plan

Using hierarchical linear models, analyses will be conducted to relate the observed development of attention and memory functions to lead-related variables, including age when first burdened with lead, duration of burden, and severity of burden. Correlational analysis will be conducted to explore differences in the relationship between lead burden and attention or memory function, depending on method of measurement.

Pre-Award Evaluation

Evaluator 1

Originality and Importance
This proposal will provide valuable information on the effect of lead burden on cognitive development in young children.

Regional and National Significance
Lead exposure among young children is of national concern, thereby making the results of this study of regional and national significance.
**Scientific and Technical Merit**

This is a revision of a proposal previously reviewed and recommended for disapproval. The research is now focused on measures of attention and memory in relation to age of first lead burden, magnitude of lead burden, and duration of lead burden.

The proposed research has a number of important strengths. The investigators provide an excellent literature review and rationale for the study. The investigators will perform frequent blood lead sampling using reliable collection methods and atomic absorption spectroscopy. This is the first longitudinal study investigating attention, learning, and memory using a multimethod approach. The investigators plan to measure a large number of potential confounders but will reduce the number that will actually be used in the analysis to avoid over-correction for lead-related variance. Finally, the study sample will include children from an entire community with ethnically diverse backgrounds, with careful attention to the potential differences that may be found between participants and nonparticipants.

A second strength of the proposed research is the study design and sampling plan. The study will include repeated measures not only of the blood lead levels of the children but also of memory and attention. This design will permit the investigators to develop growth curves that can be used to determine whether the pattern of growth and development differs from the normal pattern even before changes in levels of memory or attention are noted. Thus, the more subtle effects of low levels of lead burden can be investigated. As noted previously, the study sample allows for the study of these effects in an ethnically diverse population.

The investigators present detailed and reasonable plans regarding recruitment and tracking of study subjects. The use of indigenous community workers to collect data is also a strategy that may increase compliance with the study. The investigators have an excellent working relationship with the community. In fact, the investigators were solicited by the community to conduct an evaluation of an intervention to reduce lead levels among children in the community. The community has established a Phillips Neighborhood Lead Collaborative, which includes the investigators as members.

The investigators also present a detailed description of the study instruments. The measurements of lead levels, attention and memory, nutritional status of the child, and potential confounding variables are well described in the study proposal. Moreover, the use of multiple approaches to measure memory and attention is an important strength of the proposed study. These approaches include experimental, neuropsychological, observational, and physiological measures. In addition, the investigators will measure blood lead levels, the age at which lead burden was first noted, and the duration of this burden. Each of the variables to be developed from the study instruments, and the ages at which they will be obtained, are clearly described.

The research team is clearly capable of conducting the project, and the collaboration with the prevention study is a major strength of the proposed work. The investigators have already done a good deal of work in preliminary studies, particularly in developing study instruments and reviewing the literature on previous work in the area. The investigators have shown considerable creativity in developing instruments from previously established ones and adapting them for use with the study sample.

A final strength of the proposal is the plan of analysis, which is well thought out and clearly described. This plan is carefully integrated with the study questions and hypotheses and includes a clear and reasonable discussion of the advantages of using hierarchical linear modeling as the statistical method of preference in the analysis. The investigators were careful to avoid over-correcting for lead-related variance by including multiple correlated confounding variables. In addition to retaining the strengths of the original proposal, the current plan also retains some of its weaknesses. It was noted previously that at least four separate fundable studies were embedded in the project. Essentially, the principal investigator has dropped one (neuropsychological functioning after chelation therapy) and eliminated some of the variables from the others. There remains an ambitious series of testing, including serial measures of overall developmental functioning (using the Bayley Scales of Infant Development and the Wechsler Preschool and Primary Scale of Intelligence), attention (with at least five different measures), memory (with at least four different measures), lead, iron, Home Observation for Measurement of the Environment (HOME) interviews, and other parent interviews—in addition to measures of confounding variables such as parental I.Q., socioeconomic status, family configuration, family size, substance use, parental psychopathology, birthweight, Apgar scores, gestational age, perinatal complications, and anthropometric measures of nutritional status of the children.

The principal investigator has not addressed the issue of how the coexisting educational intervention study will impact on the generalizability of the current study’s results. Since one of the goals of the intervention study is to break the relationship between poverty, parental education, and lead poisoning, the relationships between these variables may affect the current analyses. Although one might argue that the educational intervention will not interfere with all assessments of the
relationship between elevated blood lead level and event-related potential (ERP) measures of attention and memory, certainly the role of the confounding variables will be different in this sample than it would be in almost any other inner-city sample. This issue has yet to be addressed in the present proposal.

In response to the previous review, revised power calculations are presented in the present proposal. Although power is good for the analyses that are based on the entire sample (approximately 450), power is relatively low for analyses involving the subsample of 50 burdened children and their matched counterparts. For example, power is less than 80 percent to detect a correlation of .30 between lead and attention with this sample size, according to the calculations presented in the proposal.

The use of community workers to collect neuropsychological data, while a strength in terms of fostering good working relationships with the community, may not yield optimal data for some of the measures. For example, the Bayley Scales of Infant Development usually require considerable training to administer, and it is not clear whether 50 hours of training will be enough to train the technicians in the administration of all of the instruments. Another issue involves confidentiality of the test results. While the investigators indicate a set of reasonable procedures to ensure confidentiality of the results, including blinding the technicians to lead levels and remedial services, some plan for careful monitoring of the community technicians may be necessary, at least at the beginning of the study.

Another potential problem involves the invariant ordering of the tests to be done at each session. This ordering may lead to poorer quality data for the tests performed at the end of a session because of fatigue. A better strategy would be to randomly order the tests to ensure that errors due to fatigue will be randomly distributed across the tests.

Although the plan of analysis is conceptually sound, there is no discussion of racial/ethnic differences or of the treatment effects that may result from the inclusion of subjects in the educational intervention in the prevention study. The investigators have not stated the reasons why they will repeat, in year 4, some of the baseline measures taken in year 1. This strategy is not optimal because it coincides with the last measurements of lead levels and memory and attention and does not permit the investigators to take full advantage of longitudinal collection of data. Collection in year 3 would be preferable because the data could be used in the analysis of the repeated measures of levels and attention and memory measures.

The proposed study is well thought out and includes an excellent design to answer the study questions. The recommendation is for approval.
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**Project Number** R40MC00203

**Project Period** 9/1/2000-8/31/2004

**Year 2010 Objectives**
7.11, 9.7, 16.6, 16.7, 16.19

**Study Design**
Experimental

**Time Design**
Longitudinal

**Care Emphasis**
Interventional

**Population Focus**
Neonates, Infants, Toddlers, Adolescents (pregnancy-related)

**Race/Ethnic Focus**
African-American

**Priority Research Issues**
3.8.2

**Summary**

**Statement of Problem**
Young, urban mothers and their infants are at risk for poor health and development. Compared to older women, young mothers are less likely to receive adequate prenatal care, less likely to take actions that promote infant and child health, including both the initiation and duration of breastfeeding, and less likely to be responsive and responsible in their parenting. As they develop, children of adolescent parents are at increased risk of developmental and behavioral problems, substance abuse and perpetuating a multigenerational cycle of disadvantage by becoming teenage parents themselves. Relatively few interventions for young parents have been subjected to rigorous empirical scrutiny. This study examines the long-term efficacy of an intervention designed for young, low-income mothers and their infants. The program uses paraprofessional "doulas" to provide guidance and support during the prenatal, intrapartum, and postpartum periods in order to promote good obstetrical outcomes, breastfeeding, responsive parenting, parental efficacy, and child health and development. Findings will be relevant to health and social service agencies providing care to pregnant and parenting adolescents.

**Research Questions Hypotheses**
1) We hypothesize that doula support for young mothers will improve labor and delivery outcomes, will increase initiation of breastfeeding, will increase parental efficacy during the immediate postpartum period and decrease maternal anxiety and stress related to parenting.

2) We hypothesize that doula support will have effects on the mother and her care of her child that extend beyond the postpartum period. Specifically doula support will increase duration of breastfeeding, will increase adherence with other recommended feeding and immunization practices, will decrease postpartum depressive symptoms and feelings of stress, will increase mothers’ positive feelings about the child and her feelings of efficacy as a parent, and will increase responsive parenting.

3) We will explore what factors relate to amount and type of program utilization and quality of relationships between doulas and their clients, as well as what program implementation factors relate to client outcome.

**Study Design and Methods**

The proposed study is a randomized intervention trial of an expanded doula model. Young mothers receiving prenatal care at the University of Chicago Hospitals will be individually randomized to receive either a six-month doula intervention or usual perinatal care and services.

Baseline information is gathered during an interview conducted prior to randomization during the second trimester of pregnancy. Background measures assessed include mother’s intelligence (estimated by the Peabody Picture Vocabulary Test), depression (Center for Epidemiologic Studies-Depression Scale), involvement in delinquent / antisocial behavior (questions from the National Youth Survey), locus of control (Pearlin Mastery Scale), general orientation to relationships (Relationship Orientation Inventory), living arrangement relationship with baby’s father, and intentions to breastfeed.

Short-term outcomes are assessed during a brief contact immediately postpartum in the mother’s hospital room. Outcome measures include initiation of breastfeeding, mother-reported anxiety (State-Trait Anxiety Inventory), mother’s perceptions of her baby (Neonatal Perception Inventory), mother efficacy during labor (Birth Experience Scale), and maternal sensitivity when handling the infant (assessed from videotaped interaction coded using the Parent-Child Observation Guide). The hospital medical information system is used to gather information on obstetric outcomes, including duration of labor, mode of delivery, use of oxytocin, and use of analgesia and anesthesia.

Long-term follow-up data are gathered when the children are four months, twelve months, and twenty-four months old. Outcome measures include maternal depression, parenting stress and perception of the infant (Parenting Stress Inventory), maternal efficacy (Maternal Efficacy Scale), parenting values (The Adult-Adolescent Parenting Inventory), and maternal sensitivity (assessed from videotaped interaction coded using the Parent-Child Observation Guide). Child developmental outcome are assessed at 12 and 24 months using The Communication and Symbolic Behavior Scales and the Child Behavior Checklist.

The doula-client relationship is assessed through uniform quantitative data collected on all participating families and in-depth qualitative data collected on a subset of cases. On the quantitative level, doulas track the amount, type, and quality of contact that they have with families on client contact sheets. On the qualitative level, a subset of eight cases will be selected, where doulas and mothers will be interviewed in a semi-structured format about the developing helping relationship.

**Population Description and Sampling Plan**

The target population for the doula intervention study includes all women with low-risk pregnancies receiving prenatal care at clinics associated with the University of Chicago Hospitals who will be less than 21 years old at their expected delivery date. Women with high-risk pregnancies or those who plan to deliver at another hospital will be ineligible for the doula intervention study. The target population is predominantly African-American (over 96%), and poor (over 80% Medicaid), and the study directly addresses the provision of culturally sensitive intervention through use of paraprofessional helpers.

**Analysis Plan**

Analysis of covariance will be used to assess the effect of the intervention on continuous outcomes, while multivariate logistic and multinomial regression will be used to establish the impact of the intervention on the probability of categorical outcomes.
outcomes. Content analysis will be used to identify recurrent themes and patterns in the interview narratives. Regular themes will lead to an inductive classification system that will classify families based upon their experiences.

Pre-Award Evaluation

Evaluator 1

Scientific and Technical Merit

Young mothers from low-income backgrounds and their infants are a great risk for poor health and development. These women often do not receive adequate prenatal care and tend to be less involved in activities that will promote their infant's health and development. Research suggests that infants who have such a beginning are at greater risk for behavioral and developmental problems later in life. As such, intervention designed to increase young mothers' efficacy as parents in the early stages of an infant's life may have lasting positive effects on child development.

The proposed project has many strengths. Primarily, it grows out of a tradition of intervention that has shown some very promising results in the past. Research shows that doula support during labor and delivery improves pregnancy outcomes for mothers including duration of labor, use of medication and c-sections. Moreover, the present project is the initiation of an additional doula support site among a group of sites that have experienced great success. The Chicago Doula Project uses doulas certified by the only agency developed specifically to meet the needs of urban women of color. The doulas are recruited from the communities of the young women and have themselves given birth and raised children within those communities. In the past year, the Chicago Doula Project had assisted 217 young mothers giving birth. Eighty percent of these new mothers initiated breastfeeding and of those 80%, 80% persisted with breastfeeding for at least 6-weeks. The c-section rate for these women was only 6.45% compared to a national average of 15% for adolescent parents and only 13% had an epidural during delivery compared to the national average of 50%. Further videotaped analyses of the doula supported mothers interacting with their infants relative to non-program participants suggest that the mothers who had a doula were more sensitive and responsive to their infants' cues.

The current project is the initiation of a fourth site. The PI has already received support to begin the site and 3 of 4 doulas have already received training. The research team has also begun to develop the research protocol used to assess the effectiveness of the doula project. The measures and instruments proposed appear effective for answering the research questions posed and sufficient care has been taken to ensure that the intervention and control groups will be as comparable as possible.

Another strength of the project is its qualitative piece. The study proposes a small qualitative study designed to answer some of those nuanced questions about why programs work for some and not for others. I think that this will be an important contribution to the overall interpretation of the intervention effects.

A further strength is the project's focus on long-term follow-up. Much is written about the immediate effects of doula support on labor and delivery outcomes, but understanding whether support in the early postpartum months can be helpful in developing a young woman's sense of efficacy as a parent will be very useful data.

The weakest aspect of the study is the data on the biological correlates such as cortisol, oxytocin and norepinephrine antepartum. At this time, the PI seems very unclear on the procedures for collecting these samples and on how time of day and length of time postpartum will affect these variables. It seems that more research on exactly what these data tell us is needed before we invest money in the analyses.

Also many of the investigators' time seem to add up to more than 100% effort. We will need to refigure the budget based upon realistic effort contributions.

In general this is a well present proposal. It builds on a successful tradition of intervention and has been successful in putting the necessary program pieces in place before the grant was submitted. It is well worth funding.
Evaluator 2

**Scientific and Technical Merit**

This is an extremely impressive proposal. The authors make a cogent case for the need for a providing maternal support surrounding the birth of a child, and propose the extend such paraprofessional support beyond the birth and into the early, crucial stages of infant care. This clearly meets important priorities of MCHB.

The present project builds on previous research, as ascertained from both the literature and the research teams previous work. The proposal includes both qualitative and quantitative components which meshes well with recent MCHB objectives.

The use of a clinical trial is certainly warranted at this time, and the PI recognizes the potential problems that may arise and intends to assess the extent to which treatment by moderator variables may exist. Measures are generally obtained from multiple sources at multiple time points, providing best practice methods for assessing developmentally sensitive outcomes.

The PI also intends to assess constructs from multiple domains of interest, including biological, personological, programmatic, and contextual.

When implemented by an outstanding, multidisciplinary team of researchers it is clear that this project has an outstanding chance of success.

For the record, there are few issues that the PIs might want to consider. First, it may be important to assess baseline measures of neuroendocrine functioning prior to the onset of birth in order to establish a longer baseline period. Second, it is not always good practice to preliminarily screen data for significance by using multiple, fixed effect comparisons before moving onto the more developmentally sensitive random effects/repeated measures analyses. And finally, it is suggested that a photocopier would best be funded out of indirect costs, rather than direct costs.

Evaluator 3

**Scientific and Technical Merit**

This is unique proposal that will carry out a randomized intervention trial of paraprofessional "doulas" to provide guidance and support during the prenatal, labor and post-partum (up to 3 month) in order to promote good obstetrical outcomes, breastfeeding, responsive parenting efficacy, maternal well being and child health and development.

It falls within that priorities of the MCHB and it has a potential for improving short term and long-term health outcomes of adolescent pregnant women and their infants. Because adolescent pregnancy is a common occurrence and is related to significant morbidities and costs, an intervention that would positively impact these would be of national significance.

It is a unique approach and will measure a diverse group of variables in both mothers and infants, I believe that the length of the intervention falls "too short". It provides for long-term measures and follow up mothers and infants up to 24 months of age, but the intervention extends only up to 3 months postpartum. One of the hypotheses (2) "is that Doula support will increase the mothers feeling of efficacy in parenting and will increase responsive parenting". By providing the intervention only during the first 3 months (postpartum) many of parenting challenges and difficulties will be missed.

A multiplicity of instruments will be administered at 4,12, and 24 months postpartum that range from the CES-D, The Parenting Sense of Competence Scale (PSOC), Adult-Adolescent Parenting Inventory (AAPI), Parent-Child Videotapes, Health Care Utilization, The Communication and Symbolic Behavior Scales (CSBS) for infants and a child Behavior checklist.

The plans for statistical analysis on the short-term effects are clear and sound. The plans for the 4,12, and 24 months analysis are not clearly defined, and there is a long list of variables and measures in all those previously mentioned instruments.
Statement of the Problem
The problems of an adolescent pregnancy are many and this is a high-risk population for health outcomes. An intervention program is already in place on a short terms basis and immediate benefits have been documented, this proposal intends to prolong the intervention and the evaluation to determine long-term effects and/or benefits.

Review of the Literature
The review was divided into short term effects and benefits for which there is ample evidence and a rationale for long term effects for which there is not much empirical evidence except for breast feeding support programs.

A short section was dedicated to exploring possible biologic mechanisms for the short-term objective and parenting outcomes through stress reduction and/or changes in arousal/attention levels.

Missing from this section were studies in parenting, maternal well-being and infant behavior in adolescents or young urban mothers which is one of the scopes of the projects.

Hypothesis and Specification of Variables
Five hypotheses will be tested in this study:
1) Doula support and improved short-term obstetrical outcomes
2) Doula support and improved long-term maternal and infants outcome
3) Biologic explanation through measurement of salivary cortical, norepinephrine and/or oxitocin
4) Doula greater effectiveness in mothers not co-residing with their families.
5) Client-doula factors

The Second Hypothesis carries the most variables and is the least defined along with the third hypothesis. Perhaps in these areas the gaps in Knowledge are wider, but the literature review should have better defined these gaps.

Explanation of Concepts
This section was clear and reflects the proposal aims (pertinent).

Tests and Measurements
As previously mentioned, the long-term phase (4,12 and 24 months) involves a multidisciplinary of instruments and tests.

Study Design
This is a randomized intervention trial of an expanded doula model. The investigators stated both the strengths and potential weaknesses of such an approach. The method for both consent and randomization were well described.

Population Description
The target population of young pregnant women was not described except for estimated numbers (250 deliveries per year). No preliminary information was included on either short-term obstetrical variables such as rate of preterm delivers, rate of cesarean section, neonatal morbidities infant morbidities or health care utilization. A sample size of 248 mothers will be randomized.

Data Analysis
They were clear for the short-term variables but less clear for the long-term.

Time Schedule
This is a 4-year study that will carry out a pilot phase during the first year and extended into the second year. Year 3 and 4 will be used for the long-term assessments and final analysis. The timeline is appropriate.

Financing
A total of $1,729,861.00 is requested for direct costs for four years of funding. The budget covers mostly the research staff. The doula intervention is already funded through other sources. Staffing needs are high since they have estimated a total of
1,020 study sessions.

Qualifications and Experience
Dr. Sydney Hans, the PI has a PhD in Psychology and Social Relations from Harvard University. He has an impressive list of publications mostly on the subjects of prenatal exposure to drugs and its developmental consequences and longitudinal studies in children with social/environmental risk factors. The research team is well suited and experienced and will be able to carry out this project without major difficulties.

Human Subjects
No specific concerns.
Early Child Care Study of Children with Special Health Needs

**Grantee**
University of Washington

**Investigator**
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(206) 543-8074
(206) 685-3349 fax
ibcb@u.washington.edu

**Project Number** R40MC00133


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**Summary**

**Statement of the Problem**

Very little is known about patterns of child care usage or effects of early child care in special populations. As P.L. 99-457 is implemented, case managers, family members, and service providers are being asked to make decisions about child care essentially in an information vacuum regarding children with disabilities.

**Research Questions or Hypotheses**

This study is examining the influence of variations in early child care histories on the development of children with special needs (those with disabilities or at high risk for disabilities).

**Study Design and Methods**

A longitudinal design is being used to evaluate child outcomes as a function of the complex interactions among child
characteristics, family characteristics, and the quality and type of home, early intervention, and child care environments in which the children develop. Children and their families participating in the study are being assessed when the children are 12, 15, 30, and 45 months of age.

Family characteristics being measured include demographic variables, maternal stress and social support, maternal psychological adjustment, marital relationship, and maternal attitudes about employment, child-rearing, and child care. Characteristics of the early intervention environment include the type and extent of services, age of onset, extent of maternal involvement, and extent of communication with the child care environment. Characteristics of the child care environment include quality, type of care, extent of care, and stability of caregivers.

Data for the 12-month assessment are being obtained in the child's home; data for assessments at 15 and 30 months are obtained in the home, in the child care setting, by telephone, and in the laboratory (30 month visit only). The 45-month assessment will be conducted by telephone and in the laboratory.

**Population and Sampling Plan**

The sample will consist of 160 children, half of whom have a postnatal medical course that places them at high risk for mental retardation or developmental disabilities (e.g., neonates weighing <1,500 grams or having severe respiratory distress syndrome, intracranial hemorrhage and neonatal seizures, central nervous system infection, or abnormal neurological signs). The remaining half of the study sample are identified as having mental retardation or one of a variety of developmental disabilities (Down syndrome, cerebral palsy, other physical and/or cognitive disability, other genetic disorder, or chronic illness resulting in diagnosed developmental delays).

Children are being recruited from a variety of early intervention programs and high-risk infant followup clinics. In the study sample, 63 percent of participating children are male and 78 percent are Caucasian.

**Analysis Plan**

First, in order to describe the natural history of child care usage, the data will be examined and summarized in various ways (by age, severity of risk/disability, type of disability, etc.). The interviews and questionnaires will provide rich sources of data for these summaries. Second, analyses related to the prediction of child outcomes using an ecological model will be guided by a set of primary hypotheses. These primary hypotheses concern the effects of child care on child outcomes, as well as characteristics of the child, the family, and the home and early intervention environments as they moderate child care effects.

The following discussion illustrates data analytic methods for testing a specific hypothesis regarding cognitive development at 45 months. Similar procedures will be used for testing all major hypotheses. For illustrative purposes, we will consider the endpoint to be cognitive development measured at 45 months. The first step in this specific analytic domain would be a principal components analysis of the cognitive measures obtained at this age. The purpose of the components analysis is to determine the minimal set of cognitive measures required to understand the effect of child care on cognitive development. If considerable redundancy is found among the variables, summative measures or a selected subset of measures would be used in the subsequent analyses. On the other hand, if clusters of variables are found, separate analyses by cluster might be advisable.

The next step most likely would consist of a backwards elimination multiple regression seeking an optimal set of predictors of 45-month cognitive development from the cumulative child care record. The next step in the small analysis domain would be to repeat the backwards elimination regression, but with interaction variables included in the set. In addition to such a global analysis, numerous subanalyses would be performed, including analyses that would seek to determine, for example, whether a relationship exists between cognitive outcomes and amount of child care when the mean quality of child care is partialled out—a followup question that might result from the backwards elimination analysis. Other subsequent analyses might take the form of traditional analysis of variance (ANOVA), one way of examining the same question from a different, but related, analytic perspective. Regression analyses would also be performed—including analyses of child characteristics, family background, and home environment—to determine the contribution of child care to cognitive development beyond these background factors.

Some of the research hypotheses deal with the moderating effects of child, family, and home environment characteristics on globally observed relationships between child care and child outcomes. A number of analytic approaches are planned to deal with this construct; the two most direct approaches are (1) subset analyses and (2) covariate analyses.

When the moderating hypothesis is of the form "the relationship between X and Y differs for differing levels of Z," subset
analyses will be used. When, for example, the relation between cognitive outcomes and quality of child care differs according to differences in the level of quality in the home environment, a direct comparison (such as testing the homogeneity of regression) of relations in the various subsets implied by the hypothesis will provide the direct test required. In other cases, particularly those in which the $Z$ variable is continuous, partial and bipartial correlation methods will be used to examine the moderation hypotheses. In other words, the relation between $X$ and $Y$ will be examined with $Z$ partialled out of one or both of the $X$, $Y$ variates.

Specific hypotheses concerning types of disabilities have not been proposed, although severity of disability will be included as a child characteristic. However, exploratory analyses are planned for testing the model on diagnostic groups of adequate sample size.

**Pre-Award Evaluation**

**Evaluator 1**

**Originality and Importance**
This research should make a major contribution to our understanding of the effects of out-of-home child care on the development of young children at risk and those with identified disabilities.

**Regional and National Significance**
The research proposed in this application addresses a subject about which very little is known. With the increasing number of dual-worker families and single-parent households, child care for young children, including those with special needs, has become an increasingly important issue. Thus, this study is of regional and national significance.

**Scientific and Technical Merit**
This is a revision of an application previously reviewed and disapproved. This application, like the previous one, is well written and the investigators have been responsive to reviewers’ previous comments.

One of the concerns noted in the first review was the omission of early intervention services as a potential source of influence on child and family outcomes. Early intervention effects were neither included in the literature review and model nor addressed in the data collection plan. The revised application reviews the literature on the impact of early intervention and includes potential effects of these services in the theoretical model. Early intervention is expected to have maximum effects on child outcomes when it is extensive over time, includes family involvement, and includes communication between the early intervention program and the child care provider. Early intervention is hypothesized to interact with the effects of alternate child care, with the alternate care effects as the more powerful of the two influences.

Data will be collected on numerous aspects of the child’s and family’s involvement in early intervention programs. The content of the Individualized Family Service Plan (IFSP) will also be analyzed and the range of services noted. These revisions satisfy the concerns expressed by the original review panel and significantly strengthen the potential contribution of the work.

Concern was also expressed in the initial review about the appropriateness of the strange situation attachment measure for the theoretical model used in the study and for the sample of children to be studied. This measure has since been dropped from the research protocol. A new mother-child observational measure, in which three toys are presented in separate boxes, will be substituted. This observational situation seems more appropriate for the purposes of the study.

The first application included insufficient information concerning the characteristics of the sample. This section has been strengthened, though it still lacks detail. The potential for overlap between the disability and risk groups still exists, given that the main factor separating the groups is the agency from which they are recruited, rather than nonoverlapping subject criteria.

The original review suggested that more information would have been helpful concerning how certain research procedures (such as the play observation) would be adapted for children with physical disabilities. This was not addressed in the revision. And, although the revised application provides additional information justifying the choice of the Bayley Scales of Infant Development as a developmental outcome, this justification is still not strong, particularly given the ambiguity in administering the Bayley Scales to children with cerebral palsy and other physical disabilities.

The question in the initial review concerning the type of child care environment experienced by children with disabilities has been satisfactorily addressed, with the description of service systems that provide generic inclusive child care for children with disabilities and special health needs. Although the researchers plan to oversample families who have placed their
children in child care by 15 months of age, it is not clear what proportion of children with disabilities are in alternate care settings by that age. Information is needed on the use of child care settings in the Seattle area by children with identified disabilities at that early age.

Resources appear adequate for the project, and the researchers are well qualified to conduct the proposed study. The budget is very high, given the workplan.

Approval is recommended with sizable reductions in budget and contingent upon the researcher’s providing the Maternal and Child Health Bureau with data demonstrating that the number of children with disabilities and chronic illnesses being served in child care by 15 months of age is sufficient to constitute the sample for this study. This information is needed to assure that the study design can be implemented with a sample that meets the specifications of the power analyses.
Early Detection of Autism: Comparison of Three Screening Instruments

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Project Number R40MC00270

Project Period 7/1/2001-6/30/2002

Year 2010 Objectives
1.14, 16.14

Study Design
Observational

Time Design
Longitudinal

Care Emphasis
Noninterventional

Population Focus
Toddlers, Preschool-age children

Race/Ethnic Focus
White (non-Hispanic), African-American, Hispanic (Hispanic overall), Asian (Asian overall)

Priority Research Issues

Costs

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Summary

Statement of the Problem

Autism and related disorders (Pervasive Developmental Disorders (PDD)) are often life-long disorders of development, impacting social, communication, academic, and vocational functioning. It has been demonstrated that early intervention can substantially improve prognosis, but this requires early detection. PDD and autism are often not diagnosed until age 4 or 5 and diagnosis often follows parental concern about development by as much as 3 years. The current study is comparing the sensitivity and specificity of three parent report checklists that screen for PDD and autism and age 2. The study will apply these checklists to a large group of toddlers, performing developmental and diagnostic evaluations on those who fail any of the checklists. The entire cohort will be rescreened at age 4. Analysis will determine the best checklist or set of items to screen for PDD at age 2, with an emphasis on sensitivity and being user-friendly to parents. The goal of the study is to provide a simple checklist that can be disseminated for use in pediatric offices and that will significantly increase the accurate identification and referral for early intervention of children on the PDD spectrum.

Research Questions or Hypotheses
1) What are the screening properties (positive and negative predictive power, sensitivity, specificity) of the screening instruments to be assessed specifically for each instrument: (a) What is the proportion of children screened positive at 24 months who are positively diagnosed at 24 months; (b) What is the proportion of children screened positive at 24 months who are positively diagnosed at 42 months; (c) What is the proportion of children screened negative at 24 months who are positively diagnosed at 42 months; and (d) What is the proportion of all children ascertained to be autistic at 42 months who were screened positive at 24 months?

2) Is there an optimal combination of items from the three screening tests that would provide better screening performance than any test alone?

3) Are there family characteristics (SES, family structure), developmental assessment, or intensity of intervention variables that could predict change in status over time for children diagnosed with autism at age 2 years?

**Study Design and Methods**

The study is using a time series or longitudinal study design. Two-year-olds will be screened for autism/PDD. All children who fail the initial checklist will be re-screened by telephone, and children who still fail the checklist will receive a full diagnostic evaluation. At age 42 months, all of the children in the initial sample (N=33,000 minus those lost to followup) will be screened again. Children will be evaluated who: (a) received a diagnosis of autism/PDD at 24 months, (b) failed the screening at 42 months, or (c) were flagged by pediatrician at their 36 month visit as having possible PDD behaviors.

Screening instruments include: 1) CHAT Parent Report; (2) The Modified Checklist for Autism in Toddlers (M-CHAT); and (3)Yale Autism/PDD Screener. The Informed Consent Form indicates that the family will be called if the investigators have any questions or concerns about the checklist. When the family is called, they will be told that the researchers wish to clarify some of the answers on the checklist to make sure that they are accurate or to fill in missing information. The interviewer will then read the questions and the subtext as per the Telephone Codebook.

**Population Description and Sampling Plan**

The initial pool of participants will be 33,000 children, aged 24 months, and their families. These participants will comprise two groups: (1) 30,000 unselected patients of pediatricians, and (2) 3,000 children identified to early intervention programs as having developmental issues but no diagnosis. Based on our initial screening study and consistent with the prevalence of autism in the literature we expect approximately 200 children to need telephone follow-up of whom 75 will need to be evaluated, and 60 will meet criteria for Autistic Disorder or PDD. The second group of 3,000 participants will be children who have been referred to EI programs, drawn from the same geographic region. These children will have a range of developmental delays and disorders, from mild motor or language delay, to severe retardation, but will not have been diagnosed with autism or PDD, by a physician or psychologist. Thus, a total of 33,000 participants will be screened, with an anticipated 400 contacted by phone, and 150 evaluated, of whom 120 are expected to meet criteria for Autism/PDD. Since the project involves nonselective screening of 2-year-olds in a given geographic region, and involves pediatricians, pediatric clinics, and EI providers (who serve many minority families), the minority representation of participants is expected to be representative of the region sampled, including White, African-American, Hispanic, and Asian children. The gender distribution is expected to be approximately equal for children screened, but should be about 4:1 boys to girls for children referred for evaluation and for children found to have autism/PDD.

Ethnicity is not a focus of the proposed study but could be addressed in exploratory analyses.

**Analysis Plan**

The analysis plan will focus on estimating the positive predictive power for the three screening tests, and exploring the relation of various content domains on the three screening tests to diagnostic category based on the evaluation. The outcomes of the screening process will be compared in Spanish and English speaking participants through the use of log-linear models. Analysis of a more exploratory nature will examine whether combinations of items from the 3 screening tests might discriminate 4 groups (autistic, PDD-NOS, developmentally-delayed, and non-delayed). As we have done previously, discriminant function analysis (DFA) will be used to determine the best possible prediction of group membership from the
combination of unique screening items across tests, emphasizing sensitivity over specificity. Then, direct methods will be used to compare various cut-off values of the items identified through the DFA. Finally, this process will be repeated, and combined with signal detection, to attempt to improve prediction of autism/PDD against the other 3 groups combined.

**Pre-Award Evaluation**

**Evaluator 1**

**Originality and Importance**
This is a very interesting and readable proposal that clearly sets forth an important research agenda of addressing a very real problem in clinical settings that involve children with major developmental disorders. There is no argument that children with autism, and autistic spectrum disorders present a very challenging group for clinicians, parents, and educators. It is often discussed that such PDDs can be traced to early developmental origins, but actual accurate early identification remains an elusive goal. And as the PI suggests, such a goal is important given that it may well be the case that early identification and intervention results in substantially better prognoses than does later identification and intervention.

**Scientific and Technical Merit**
Beyond the sheer importance of the topic, there are a number of additional strengths to the proposed investigation. The PI makes a strong case for the beginning work that has been accomplished on the development of screening tools, and these investigators have begun a critical pilot examination of the M-CHAT qualities that might suggest that this screening instrument has the capacity to contribute to the solution of early and accurate identification. To date the data are encouraging, but the true validation work has yet to be accomplished.

The design and research plan seems well considered overall, and the measurements appropriately chosen to reflect the best assessments currently available. The PI has developed relationships with the Yale faculty related to the screening device developed at that site, and a subcontract is included that will enable collaborative effort toward the goals of this research. And not only will the research address comparative issues between the three screening tools, but the aim of determining the best set of items from among the three measures is a thoughtful one as well. The sampling plan is ambitious, and will result in sufficient numbers to provide some confidence in the results, and the plans to minimize sample attrition and sampling biases reflect a thoughtfulness in regard to methodological rigor.

There are a few issues to raise in the proposal. One area that could have been better developed is the conceptual basis for claiming that the earlier the intervention, the better the outcomes for children with Autism/PDD. Where is the evidence to indicate that children who can be identified by age two show substantially better developmental and behavioral competencies later than do children who are not identified until 4 or 5 years. These data would make a more compelling case within the body of the proposal for the need for early screening. Further, the PI suggests that 18 months is a goal for screening, and will be attempted in later studies. If 18 months reflects a more important standard, which the early intervention model discussed would assume, then its hard to understand why 18 months would not be the target age for this study. This is especially the case when the 1,300 child pilot study will already offer substantial knowledge about the age 2 years period.

It appears that all families who participate will complete all three of the screening devices at the two age periods. This is not directly stated that I could find, but it does appear to be what is suggested. Yet, there are some questions about such an approach. How much overlap exists between items ... there is some to be certain. The CHAT and the M-CHAT are exactly the same for the first 9 items. One might presume that the CHAT and the M-CHAT will not be given separately, but rather that the M-CHAT will be given alone because it is in fact the same as the CHAT measure through those first 9 items. Is there any methodological rationale to be considered for the order in which the measures are completed? Should these be counterbalanced in some fashion to protect against any biases that might be present from overlapping questions or other issues?

Pediatricians are asked to evaluate those children they see as part of a 36 month well child visit for any signs of Autism/PDD, and then to refer these children and their families to the project for evaluation. This seems like a good strategy, but what assurances are there that the pediatricians are sufficiently aware of PDD and its manifestations at age three.
How will comparability in understanding or information across pediatricians be assured so that children who are demonstrating such behaviors are appropriately referred? Also, will failure to attend well child visits at 36 months present problems for this data collection and identification strategy? What proportion of families complete these well child visits, and what are characteristics of families that typically do not?

Evaluator 2

Scientific and Technical Merit

This proposal has a number of interesting strengths. First, the PI and the assembled research team have a history of providing an innovative blending of large datasets, sophisticated data analyses, and theoretical models of child development. This proposal is no exception as the PI intends to collect a very large dataset regarding the possibility of using an early screening for detecting autism. Clearly, the strength of this proposal is the research team and it is reflected in the thoughtful manner in which this proposal has been put together.

Yet there are a few questions that could be better addressed by the PI. First, this project is based upon the assumption that early detection can lead to improved long-term outcomes. Even though the PI provides a half-a-dozen references to support this assumption, I would like to see further consideration of the issue in terms of effect size gains due to early intervention and/or some cost effectiveness studies. It may in fact be too soon for these kinds of considerations, but it seems to me that we must have some quantifiable estimate of the benefit that early screening could give, before we undertake a mission to identify these children.

Along this line, has the PI considered the possibility that intervention strategies may work better with those with the least severe cases of autism and/or PDD? Hence, it might be even more important to detect those children who are marginal or borderline cases, rather than those for which the case is very severe. In this case, it might be more productive to have a third "marginal" group, which falls in the gray area between severe autism and normality. It would seem that the PI sort of suggests this strategy (e.g. the false positives) but doesn’t follow up on this much.

I am a bit puzzled about the nature of the expectations of the study. Given that the MCHAT is embedded within the CHAT, isn’t it impossible for the MCHAT to do a worse job of identifying autism? If so, isn’t the main question simply one of trying to shorten the MCHAT without losing much in the way efficacy? If this is true, then the comparison of the CHAT with the MCHAT is a bit skewed in favor of the MCHAT, thus rendering this comparison a bit of a fait accompli. Whereas the data will be collected and this comparison can be done, it doesn’t follow that the context of administering the CHAD as a subset of the MCHAT won’t change the nature of how the sample responds to the CHAD items. This is particularly so since the PI has justifiably, in my view, changed the nature of the screening instrument in numerous methodologically sound ways. Nevertheless, the CHAD obtained will be, in many ways, much different than the CHAD administered independently of the MCHAT.

Another shortcoming is that the screening instrument is tied to the 2-year well--child visit to a child’s pediatrician. Whereas this is in some way imminently sensible, it also suggest the possibility of a selection bias of children seen as thus limits the generalizability of the study. For example, children who live in poverty may be less likely to be seen at the two year checkup in a peds office. Further, such children may have less educated parents and thus the use of the parent-report instrument may be less useful with these children because of parental differences in how they respond to the screening instruments. The PI has done a commendable job in creating both an English and a Spanish version of the instrument. But we do not know what the reading level of the instrument is rated at … and thus we may not know how this instrument would work outside the targeted population of children whose parents faithfully get them their 24-month physical.

Another issue that needs to be addressed is the ultimate effect of using an autism specific screening measure, rather than a more broad-based measure of developmental delays (e.g. the ITSEA, Carter). If it turns out that a better strategy is to screen for many different types of developmental disorders than for just autism, there is certainly possible that adding this instrument to other "screens" will make it less likely that any screening device will be practical enough to be administered … as part of a set. Nevertheless, this is not a terrible problem for this specific proposal … but it does suggest future difficulty in using the instrument as part of a typical well-child assessment.
The timing of the assessment gives one pause for concern. Because not everyone (or even anyone) will be assessed at exactly 24 months, the PI intends to use an age range ... again, a sensible thing to do. Yet also fraught with peril. The lower bound is 21 months which is only 3 months from the 18-month age which the PI suggests is not developmentally appropriate. Yet natural variability is likely to make more than a few 21 month-olds look like 18-month olds, and yet be otherwise normal. Likewise, the 27 month-olds are likely to be more noticeable in their delays than the 21 month-olds. The upshot of this is the strong possibility that we have a heterogeneous sample with respect to age, such that instrument may work much better for 27 month-olds than 21 month-olds. In fact, one could even hypothesize that their is a nice monotonic relationship between age and efficacy, even within the narrow window assessed here. Have the PI’s thought about evaluating this possibility?

Obviously, a major concern is the possibility of selection bias due to non-response to the follow-up mass mailing. Granted, the PI’s recognize this problem, and even report that in a pilot study, only 46% have actually responded. The real question that needs to be addressed is how the PI’s plan to handle this non-response.

Technically, there are a few issues that should be collected. The data collected from the screening instruments will not be at the ratio level of measurement, unless certain rare measurement structures happen to fit the data. Likewise, have the PI’s considered using logistic regression rather than discriminant analysis when developing their weighted composite? Logistic models have no normality assumption on the items the way that discriminant analysis does.

In summary, this is an impressive proposal put forth by an excellent research team. The issues raised above are important, but they do not in any way constitute fatal flaws in the project.

Evaluator 3

**Originality Importance**

This study addresses Autism and evaluates three instruments developed to facilitate early diagnosis. Given the incidence of autism, 1:300-1:500 and the effectiveness of early treatment it is critical to make a diagnosis and initiate treatment early. Studies have demonstrated effectiveness of early intervention in improving outcome. The development of a strong effective and efficient tool for diagnosis would significantly improve the early identification, initiation of treatment, and ultimately the outcome for patients with this disorder. The results of this study could be significant.

**Regional and National Significance**

Very little detail is provided with regard to significance nationally or regionally. Information is provided regarding the importance of early diagnosis and the contrast of parental first concern at 17 months versus average diagnosis at 4 years. A delay, which may impact outcome since early diagnosis and prognosis, can significantly improve prognosis.

**Scientific and Technical Merit**

Identifying an effective tool for early, accurate diagnosis of autism would be a significant event. This study proposes to compare three tools, the CHAT, the M-CHAT (modified checklist for autism in toddlers) and the Yale Autism/PDD Screen. Two studies are proposed. In the first they propose screening 33,000 2 year olds (30,000 unscreened and 3,000 from hi-risk sample referred for EI). Children screened positive will receive detailed clinical evaluations. The completion of a screen by families with confirmation of failure by phone interview constitutes a screen failure) Those who fail and agree will have a detailed evaluation to make diagnosis. Study two will reevaluate all previously evaluated children at 42 months. In addition, all 33,000 will be followed by asking pediatricians to identify those with possible PDD at 36 months and by mass-mailings of follow-up checklists to families at 42 months with detailed evaluation of all those who fail at 42 months.

Preliminary study assessed the CHAT and M-CHAT. The 57 children who failed the screens and were referred for detailed evaluation were also given the Yale Autism/PDD Screen to complete to allow comparison. Results from this preliminary study were encouraging re effectiveness of the tools, their consistency and their ability to positively identify those with autism. Unfortunately the time required to obtain the initial sample is not provided making it impossible to determine the length of time required to acquire a sample of adequate size. This would be useful in assessing the time needed to collect sample of 33,000.
The study states that they expect to need participation of 300 pediatric offices to secure adequate recruitment. A significant number given the fact that the preliminary study solicitation of all physicians resulted in only 98 participating. It would be important to more carefully outline recruitment strategies to help insure adequate enrollment numbers.

An additional concern has to do with procedures for participants. The application states that parents/guardians of all 24 month olds will be given the informed consent and the screening checklist by office staff and asked to fill them out in the waiting room or with the provider. While parents are told that participation is voluntary it is not clear how such voluntary participation is assured. In addition, no protocol describing office staff behavior and procedure with regard to screen distribution and consent obtainment is supplied. From both a study design standpoint but more importantly with regard to human subject issues such a protocol is a necessary part of this study. Completed screens will be sent to Uconn for eval and prior to contacting those families whose children have failed, the physician or EI will be called to request permission to contact the family. This is a strength of this proposal. However follow-up with the physician after detailed evaluation is not well described in the proposal. This is clearly a critical aspect of such a study.

Study two proposes to follow-up at 42 months the initial 33,000 screened including the expected 150 identified. It is proposed that physicians will be sent reminders about screened children in their practices as they approach their 36 month check-ups and docs are asked to assess theses children with regard to concerns of autism/PDD at their next well child care visit. It is unclear what criteria providers will use to make this assessment however those children whom they identify will be contacted by researcher and offered a detailed evaluation.

All families will also be sent a mailing with checklist and asked to complete and return in mailed envelope. Those that don’t respond will have notifications sent to PCP who will be asked to assess them at their 42-month check. Children who fail this screen will be offered detailed evaluation. Thus described is an ambitious, time consuming study, which requires good support and interaction with PCP offices.

Data evaluation seems reasonable. Initially however, no details are provided regarding the safety of data storage and assurance of confidentiality. This is made more important by the conflicting IRB info in the two face sheets given. If there is no IRB approval given the study’s timeframe it would be important to focus on this issue since a delay could significantly slow study especially given sample size desired. Specific issues regard the consent procedure. In addition, no exclusion criteria are discussed but one might suspect that certain bias or characteristics might influence staff distribution of the survey and consent.

Another issue is whether there is bias in the initial participation? Are there differences among families who initially choose to participate in the study for the PCP’s office? Of the surveys distributed – which families complete them and are they different from those who choose not to participate?

Of the instruments and materials provided – the telephone interview instructions are thorough and carefully written. Attention is paid to establishing clear pass and failure criteria for detailed evaluation.
Economic Impact of Breast-Feeding Promotion Intervention

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Project Number R40MC00198

Project Period 9/1/2000-8/31/2004

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Summary

Statement of the Problem

This study will investigate whether the provision of individualized pre- and post-natal lactation consultant services to low income women in the Bronx, New York results in: increased breast-feeding, healthier children overall, and for selected diagnoses, and reduced health care costs in the first 12 months of life. Professional, individualized breast-feeding assistance, including home visits is generally unavailable to low-income women, despite the fact that they are among the most effective breast-feeding promotion interventions. Data from this study will answer the question of whether the costs of such an intervention are offset by reduced health care costs of children who receive the intervention.

Research Goals and Objectives

Major Hypothesis:
* The economic benefits of intensive breast-feeding promotion interventions will exceed the economic costs of providing such interventions.

Supporting Hypotheses:
* The pre- and post-natal breast-feeding interventions will have a positive impact upon breast-feeding intentions, initiation, and duration.
* The pre- and post-natal breast-feeding intervention will be associated with reduced incidence and severity of "breast-feeding sensitive" morbidities (i.e., otitis media, gastrointestinal, and respiratory infections) among other conditions.

**Study Design and Methods**

We will conduct two concurrent randomized, clinical controlled trials to evaluate the economic benefits of pre- and post-natal breast-feeding promotion interventions. Participants will be recruited from two Montefiore Medical Center (MMC) community health centers that care for nearly 1,000 low-income women and their children who are at high risk for not initiating, or early cessation of breast-feeding. One site operates on a Family Medicine model, the other on an OB-Gyn model.

The interventions will consist of individualized face-to-face sessions with a trained lactation consultant, during the pre-natal period, and intensive post-partum support up to weaning or 12 months. The two trial sites will each enroll 170 women, respectively, evenly divided between intervention and control groups. Cost, breast-feeding practice, and health outcomes will be tracked for 12 months through 8 research interviews, and analysis of health center billing and encounter records. Health care costs for the intervention and control groups will be analyzed, as will differences in breast-feeding practice and child health outcomes. Concurrent trials allow us to: control for sites effects, increase generalizability, and capitalize upon economies of scale.

**Population Description and Sampling Plan**

The following description of the sample is drawn from the first 185 baseline interviews conducted:

- Age (mean): 24
- Race/Ethnicity:
  - Black - 37%
  - Puerto Rican - 31%
  - Other Hispanic - 16%
  - Other - 16%
  - Foreign born - 37%
- Education
  - <12th grade - 32%
  - HS or GED - 20%
  - College (some/all) - 38%
- Parity
  - 0 - 40%
  - 1 - 33%
  - 2+ - 25%

**Analysis Plan**

General descriptive statistics will be generated for all variables, both in aggregate, and by treatment group. Bivariate analyses will determine the appropriate variables to be entered into a multivariate regression analysis to determine the predictors for our main hypotheses. Costs associated with the intervention will be assigned based upon detailed logs maintained by the Lactation Consultants, which disaggregate patient care, administrative, and research time. A cost-offset analysis will determine whether the costs of the intervention are offset by the (hypothesized) reductions in health care utilization and costs of the group receiving the LC intervention.
Pre-Award Evaluation

Evaluator 1

Originality and Importance
This is an improved application on a subject of importance and priority by MCHB as well as unique in the sense that combines several successful strategies and will measure the economic impact (benefit) of such intervention for promoting breastfeeding.

Regional and National Significance
Both the intervention (if successful) and the cost analysis will serve to model programs including the WIC Nutritional Supplementation

Scientific and Technical Merit
Statement of the Problem
It is much clearer in this proposal since there is baseline information on the population to be studied. The impact of breast-feeding on infant health outcomes are defined as "breast-feeding sensitive morbidities." An estimate of costs savings is also included when comparing exclusively breast-feeding vs. formula feeding.

Hypotheses and Qualifications of Variables
This is a hypothesis driven randomized intervention trial. Variables are defined and respond to the hypotheses.

Concepts
Concepts are well defined and pertinent. Breast-feeding patterns are categorized by percentage of time and dosing. Among the "breast-feeding sensitive morbidities, there are 3 that need further definition: 78.0 disease due to vir/chlam, 79.0 viral /chlam infection and 79.9 u viral /chlam infection. If these three conditions include chlamydia infection, they are either ophtalmic or in the genital tract. (?)

Study Design
Because the participating sites respond to different health care models (Family Practice vs. OB/GYN/Peds) they increased the sample size to determine per site analysis in response to the prior review and this is an improvement.

The Sampling plan is well described an although acknowledging potential within site contamination (Hawthorne effect) they are taking in consideration neutral non-judgmental language and emphasis upon confidentially of interview responses. In addition, the factors that account for the initiation and maintenance of BF are complex and less responsive to just waiting- room interactions among participants.

The amount of $847,588.00 is requested for 4 years of funding.

In summary, this is a much-improved proposal that will impact upon health care practices and policies for breast-feeding promotion interventions.

Evaluator 2

Scientific and Technical Merit
As this is a revision of a previously approved yet unfunded project, only those issues that the committee raised while stipulating to the obvious strengths of the proposal will be considered here.

First, the PI should be complemented for it has been quite responsive to the suggestions of the committee. It is agreed that the PI's lack of concern of possible contamination of the control group at each site in rational. In fact, if it were as simple as
being introduced to an enthusiastic mother to both initiate and maintain BF practices, there would be no necessity for this grant.

The PI has expanded the list of exclusions to include those with medical complications which might contraindicate BF. The PI also addresses the need to consider adjusting local costs in order to get a better estimate of national savings. Further, the PI intends to address possible site effects by expanding the size of the study to compare the effects of the intervention by site, which will compare the OB/GYN/Peds model to the Family Meds model, which is a much needed addition. Likewise, some issues of data analysis were clarified.

A few issues remain a bit up in the air. For example, the PI agrees that making certain variables into categorical variables should be corrected. Yet other important risk factors remain dichotomized. For example, the PI intends to create a variable which indicates the number of siblings as either 0 or more than 1. Yet is reasonable to assume that the constraints on a mother's time is not a constant factor when comparing having 1 sibling to 2 siblings, or 3 or 4, etc. It seems perfectly plausible that there should be a dose-response effect, in which the more siblings one has, the more constraints on the mother's time, at least up till a certain number. Dichotomization of this construct would seem the throw away the potential information in this variable. The same thing could be suggested for when the mother returns to work, in which the exact time would be a preferable measurement to just within 6 weeks or not.

One additional issue should be addressed. Waiving parent/guardian consent for mothers less than 18 years of age is potentially problematic. Whether or not the study is minimal risk, or not, has never been the issue when considering the need for parental consent. As a general rule, waiving parental consent must turn on considerations other than the low risk of the study. It is not clear, in this circumstance, that the PI has made of case of why NOT obtaining parental consent would be particularly necessary.

In summary, this is a very strong proposal that should be funded. The only major concern remaining is the issue of parental consent.
Effect on Breastfeeding of Pacifiers and Bottle Feeding

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Project Number R40MC00063

Project Period 10/1/1996-9/30/2001

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Summary

Statement of the Problem
Healthy People 2000 goals state that 75 percent of women will initiate breastfeeding and 50 percent will continue to breastfeed at 5–6 months. Currently, about 59 percent of women initiate breastfeeding and as few as 20 percent are still breastfeeding at 6 months. Proper sucking technique is believed to be critical in establishing breastfeeding and preventing early breastfeeding problems. Observational studies of pacifier use indicate a possible association with shorter breastfeeding duration; however, the effects of pacifier use and artificial nipple use during bottlefeeding or breastfeeding have not been evaluated using rigorous scientific methods. Given the numerous health benefits of breastfeeding, scientific investigation of the effect of early artificial sucking experiences on the ability of newborns to successfully breastfeed is of profound relevance and importance to maternal and child health in the United States.

Research Questions or Hypotheses
The specific aim of this study is to minimize obstacles that prevent the successful establishment of breastfeeding. This
study is designed to ascertain the effect of artificial nipple experiences (pacifier use and bottlefeeding) on the successful establishment of breastfeeding. Interaction between exposure to artificial sucking experiences and successful breastfeeding are hypothesized to occur, placing infants who experience both early pacifier use and bottlefeeding at highest risk and those exposed to later pacifier introduction and no supplemental feeding at lower risk for adverse outcomes.

The specific hypotheses addressed by this study are as follows:

1. Early pacifier use (within 2–5 days of birth) compared to no pacifier use by breastfed infants is associated with reduced breastfeeding duration and increased breastfeeding complications during the first month of life. Specifically, it is hypothesized that early pacifier use (a) decreases the duration of exclusive breastfeeding; (b) decreases the duration of overall breastfeeding; (c) increases the incidence of maternal breastfeeding complications including nipple trauma and engorgement; (d) increases the incidence of infant breastfeeding complications, including increased postnatal weight loss, increased time until birthweight is regained, and incidence of feeding-related hyperbilirubinemia; (e) decreases the chances that the mother will attain her personal breastfeeding goal; and (f) increases the incidence of early supplemental feeding during the first 2 weeks of life.

2. Early pacifier use (within 2-5 days of birth) compared to late pacifier use (after 4 weeks of life) by breastfed infants is associated with reduced breastfeeding duration and increased breastfeeding complications during the first 6 months of life. It is hypothesized that early pacifier use (a) decreases the duration of exclusive breastfeeding; (b) decreases the duration of overall breastfeeding; (c) increases the incidence of maternal breastfeeding complications including nipple trauma and engorgement; (d) increases the incidence of infant breastfeeding complications, including increased postnatal weight loss, increased time until birthweight is regained and incidence of feeding-related hyperbilirubinemia; and (e) decreases the chances that the mother will attain her personal breastfeeding goal.

3. In breastfed infants who require early supplemental feedings, bottlefeeding as compared to cup feeding is associated with reduced breastfeeding duration and increased breastfeeding complications. It is hypothesized that early supplemental bottlefeeding in breastfed infants (a) decreases the duration of exclusive breastfeeding; (b) decreases the duration of overall breastfeeding; (c) increases the incidence of maternal breastfeeding complications including nipple trauma, engorgement, early breastfeeding cessation (while in the hospital), and longer postpartum length of stay; (d) increases the incidence of infant breastfeeding complications, including increased postnatal weight loss, increased time until birthweight is regained, increased incidence of feeding-related hyperbilirubinemia, lower rates of full breastfeeding at discharge, and increased rates of required early followup (within 48 hours); (e) decreases the chances that the mother will attain her personal breastfeeding goal; and (f) increases the incidence of early supplemental feeding, increasing the numbers of supplemental feedings required in the hospital and during the first 2 weeks of life.

**Study Design and Methods**

This randomized, single-blinded, clinical trial seeks to evaluate the effects of artificial nipple exposure in breastfed infants on the incidence of breastfeeding complications and breastfeeding duration. Healthy breastfed infants of participating women will be randomized to two pacifier study groups: (1) Pacifier use beginning after hospital discharge (within 2-5 days of birth) or (2) pacifier use beginning during the fifth week of life. Participating infants who require supplemental feedings as part of their newborn care will be randomized to the supplemental feeding intervention. Supplemental feedings will be administered by cup or bottlefeeding. Interviews conducted during postpartum hospitalization, feeding observations, chart reviews, and 6 months of prospective followup will be used to ascertain differences in breastfeeding complications and duration.

**Population and Sampling Plan**

Pregnant women will be recruited prenatally to participate, and informed consent will be obtained. Approximately 20 percent of the women participating in this study are being recruited from minority and/or impoverished populations.

**Analysis Plan**

Descriptive statistics will be prepared, and normality of continuous variables will be checked. Comparability of the intervention groups will be analyzed using the chi-square test, Fisher’s Exact Test, Student’s t-test, and the Wilcoxon test as appropriate. Variables for the comparison will be prespecified. Three primary outcome comparisons will be made: (1) The effect of cup feeding versus bottlefeeding on the duration of breastfeeding among those who required supplemental feeding
while in the hospital; (2) the effect of early versus late pacifier introduction on the duration of breastfeeding to 6 months; and (3) the effect of early versus no pacifier introduction on the duration of breastfeeding to 1 month (early group versus the late group in which pacifier use does not begin until the fifth week). Survivorship methods including the Kaplan-Meier regression model and the Cox proportional hazards model will be used to adjust for possible confounding variables. Secondary analyses will examine the effects of both interventions simultaneously.

**Pre-Award Evaluation**

**Evaluator 1**

*Originality and Importance*
Rates of breastfeeding initiation and continuation are disappointingly low in the United States. This project is designed to address one reason for poor continuation of breastfeeding: "Nipple confusion," brought about by the early (in the first few days of life) introduction of pacifiers and/or bottle feedings. The investigators postulate that under these circumstances an infant learns improper sucking techniques, which interferes with breastfeeding. The infant is then less able to empty the breast effectively, which may lead to difficulty in establishing an adequate milk supply or other complications. When this happens, the infant may be given more supplemental feedings, which may only exacerbate the problem, leading to early cessation of breastfeeding. This biological mechanism makes intuitive sense and is in accord with clinical experience.

*Regional and National Significance*
The United States is far from achieving the Surgeon General's targets for breastfeeding initiation and duration, and the trends are actually worsening. Research that might improve breastfeeding success is important to public health and Maternal and Child Health Bureau (MCHB) goals. Therefore, this project has regional and national significance.

*Scientific and Technical Merit*
The proposed randomized, factorial design is the appropriate experimental procedure for testing the investigators' hypotheses. Randomization will be stratified by insurance source to ensure that differences in socioeconomic status are accounted for in the treatment groups. The research design is attractive because it requires minimal interference with usual practices (only half of the parents will have to delay the introduction of pacifiers, and alternative ways of comforting their infants will be provided). No change in parental behavior is required for the bottle/cup portion of the study, because this applies to supplemental feedings given by hospital staff.

It is important to remember that there are numerous other reasons for early cessation of breastfeeding. These include lack of cultural support for breastfeeding, lack of adequate maternity leave, lack of child care at or near the workplace, and lack of facilities for pumping breast milk in the workplace. These other reasons may be as or more important than "nipple confusion," and the investigators must detect an effect of their treatments within this generally unsupported milieu. Power calculations are provided, but unfortunately no data are provided to support the expected differences described for the supplementation or the pacifier. This renders these calculations less persuasive than they could be.

It is not clear why secondary analyses are required for investigating the postulated interactive effects. Such effects can be obtained as part of the overall data analysis strategy by simply categorizing the infants by their exposure to supplemental feeding and the type of supplemental feeding (nested design).

The single-blinding is questionable. How can the interviewer be blind when the subjects are asking questions about supplemental feeding and breastfeeding? The sample size is well-justified. However, crossover may decrease the expected differences among the supplemental feeding groups and early and late use of pacifier groups.

The research will be carried out in a community hospital with 2,800 deliveries each year. This hospital includes a high proportion of women who deliver healthy infants and choose to breastfeed them. The data collection forms are already available. The principal investigator has developed these for another ongoing research project; thus, no investment is needed for their development.

The principal investigator, Dr. Cynthia Howard, is a pediatrician with additional training in public health. The other members of the proposed staff are well-qualified for their roles.

The personnel commitment for the statistical analysis seems excessive for a project that is essentially a chart review plus several brief telephone interviews to ascertain whether and to what extent breastfeeding is continuing. Similarly, the personnel commitment for "vision" and general "consultation" seems excessive.

There are no concerns regarding the use of human subjects. Subjects will receive normal pediatric care. Those instructed to
delay the introduction of a pacifier will receive instructions in comforting a crying baby. This study has a plausible, biologically based hypothesis and an appropriate, realistic design. Study findings will likely lead to a change in hospital practice and how parents are counseled about comforting their infants. These changes may result in an improvement in the duration of breastfeeding. The major weaknesses of the study are the excessive budget and the lack of persuasive power calculations. Nevertheless, the recommendation is for approval.
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Project Number  R40MC00177

Project Period  1/1/2000-12/31/2002

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Summary

Statement of the Problem

Contemporary early intervention services, guided by Part H of the Individuals with Disabilities Education Act (IDEA) (renamed, Part C of the re-authorized IDEA), are designed to enhance the responsiveness of the caregiving environment in a way that is assumed to have an impact far beyond the early intervention experience. Little longitudinal research has been conducted to evaluate the relations among services provided in early intervention programs, and child and family outcomes during the adolescent period.

Research Questions or Hypotheses

The broad project goals are to: (1) locate key points of change, and potential points of intervention, in the developmental trajectories of children and families between early childhood and adolescence; (2) focus on the differential impacts on maternal and paternal well-being and on the particular roles of fathers in parenting an adolescent with disabilities; and (3) examine the relation between adolescents with disabilities and the health care system. The study also aims to elucidate
predictors of long-term vulnerability and resilience among recipients of early intervention services in order to inform policy decisions regarding long-term service planning for children with special health needs and their families.

**Study Design and Methods**

This study is a continuation of an observational, prospective, noninterventional, longitudinal investigation funded by the Maternal and Child Health Bureau: MCJ-250644, Early Intervention Collaborative Study: Age 10 Follow-Up (July 1, 1994 through June 30, 1997), MCJ-250583, Early Intervention Collaborative Study: Preschool Phase (April 1, 1989 through Dec. 31, 1993) and MCJ-250533, The Early Intervention Collaborative Study: Phase One (Jan. 1, 1986 through June 30, 1989). Seven waves of in-home and school-based assessments have been completed for an initial sample of 190 children and families from their entry into an early intervention program (mean age 10.6 months) through age 10. Early study outcomes included aspects of children's cognitive and social development and family adjustment. Follow-up home-based child and family assessments and school-based data collection are being conducted at age 15. Core adolescent outcomes included three aspects of social competence: social connectedness, autonomy, and efficacy. Core family outcomes include four aspects of parent well-being: depressive symptoms, parenting stress, parent-child relationship, and perceived senses of competence as a parent.

**Population and Sampling Plan**

The sample is comprised of 148 children who had early developmental delays or disabilities (Down syndrome, motor impairment, or developmental delay of unknown etiology) and their families who received early intervention services from community-based programs in Massachusetts and New Hampshire between 1985 and 1991. At age 10 (the last data collection point for which we have complete data), 62.2% were mentally retarded. The majority of the participating families are Euro-American (92.5%); 36.9% of families have income below the U.S. median; 62.8% of mothers are employed. Race or ethnicity is not a focus of this project. At age 10, 90% of the children received special education services. The mean cognitive composite at age 10 (on the Stanford-Binet Intelligence Scale) was 63.0 (SD=30.2) and the mean adaptive behavior score (on the Vineland Scales of Adaptive Behavior) was 52.3 (SD= 21.8).

**Analysis Plan**

The main approach to the analysis of this longitudinal data set will be based on hierarchical linear modeling (HLM). First, baseline models will be developed to determine the shape of the overall trajectory in measures of children's development and parental well-being. Next, explanatory models will be developed to test specified hypotheses about predictors and moderators of development in children and change in parental well-being over the entire 15 year study period. Finally, structural equation models will be employed to test the proposed overall conceptual framework.

**Pre-Award Evaluation**

**Evaluator 1**

**Originality and Importance**

This project seeks funding for its Phase IV investigation into adolescence of a cohort of children and families who participated in the EICS. The proposal represents the next logical step in the longitudinal research related to the EICS program by this investigative group. The worth of the research overall is dependent upon the longitudinal questions that are involved. Importantly, little research has addressed the adolescent period to which the EICS now will turn its attention.

**Regional and National Significance**

The EICS has been a premier research program supported by the Maternal and Child Health Bureau, and the volume and quality of the work that has emerged from this study speaks to its significance. The proposed work will begin to fill an important void in the field of developmental disabilities, magnifying the national significance of this project.
**Scientific and Technical Merit**

There are several strengths apparent in this work. The sample remains intact and the sample subjects are interested in continuing their involvement. The availability of nearly 140 children and their families is an incredibly valuable resource that could not be easily duplicated. The investigators have articulated a conceptual framework that guides their choice of measurements. The framework offers a number of intriguing possible explanations of competence and well-being outcomes, the measurements appear well selected to represent reliable indices of the constructs of interest, and the basic data analytic strategies to be employed are appropriate to questions at hand. Finally, the Project Manager continues to be a staff member present from the inception of the EICS. The investigative team is exceptional and there is little doubt that excellent work will continue to emerge from this ongoing investigation.

The hypotheses reflect a rich use of the data available from earlier data collections in the project as well as the data to be collected in this phase. The research focus that addresses developmental trajectories of the adolescents with developmental disabilities incorporate an array of mediated relations and growth trajectories that can be explored and provide a more comprehensive view of the processes that are likely involved. The same is true for the second focus on parents and families. Lastly the research focus on health status of the adolescent remains a particular strength of the work to be accomplished.

Attrition will influence study power and the analysis plans, but does not suggest that the work cannot be accomplished. The plan is now 10%, which seems reasonable given the level of involvement families have had with this project. The PI also presents strategies for re-contacting, re-acquisition, and maintenance of the sample.

Discussion about the characteristics of the available sample families, particularly in relation to fathers and siblings, suggest that a sufficient number of fathers and siblings are available for study. Also, plans are made in the procedures for collecting questionnaire data so that information between parents will not be shared (eliminating possible collusion), and the PI presents a table in which the measurements and their formats are listed.

Finally, the PI has added a teacher report index of children's social competence. This will obviate the issue that all the child assessment data came from a single source ('within family').

The principal investigator, along with the rest of the team, is exceptionally well qualified to conduct this work. They have worked together productively for some time and will no doubt continue to do so.

The budget seems appropriate to the work scope.
Enhancing Breastfeeding Duration in Premature Infants

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Boston Medical Center Corporation

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Project Number R40MC00252

Project Period 7/1/2001-12/31/2003

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Summary

Statement of the Problem

Breastmilk is the optimal form of nutrition for all babies. Unfortunately, the families who would most benefit from the "health, nutritional, immunologic, developmental, psychological, social, economic, and environmental benefits" of breastfeeding practice it least. Breastfeeding rates in the US fall well short of stated goals and wide disparities exist along predictable socioeconomic and racial lines. For premature infants in the Neonatal Intensive Care Unit (NICU), the health benefits of breastmilk are even more crucial than for term infants. Specifically, breastmilk protects against a host of infections, including necrotizing enterocolitis (NEC), an often-fatal illness that occurs most commonly in premature infants. Breastmilk aids digestion and absorption of nutrients, assists gastrointestinal function, and protects against sepsis and meningitis. It also improves visual function and enhances neurocognitive development. Unfortunately, breastfeeding a premature infant is a complicated, sometimes overwhelming proposition. Programs are needed to increase support for mothers who choose to provide breastmilk for their high-risk infants.

Boston Medical Center (BMC) is an inner city teaching hospital where the majority of patients are from poor minority
backgrounds. BMC is also a UNICEF/WHO designated Baby-Friendly hospital which indicates an effective commitment to supporting and promoting breastfeeding. One intervention which has been shown to work to increase breastfeeding duration rates among minorities and impoverished women is peer counseling. Peer counseling programs train and employ women from the community, who share a similar social and cultural background with the new mother. The purpose of this study is to determine if the use of peer counselors in the NICU setting will increase breastfeeding duration rates among premature infants.

**Research Questions or Hypotheses**

Primary hypothesis: Impoverished women who are supported by peer counselors will be more successful at breastfeeding their premature infants than women who are not supported by peer counselors. By providing peer counselors, we will increase breastfeeding duration rates among premature infants from low SES backgrounds.

Secondary hypotheses: Women who receive peer counselor support will exclusively breastfeed their premature infants longer than women who do not receive peer counseling.

We will be able to delineate determinants of breastfeeding among women in our study beyond what has already been described in the literature.

**Study Design and Methods**

The study is a randomized clinical trial conducted in the BMC NICU. Research assistants will enroll 242 infants and their mothers within 72 hours of birth. Infants will be stratified into two groups based upon gestational age. Infants and mothers will be considered eligible if they meet the following criteria:

1) Consent to participate;
2) Mother with intent to breastfeed and medical clearance to breastfeed;
3) Mother's age > 18 years;
4) Infant's gestational age >26 or <37 weeks;
5) Infant is AGA or LGA;
6) Mother speaks English, Spanish, or French Creole;
7) Infant has no congenital abnormalities (for example, trisomies, cleft lip/palate);
8) Mother has no intention of giving up the baby for adoption and infant is not in custody of Department of Health and Human Services; and
9) Mother is not incarcerated.

At the time of enrollment the research assistant will complete the Enrollment Questionnaire to obtain the following information:

1) Mother's ethnic background, place of birth, age, educational status, other children, insurance status, language spoken, and marital status;
2) Infant's date of birth, type of delivery, gender, birthweight, gestational age, and Apgar score; and
3) Determinants of breastfeeding including previous experience with breastfeeding, social supports, employment history, cultural beliefs about breastfeeding.

After enrollment is complete, the research assistant will open a sealed envelope indicating whether the mother has been assigned to the intervention or control group. Randomization will be done using a computer generated list of random numbers.

Mothers in both the intervention and control groups will receive the following:

1) Breastfeeding help from the postpartum and NICU nurses;
2) Access to any one of four breastfeeding rooms at BMC;
3) Access to breastfeeding classes offered three times a week;
4) Access to the lactation consultant;
5) Access to the video, You Can Make the Difference, which gives instruction and support about kangaroo care aimed specifically at minority and low socioeconomic mothers;
6) Access to a double set-up, electric breast pump which will be paid for either by the family's health insurance or by Pumps for Peanuts; and
7) A gift certificate to a local supermarket for participation in the study.

Mothers in the intervention group will also receive peer counselor support. The peer counselor will:
1) Meet with the mother in person within 72 hours of birth in order to: (a) help the mother initiate breast pumping and educate the mother in the technologic aspects of breast pumping; (b) discuss the You Can Make the Difference video (kangaroo care) with the parents; (c) discuss the benefits of breastmilk in lay terms; and (d) help parents feel more at ease in NICU setting.

2) Have contact with the mother weekly for six weeks. This time frame was chosen as it is the average length of stay for premature infants in our NICU. The contact may occur out of hospital if the infant is discharged. During the contact the peer counselor will provide support and technologic assistance regarding breastfeeding.

At the time of enrollment, the 242 infants will be stratified into one of two groups: >26 weeks - <32 weeks or >32 weeks - <37 weeks. Stratification by gestational age is necessary because prior to 32 weeks suck/swallow coordination is not developed. This is a major confounding variable which is better controlled for by stratification rather than during analysis. Since viability prior to 26 weeks is approximately 50%, we choose not to enroll infants until 26 weeks, when viability increases to approximately 80%.

The principal outcome will be breastfeeding rates at 4, 8 and 12 weeks post-birth. Breastfeeding will be defined as intake of any amount of breastmilk.

**Population Description and Sampling Plan**

In 1997, 1,569 women gave birth at BMC. Race distribution for those women was 53% black, 23% Hispanic, 14% white and 10% other. Of the 1,569 births, 217 (13.8%) were low birth weight and 233 (14.9%) were preterm.

Recruitment is based upon the following sample size calculations. Preliminary data indicate that current breastfeeding rates at 4, 8, and 12 weeks post birth are 30%, 20%, and 10% respectively. We estimate that in the intervention group breastfeeding rates at the same monthly intervals will be 70%, 50%, and 40%. This is based upon our preliminary data with full-term infants at BMC and the literature about the effectiveness of peer counselors. Assuming an alpha of .05 and a power of 80%, the sample size necessary at 4 weeks is 58, at 8 weeks 92, and at 12 weeks 78. Because we have two groups (stratified by gestational age) we need a final sample size of 184 (92 x 2) infants. In order to ensure a final sample size of 184 we have made the following assumptions:

1) Survival in the younger gestational age group will be 80%;
2) Survival in the older gestational age group will be 90%; and
3) Follow-up at 12 weeks will be 90%.

Hence, in the younger gestational age group we need to enroll 128 infants (80% survival and 90% follow up) and in the older gestational age group 114 infants (90% survival and 90% follow up). Our enrollment will total 242 infants.

**Analysis Plan**

Data analysis will follow the guidelines established by the Standards of Reporting Trial Groups. The 32-item checklist will be used by the principal investigator when the report of the randomized control trial is prepared. The following content areas will be addressed: (a) participant assignment; (b) masking; (c) participant follow-up; and (d) data analysis. Data analysis will proceed in the following manner:

1) Data entry will occur throughout the study;
2) After half of the families have been enrolled, eligible families who do not agree to participate will be compared to those who do agree to participate with respect to baseline variables in order to ensure that no systemic sampling bias has occurred. This bears on the generalizability of the study results.
3) At the conclusion of study enrollment summary statistics will be calculated. Families who agreed to participate will be compared to those who did not with respect to available baseline variables and intervention families will be compared to control families.
4) At the completion of the study, analyses will determine if the intervention and control families are still equivalent with respect to sociodemographic variables as well as potential confounding variables such as ethnicity, parity, history of breastfeeding, etc. It is expected that the distribution of these variables will be similar in the four groups (2 intervention, 2 control stratified by gestational age) because of random allocation, sufficient sample size, and a minimal drop out rate.
5) The major dependent variable will be the rate of breastfeeding at 4, 8, and 12 weeks chronological age. Breastfeeding will be defined as an infant receiving any amount of breastmilk. If the control and intervention groups are equivalent, a chi square analysis will be used to compare the rates of breastfeeding. If the groups are not equivalent than multiple regression techniques will be used to control for any potential confounding variables. Separate analyses will be conducted for the two
gestational age groups.

**Pre-Award Evaluation**

**Evaluator 1**

**Originality and Importance**

This study seeks to identify strategies to enhance breastfeeding in premature infants, a practice that has been shown to have significant benefits but is all too often interrupted especially among NICU infants. Breastfeeding is considered the optimal nutrition with significant benefits for premature infants. This study focuses on the exploration of strategies to enhance breastfeeding in the particularly vulnerable NICU population. Specifically this study seeks to explore the utility of peer counselors in increasing breastfeeding rates in this population. Other factors associated with breastfeeding success including access to quality breast pumps and education regarding kangaroo care are also explored. The MCHB Title V and Healthy People 2010 both identify breastfeeding as a priority objective. This studies attention to impoverished mothers whose infants are disproportionately represented in NICUs is also responsive to current initiatives and efforts to decrease racial disparity.

**Regional and National Significance**

Enhancing breastfeeding practice is a goal identified by multiple stakeholders and this project represents an opportunity to identify strategies for expanding the practice particularly among premature infants who receive substantial benefit from breast milk. When considering results of this study it will be important to consider facility factors such a ‘baby-friendly status’ which by themselves have been demonstrated to increase breastfeeding rates. Research by the PI has documented this finding. Therefore facilities seeking to increase breastfeeding rates would probably experience similar benefit from adopting the practices of the Boston Medical Facility. These features may also dampen somewhat the rise in breastfeeding one might expect from this study since baseline rates are already increased. Factors to consider in final evaluation.

**Scientific and Technical Merit**

This application has been revised to respond to the comments made by previous reviews and is much improved from these efforts. The majority of concerns raised previously focused on the study design and tools involved. Particular attention will be paid to these changes.

The enrollment questionnaire has been expanded to include an additional 21 questions aimed at exploring the social and emotional issues which might influence a mother’s breastfeeding choice. From the application it is not clear how these questions were chosen or developed. The inclusion in the application of some discussion specific to question selection would be of use. The literature review provides some information but more detailed description would be of use.

Several concerns of reviewers were addressed through the revision of the Boston Medical Center NICU Breastfeeding Peer Counseling Manual. Particular among these was a concern regarding telephone follow-up efforts of peer counselors and research assistants. With regard to peer counselors, if the mother and counselor miss a face-to-face interview the peer counselor will call the mother daily for a week and conduct a phone interview once connected. However, if after daily phone calls for a week following the scheduled encounter there is no contact, the mother will be removed from the study. What remains unclear to this reviewer is the initial 72-hour post birth requirement. The research assistant and subsequently the peer counselor are both required to meet with the mother within 72 hours post birth, if this is not accomplished I would assume that enrollment would not proceed. This close time frame might lead to some confusion or conflict so warrants monitoring.

With regard to the research assistant, if there is trouble contacting the mother at any of the designated 4,8, and 12-week points, the research assistant will continue to call on a daily basis for one week. When reached, the mother will be asked to recall practices performed on the exact day that feeding data was to have been collected. The author suggests that this should not introduce significant recall bias since the primary question addressed in this study is any amount of breastfeeding. The 4 levels of breastfeeding, breastfeeding exclusively, more breast than milk, more milk than breast and no breast milk will augment information but should only contribute to minimal bias since confusion would be expected on the middle to levels which both involve some breastfeeding.
With regard to a change in medical status of a NICU infant, if the infant is placed on IV feeds, the research assistant will record the type of feeding given on the last day of oral intake and make note of this adjustment. How this will be addressed statistically is not as clear and will be significant if numerous infants experience this change. In addition, recording of specific health factors would be useful in assessment of medical factors, which might interfere with breastfeeding.

With regard to data collection, in response to about maintaining masking of research assistant with regard to group, the study design was revised to designate one assistant responsible for the collection of data at 4, 8, and 12 weeks who will have had no other contact with the study. In addition the research assistant will read the statement “It is important that I do not know which study group you are in. Please try to only answer the questions asked without mention of which group you were assigned to” prior to the initiation of data collection.

This reviewer continues to have questions regarding the addition of kangaroo care component to this study. While of documented benefit, it is not altogether clear how accurately one might assess its influence particularly as it is proposed in this study. Perhaps it might be clearer and less confusing if assessment of the practice rather then its frequency of use would be sufficient.

In reviewing this proposal there was one issue of concern not well addressed. A recent Lancet article was cited which showed benefits of peer counseling greatest with more face-to-face meetings. While the proposed study notes this finding the only plan is to document face-to-face versus phone contact and see if there are any differences. It would be useful to pay more particular attention to this issue and monitor for similar findings, which might suggest increasing face-to-face contact to maximize the benefits of peer counseling.

Evaluator 2

Scientific and Technical Merit

This revised application, again reflected the recommendations made by a prior review. The goal is to increase the breast-feeding duration rates among mothers of premature infants and to study the determinants of such in low-income mothers. A randomized control trial of 242 mothers of premature infants from 26 to 37 weeks GA, which will offer standard care or standard care plus a peer counselor is proposed.

The major clarifications in this application relate to the definitions of Breast Feeding: exclusive BF, mostly BF with some formula, mostly formula with some BF and exclusive formula.

Clarification in the process of contacting participants through phone included the removal of the study participant if no contact was achieved in one week.

The intervention groups will be assigned a peer counselor who will contact the mother before her discharge and will continue weekly contacts for 6 more weeks. The counselors will attend a 5-day Breast feeding course and will be expected to pass an exam with 80% of higher.

Because all mothers receive incentive intervention to initiate breast-feeding, the mayor focus of this study is the provision of peer support to enhance the continuation of breast feeding within the context of a pre-term infant admitted to a NICU for which the duration of stay might be for several weeks.

The Principal Investigator, Dr. Philips is recognized as a national breast-feeding leader who contributed to her hospital being recognized as a baby friendly hospital by the WHO/UNICEF. She has extensive experience in the field and can carry out this study without major difficulties.

This study’s relevance corresponds to MCHB priority (14) inasmuch as the determinants for breast-feeding pre-term infants will be measured as part of an intervention trial. The health benefits of Breast Feeding are many and the potential benefits to pre-term infants and their mothers warrants this intervention trial’s funding.
Evaluator 3

Originality Importance
This is a relatively original study, blending breastfeeding and the special circumstances involved in feeding premature infants. Increasing the rates at which premature infants are fed breast milk could have important consequences for the health and development of these high-risk neonates. In addition, the study will be carried out in a hospital that serves predominantly poor, minority families, families that are less likely to initiate and maintain breastfeeding. The study builds on extensive experience and research from around the world on interventions to increase rates of breastfeeding. The particular intervention they are testing, peer counselors, apparently has been tried successfully with mothers of full-term infants, but not with mothers of premature babies. They estimate a cost of about $105 per mother for seven face-to-face contacts between mother and counselor. This is a modest cost intervention relative to the overall cost of caring for a preterm infant, and thus is possible to be considered for replication if successful.

Regional and National Significance
Increasing breastfeeding rates is a national goal described in Healthy People 2010. Studies to improve these rates among a variety of families of varying sociocultural circumstances are a research issue identified in the MCHB Research Agenda. Identifying practical methods to increase breastfeeding among the populations targeted by this investigator would be of national significance.

Scientific and Technical Merit
As proposed, this is a doable research project. Its success relies heavily on the participation of mothers who have unexpectedly delivered a premature infant whose health is likely precarious. It would have been very helpful had the investigator piloted some variation of the intervention prior to crafting this proposal. As it stands, the sample size estimates rest on some optimistic assumptions about participation rates, the intervention rests on an untested new role of counselor, and data gathering uses an apparently untested interview strategy and unvalidated data gathering instruments.

The literature review and many of the suppositions of this project focus on promoting breastfeeding, whereas this project’s success depends on one aspect of breastfeeding, i.e., breast pumping. The investigator has implemented a program to assure the availability of breast pumps to mothers delivering in the hospital at which the project will take place, and obviously has considerable experience with lactation education. However, the possible distinction between promoting breast feeding in general, and promoting breast-feeding that will rely almost exclusively on breast pumping is not discussed.

The investigator provides an extensive list of the various factors that have been significantly associated with breastfeeding rates. Some, such as race, socioeconomic status, and marital status are certainly not reasons why a woman would or would not breast feed, but are merely correlates. Other factors may be more causal, but their relative impact is not discussed. The investigator has not provided a rationale or a theory for why the proposed peer counseling might work in light of these many intervening factors. It is apparent from the brief description of the contents of the mother-counselor contacts that some assumptions about barriers to breast-feeding have been considered. But these assumptions are not discussed and the rationale for the peer intervention is never provided.

Much is made of the fact that the project is being done in one of the few hospitals in the U.S. that has been designated Baby Friendly. The investigator argues that this makes it easier to do the project since many of the forces that might otherwise limit breastfeeding have been dealt with in her hospital. Although this supportive environment may make the intervention more effective and the data easier to analyze, it also makes it more difficult for the intervention to be reproduced in hospitals that do not so actively support breast-feeding. In addition, the investigator presents the designation as Baby Friendly as a 0/1 variable; that is, hospitals either are or are not supportive of breast-feeding. Of course that is not the case, and it would be naïve to assume that the supportive environment of a hospital could be captured so easily.

The proposal has a second research question it intends to address in addition to testing the peer counselor intervention. This second question, to investigate the determinants of breastfeeding among the study group. This second part of the project is not discussed in any detail within the proposal. It is understandable that the investigator would like to make full use of the data that is collected, but as described, the analyses related to this second question sound like an after-thought. The proposal says, "We will be able to delineate determinants of breastfeeding among women in our study beyond what has already been
described in the literature.” I assume they hope to delineate determinants of breastfeeding among women represented by those in their study. The literature review to support these analyses is not evident in the proposal. The length of this study, three years, and the degree of support for the PI and research assistants, should provide sufficient time and resources to explore some of these determinants. However, it does not appear that a great deal of thought has been given to this aspect of the study and to the opportunity the study’s design provides.

The investigators mention several circumstances when mothers will be eliminated from the study. I hope they don’t mean that, since a lot of information will be lost about women who appear to find the peer counselor’s assistance not sufficiently valuable to continue either receiving contact or providing information to a research assistant. Mention is also made of some comparison of mothers who decline to participate in the study with those who do participate. The nature of these comparisons and a description of what data will be available for comparison are not provided.

There is a small inconsistency in the rationale for the methodology. At one point in the proposal the choice of six peer contacts was justified based on a previous study; at another point it is justified based on the average length of stay for premature infants in the study NICU.
Epidemiology of Elevated Homocyst(e)ine and Risk of Preeclampsia

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Project Number R40MC00186
Project Period 1/1/2000-12/31/2001

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Year 2010 Objectives
16.5, 16.16

Study Design
Observational

Time Design
Longitudinal

Care Emphasis
Noninterventional

Population Focus
Pregnant women (not otherwise identified as adolescents)

Race/Ethnic Focus
No Stated Race, Ethnic Focus

Priority Research Issues

Summary

Statement of the Problem

Hyperhomocyst(e)inemia is an independent risk factor for vascular disease, including atherosclerosis and thrombosis. Elevated plasma homocyst(e)ine [H(e)] is also seen in patients with preeclampsia both in the acute phase of the disorder and postpartum. The association of elevated H(e) with preeclampsia is consistent with other data implicating placental vascular abnormalities in the etiology of this common pregnancy complication. Preeclampsia, although rarely clinically manifest prior to the third trimester, begins early in pregnancy. The vascular endothelial injury that characterizes preeclampsia is present as placental development occurs.

Research Questions or Hypotheses

Given 1) evidence of an independent association between elevated H(e) concentrations and increased risk of endothelial dysfunction and vascular disease; 2) the excess risk of preeclampsia in women with elevated H(e) concentrations at delivery or during the postpartum period; and 3) the emerging evidence of the role that genetic and dietary factors play in the metabolism of homocysteine, we are conducting an epidemiological study to examine the hypothesis that elevated serum
H(e) measured in the second trimester of pregnancy is associated with the later development of preeclampsia.

**Study Design and Methods**

Within a large prospective cohort study population, we are conducting a nested case-control study of maternal biological markers and clinical data.

**Population Description and Sampling Plan**

We are assessing the risk of preeclampsia associated with maternal serum folic acid and H(e) concentrations measured in the second trimester. The hypotheses are being evaluated using biological samples and medical records information for a cohort of 5,652 women who delivered at Swedish Medical Center. Serum samples were drawn during the second trimester for prenatal screening and diagnostic purposes. Serum samples are being evaluated for all women who developed preeclampsia (N=170); for all women who developed gestational hypertension (without proteinuria) (N=339); and a random sample of normotensive controls (N=509) in order to test our study hypotheses. Serum specimens are being evaluated in order to determine maternal second trimester H(e), folic acid and vitamin B12 concentrations.

**Analysis Plan**

Using logistic regression and other analytical procedures, we will assess the relation of the aforementioned micronutrients with maternal H(e) concentrations; and risk of developing preeclampsia (and gestational hypertension). Results from our proposed study may yield important information concerning the etiology of preeclampsia. Results may be used to design effective nutritional, dietary supplementation or food fortification programs targeted towards preventing the occurrence of hypertensive disorders of pregnancy.

**Pre-Award Evaluation**

**Evaluator 1**

**Originality and Importance**
No statement of originality and importance.

**Regional and National Significance**
No statement of regional and national significance.

**Scientific and Technical Merit**
This is a well written and well thought proposal that intends to look into explaining some of the pathophysiologic mechanism associated to the development of pre-eclampsia by determining second trimester levels of homocyst(e)ine, folic acid and vitamin B12 levels. But weather the high levels of homocyst(e)ine and/or the low levels of folic acid and vitamin B12 are truly involved in the development of pre-eclampsia or are clinical markers for the risk, this might help providers in predicting this risk. The long term benefits of proving such associations might not only be related to the risk assessment but to the potential interventions with nutritional supplements in pregnant women at risk for pre-eclampsia. Given that the true etiology of pre-eclampsia is still unknown, this proposal is extremely attractive in as much as it is looking into areas of sufficient knowledge as to provide a rational justification, but limited knowledge so far in pregnancy.

There are known difficulties in studying pre-eclampsia, the first one being the lack of a gold standard for a diagnosis. In studies in which renal biopsies have been performed in women with pre-eclampsia, about one fourth of them (either primigravides or multiparas) have been found with preexisting renal disease, and from 50% to 60% have been identified to demonstrating the pathogenic histopathologic lesion.

Therefore, verifying true pre-eclampsia just on the basis of clinical diagnosis might have some limitations. If the clinical diagnosis exceeds the true pre-eclamptics, this might limit the accuracy of the conclusions, but we recognize this will always be an inherent limitation in the study of this condition. The intervention trials previous funded have had to deal with the
same issue. In order to be consistent they will use ACOG criteria for the diagnosis of Pre-eclampsia, Gestational Hypertension and Chronic Hypertension. They already carried out an analysis of some medical records in terms of reliability with the diagnostic criteria and there is excellent agreement (Kappa 0.89).

Another concern is the fact that the samples in this repository have been frozen for as long as 5 years. They have evidenced in the proposal that the homocyst(e)ine concentrations in stored plasma (-20 C) are stable for up to 10 years and correlate with fresh plasma.

The significance is not only National, but worldwide as pre-eclampsia is a condition known to occur in virtually all countries.

The scientific rationale and description of the problem are clear and based in a through literature review. There a number of biochemical markers that have been detected during the second trimester that suggest that vascular endothelial injury is present early on and clinically manifested later.

Elevated homocyst(e)ine concentration are independently associated with endothelial dysfunction and vascular disease. It seems logical, then to look for this type of abnormality in pregnant women in an attempt to establish a connection to pre-eclampsia. Their preliminary data with 52 cases and 56 controls in the proposed study population confirms this. They have additional data from an African cohort (185 normotensive and 138 pre-eclamptic patients in Zimbabwe) which also supports their hypothesis, although the African normotensive cohort had higher levels than the American cohort.

The specific hypotheses are:
1. Elevations in maternal serum homocyst(e)ine concentration during the second trimester are associated with an increased risk of pre-eclampsia later in pregnancy.
2. Relatively higher levels of folate and vitamin B 12 in the second trimester are associated with reduced homocyst(e)ine concentration and thus , reduced risk of pre-eclampsia.

Hypothesis 1 and 2 apply to gestational hypertension but at a lower magnitude.

The concepts and laboratory essays are well defined and appropriate.

The study design is a prospective nested case control utilizing samples from a repository taken during the second trimester of pregnancy women who subsequently delivered at the Institution and for which a clinical data base exists. Controls will be selected from the same population using a scheme that divides the 36 month specimen collection time into 12 quarters (3 month period). Stratified random sampling will be done from these 12 quarters.

The medical records will be abstracted for demographic characteristics, medical history, health habits, height pregnancy weight, family history of birth defect and utilization of medical care during the index pregnancy. The form was included as an appendix.

The sample size estimation accounts for enough subjects to have power to detect 15% differences in the levels of any of the biomarkers.

The section describing power calculations and statistical analysis of the data reflect the findings in the preliminary studies as well as all the different tests that may be applicable.

The time schedule is reasonable (two years) and the budget reflects the cost for laboratory analysis and staff. There is an additional item (a-70 Freezer) that was justified in the basis of additional space needed because the actual samples will be aliquoted and divided in three.

One concern is the ethics and/or legality of using samples from a repository established from unused portions of specimens collected for prenatal screening tests. The investigators specify that “the protocol for collecting serum specimens has received annual review from the Swedish Medical Center’s IRB since 1994”. I have to assume that the patients signed a consent form.
or a release since their clinical data can be tracked and tied to the laboratory specimens.

In essence, this is an excellent proposal in which logic and rational approach to new biological markers associated to the risk of pre-eclampsia will be tested. If proven, these findings might be used to develop intervention trials in early pregnancy to try to reduce the risk or the severity of pre-eclampsia. It is a highly meritorious endeavor. Future interventions may be designed using Supplements of these micronutrients.

Evaluator 2

Originality and Importance
The failure of well designed clinical trials to find salt restriction, prophylactic therapy with diuretics, calcium and low dose aspirin effective in prevention of pre-eclampsia suggests that there are as yet unidentified etiologic factors that may be associated with the disease. The investigator review theirs and other previous studies noting the association between elevated homocyst(e)ine concentrations with the risk of pre-eclampsia in two populations and evidence linking endothelial dysfunction, a lesion often found in pre-eclampsia, with elevated homocyst(e)ine concentrations in circulation. The current proposal intends to assess the impact of elevated serum homocyst(e)ine in the second trimester of pregnancy on the later development of pre-eclampsia and gestational hypertension and to assess the risk of pre-eclampsia and gestational hypertension associated with maternal serum folate and homocyst(e)ine concentrations measured in the second trimester. The work is important in addressing the basic etiologic factors contributing to pre-eclampsia and gestational hypertension. If successful, the work may contribute to dietary recommendations for pregnant women. The work is original and important to the MCH agenda.

Regional and National Significance
The results of this work would be of national significance.

Scientific and Technical Merit
Strengths:
Drs. Sorenson and Williams and colleagues are well supported by grants from the NIH and MCHB. They have worked together closely on studies of pre-eclampsia and preterm delivery. This is a very strong and productive research team working in an important area of maternal and child health. The previous work done by the investigators demonstrates their ability to carry out such a study and suggests that they will be successful this current proposal.

Concepts and working definitions are well explained. The definition of pre-eclampsia, chronic hypertension and gestational hypertension has been operationalized and are used in other NIH studies. Hypotheses are clearly stated and researchable. The setting, Swedish Medical Center, was the site of an earlier and successful study in which medical records and serum samples were abstracted/collected in a similar way to identify factors associated with pre-eclampsia.

The cases of pre-eclampsia (n=170) and gestational hypertension (n=339) will be identified from a cohort of women, from which all will be selected. A stratified sample over time of 509 normotensive controls will be selected. This method of selection is appropriate and has been used in their previous studies.

Procedures for abstraction of medical records are described and a preliminary form included. Procedures for serum homocyst(e)ine assays and serum folate and Vitamin B 12 assays are described and appear to be standard tests. The study design, a nested case-control design is appropriate for this research. The sample size computations are well supported.

The statistical analysis is carefully developed and appropriate to the study design. A careful discussion of the limitations of the study and efforts to control their effects are given.

Weaknesses:
There appear to be very few weaknesses in the technical execution of this project within the constraints of the setting.

This study will associate the retrospective measures of homocyst(e)ine, serum folate and Vitamin B 12 in the second
trimester (12-24 weeks) with the presence or absence of pre-eclampsia. or gestational hypertension from 20 weeks on to
delivery. The investigator has noted that blood homocyst(e)ine concentrations are elevated due to low blood folate levels and
that serum folate levels are affected by diet, vitamin supplements, smoking and selected drugs and illicit drug use. B
vitamins such as vitamin B 12 are decreased in smokers. Serum folate levels are thought to reflect short-term status and
while red blood cells represent status over a longer term. This study is based on serum levels. They quote the work of
Malinow that shows that plasma folate is inversely correlated with plasma homocyst(e)ine. A previous study has established
the homocyst(e)ine and pre-eclampsia relationship. This study intends to tease out the relationship of homocyst(e)ine from
Vitamin B 12 and serum folate in pre-eclampsia, and gestational hypertension, controlling for other confounders. An
important issue is that there is sufficient variability in the markers. Data is presented for homocyst(e)ine, however, no data
are provided for Vitamin B 12 and serum folate. How these variables vary with smoking and other potential confounding
factors may affect the ability to draw appropriate conclusions.

In summary, this is a very well written technical proposal. It follows on preliminary research establishing the relationship
between pre-eclampsia and homocyst(e)ine levels. It seeks to do the same for gestational hypertension and pre-eclampsia but
control for potentially confounding variables in the current study. Success would seem to rest on the carefully laid out
technical aspects and the hope that there is sufficient variability in the markers and covariates.
Epidural and Intrapartum Fever: A Randomized Trial

**Grantee**  
Brigham and Women's Hospital

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**Project Number** R40MC00248

**Project Period** 1/1/2001-12/31/2004

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**Study Design**  
Experimental

**Time Design**  
Mixed

**Care Emphasis**  
Interventional

**Population Focus**  
Pregnant women (not otherwise identified as adolescents)

**Race/Ethnic Focus**  
No Stated Race, Ethnic Focus

**Priority Research Issues**

**Summary**

**Statement of the Problem**

Epidural analgesia is used by more than half of laboring women for pain relief during labor. The association of epidural use with fever has been reported in a number of studies but whether there is a causal connection has remained controversial. There is also not a consensus regarding the cause of this fever. While epidural-related fever is generally believed to result from thermoregulatory alterations, some investigators believe it is due to infection. In addition, our recent work suggests that, whether or not it is due to infection, the fever occurring with epidural use may not be benign for the fetus. We have found that in a term, low risk population, infants of febrile mothers are more likely to have lower Apgar scores, to require bag and mask resuscitation after delivery, to be hypotonic during the first day of life and to require oxygen treatment in the nursery. To date, no study has systematically investigated epidural-related fever. Given the potential adverse effects, it is essential that the etiology, physiologic correlates and clinical consequences of this epidural-related fever be systematically investigated.

**Research Questions or Hypotheses**

Our study will systematically evaluate the effects of epidural analgesia used for pain relief during labor by low risk women having their first baby. We will evaluate the causal connection of epidural analgesia with intrapartum maternal fever,
infection and markers of inflammation during labor. We will also examine the association of epidural-related fever with histologic chorioamnionitis, markers of inflammation, and neonatal outcome.

Study Design and Methods

Our study is a multicenter, randomized trial. Women agreeing to participate will be randomized during the second trimester of pregnancy to one of two treatment groups:
No epidural group: Women in this group will be asked to try to avoid requesting epidural analgesia. To enhance the ability of women to manage the pain of labor without an epidural, a labor support person (doula) will remain with each woman throughout the course of labor.
Epidural group: Women in this group will not be asked to avoid an epidural and will be free to ask for an epidural at any time.

Women in both groups will complete a short questionnaire at enrollment requesting baseline data such as height, pre-pregnant weight, education, and use of tobacco and alcohol. In labor they will have their temperature taken every 2 hours. Maternal and cord blood samples will be obtained. Placental swabs for culture will be taken, and the placenta will be sent for histological examination. Maternal and infant hospital records will be abstracted for information about the course of labor and postpartum stay.

Population Description and Sampling Plan

We plan to enroll 1500 women in the trial over a 3 year period. Women enrolled will be healthy nulliparas, at least 18 years of age, with a singleton pregnancy who are planning to deliver at Brigham and Women's or Massachusetts General Hospital. The expected racial/ethnic distribution of women delivering at the two hospitals is as follows: 60% white, non-Hispanic; 19% Hispanic; 10% Black, non-Hispanic; 5% Asian/Pacific Islander; 7% Other.
The study is committed to minority recruitment. While our study is not designed to specifically address racial differences in the effect of epidural, such differences could be explored in secondary analyses.

Analysis Plan

An intention to treat analysis will be performed to compare rates of intrapartum fever, infection and cytokine levels according to randomization group. Calculation of the number of subjects for enrollment takes into account the expectation of moderate crossover in both randomized groups. The study will include a variety of designs and analytic techniques to evaluate the associations of epidural-related fever with markers of inflammation, histologic chorioamnionitis and neonatal outcomes.

Pre-Award Evaluation

Evaluator 1

Originality and Importance
The proposed study appears to address an issue of importance if the assumed linkage between epidural use and neonate adverse outcomes (e.g., seizures) is true. It appears that the study is original in that clinical trials have not been conducted on the research question and seem warranted.

Regional and National Significance
The issues addressed are of national significance. It appears that epidural use is becoming more common, and therefore understanding its consequences is important. No direct link to one or more of the 15 priority issues/questions of MCHB is now being claimed.

Scientific and Technical Merit
The proposal is clearly written and provides clear justification for the proposed study. The methods and analyses are also clearly articulated.
The cited literature provides a good rationale for the need to conduct the proposed study. The investigators have contributed extensively to this literature, as evidenced by the preliminary studies. Their expertise and ability to work together was clearly demonstrated in this section. The aims of the study address the questions raised by the literature review.

The underlying model and concepts are clearly articulated. Definitions were provided that even a person without medical or biological training could understand. Similarly, both the graphical representation and the text describe clearly the conceptual model underlying the study, hypothesizing two possible mechanisms by which epidural anesthesias could cause fever in the absence of infection, through higher levels of cytokines or as a direct effect of heat. The hypotheses follow directly from the model and test, in step-down order whether epidural analgesia is linked to intrapartum fever and infection, whether epidural is linked to higher levels of cytokines among all women and among women without infection, whether epidural-related fever is related to histologic chorioamnionitis among women without infection, and whether epidural-related fever is related to adverse neonatal outcomes among infants without infection.

The methods involved in the study include assessments of women and babies and collection of biological specimens. The use of assisted labor for the no-epidural group raise questions about whether it is truly a control group, although one is convinced that some sort of support would be needed to lower the rate of requested epidurals in this group. It was not clear what other analgesia the women without epidurals might receive – although that should be comparable across the two groups to the extent that the assisted labor does not influence those choices or other aspects of labor such as duration or frequency of vaginal exams. Chart extraction will be used to collect information regarding labor and delivery and indications of infection. As understood by this reviewer, labor-assistant were also going to collect at least some of this information as well as another member of the staff among women in the epidural group. It is assumed that chart review and/or observations of research staff during delivery will provide comparable levels of data across all women, although one worries that some of the covariates such as the number of vaginal exams and hourly temperature reading may be documented less well in the epidural group than in the assisted labor group.

Biological specimens will be collected on a 30% random sub-sample and for any women with fever. It was not clear how women who develop fever during delivery will provide as much blood since one of the draws is at admission. One suspects this is not relevant if the data to be collected would be the presence of cytokines or indications of infection when fever is present for these women.

The study design is both a randomized clinical trial and a case-cohort study. The first two aims are addressed by comparing the intent-to-treat groups to see if epidurals are linked to fever and infection. Cross-over rates threaten the power of these analyses, but not the study design itself. However, “treated sample” are also proposed, and it was not clear to this reviewer how results would be interpreted if the intent-to-treat analyses did not support the hypothesis and the "treated sample" analyses did. The last aims are addressed by limiting the sample to women without infection or children without infection. This portion of the study does not involve a clinical trial, and it is viewed as a descriptive study. A minor concern involves the investigators’ argument that they have a random sample from the total population because they are examining bloods from a randomly selected subset of the sample. Technically, this is not the population to which they wish to generalize and thus, should not be regarded as a random sample of that population.

Both population and sampling plans are well described. Based on prior experience with clinical trials of delivery practices and the numbers of women meeting criteria who deliver in the two hospitals, the investigators feel confident they can identify and recruit sufficient numbers of women into both arms of the clinical trial. Power analyses justify the selection of the sample sizes, even if one assumes much worse cross over rates than are anticipated. The empirical basis for estimating epidural rates in the two analysis groups is explained in detail and seems well justified.

The proposed statistical analyses are described separately for each specific aim. Aims 1 & 2 are based on random assignment and two sets of analyses are proposed. The first is the "intent-to-treat" comparison and second is "treatment received" comparison. Although not explicitly stated, this reviewer assumes that a simple chi-square analysis will compare the proportions of women in the two groups showing fever or maternal infection unless preliminary analyses indicate group differences on demographic or medical characteristics. It is stated that if those group differences emerge, then logistic regression analyses will compare the treatment groups with those indicated variables as covariates. There are potentially three problems with this suggested analysis. First, nothing was said about how the investigators would interpret findings if...
the two sets of analyses produced different findings. In particular, the most worrisome condition would be if the intent-to-treat analysis yielded non-significant differences and treatment received analyses yielded significant differences. Second, while the proposed strategy is used frequently to identify confounders, it seems to be that it would be better (and perhaps more powerful) to specify classes of confounders to include as covariates in all analyses. This latter is a minor concern. Third, the proportion of women developing infections in each group is to be computed as a weighted average of the proportion of women with infection among the women with fevers and the proportion of women with infections without fevers. A preferred best estimate would be examining the proportion of women with infections among the randomly selected women-regardless of fever status—or at least computing the weighted average of proportion of women with infection among the randomly selected women (30% selected) and among the women selected with fever who had not been randomly selected (100% selected).

The second set of analyses involves viewing the data as coming from a case-cohort design in which only women or children without infection are studied. The only problematic issue with the described analyses involves the interpretation of the 30% sub-sample as a random sample of a known population. Technically, this would be true if the entire study sample was a random sample of a known population (i.e., pregnant women who were neither committed to having or not having epidurals). As described in the application, it is in actuality a large sample of convenience, not a random sample. The limitations of the final analysis, examining adverse outcomes in babies, were clearly presented.

The PI, Ellice Lieberman, MD, DrPH, will direct the main aspects and all phase of the study (35%FTE). She is Associate Professor of Maternal and Child Health and Obstetrics, Gynecology, and Reproductive Biology at Harvard and Director of the Center for Perinatal Research at the Department of Obstetrics and Gynecology at Brigham and Women’s Hospital. She has extensive experience in perinatal epidemiology research and is a well-published investigator.

The remaining senior staff provide expertise in all areas of the study. The contributions are as required at 5% participation or in kind efforts and cover from immunology, maternal-fetal medicine, obstetrical, and neonatal medicine, and infectious disease (a total of 26% FTE, 21% funded and 5% in kind). An experienced full-time study coordinator, E. Shearer, MED,MPH and 70%FTE study programmer, A. Cohen, will provide the logistical backup for management and data development. In addition, staff will include 2 full time recruiters, a part-time recruiter, a 60% research assistant, 50% lab tech, and 35% data entry. Project staff is scheduled to start 5 to 7 months into the first year and are budgeted accordingly.

The budget has been substantially reduced but it is still beyond what the MCHB Research Program can afford. The revised proposal answers clearly questions about speeding up recruitment.

Resources and facilities are more than adequate.

IRB approval has been obtained (7-5-00), and ethnical questions about randomly assigning women to the epidural or no-epidural groups were addressed.

A similar proposal is under review at NIH.

Evaluator 2

Originality and Importance

This revised application seeks funding for a randomized trial to investigate the effects of epidural use on intrapartum temperature in low risk women. The study aims to definitively determine whether epidural causes fever and whether epidural-related fever is due to infection. In addition, it will evaluate the physiologic correlates of epidural-related fever and the consequences of this fever for neonatal outcome. During term labor, most fever is associated with epidural use. Understanding this fever is essential since 40-45% of women receive epidural. While the association of epidural with fever has been reported in several studies, it remains controversial. At the center of this controversy is one study that documented higher rates of histologic chorioamnionitis with epidural-related fever. But for this one study by Dashe and colleagues, epidural-related fever is generally believed to result from thermoregulatory alterations. The investigators’ previous work suggests that epidural-related fever (even if not due to infection) may be harmful for the fetus. This is a potentially extremely important observation. In a term, low risk population, epidural-related fever was associated with lower Apgar
scores, bag and mask resuscitation, hypotonia, oxygen treatment and neonatal seizures. The investigators hypothesize that epidural-related fever is not due to infection but results from increased cell-mediated immune activity. Given the available literature, this is a reasonable hypothesis. Both fever and localized inflammation (chorioamnionitis) may be induced by noninfectious agents, producing manifestations similar to infection. The investigators propose a 4-year trial in which 1500 low risk, nulliparous women will be randomized to epidural or no-epidural groups. Women in the no-epidural group will be asked to avoid epidural use and provided with labor support to assist them. Cytokine concentrations in maternal admission and delivery and cord blood will be determined and used as correlates of immune activation. The presence of histologic chorioamnionitis and placental infection will be determined. The rate of fever, infection and cytokine levels will be compared across randomization groups using intention-to-treat analyses. Since epidural is such an integral part of practice and its benefits for pain relief so clear, it is critical that the etiology, physiologic correlates and clinical consequences of epidural-related fever be understood so that women can make informed decisions about pain relief. The investigators plan to collect maternal admission and delivery blood samples. They also will collect cord blood, and placental tissue. The investigators will measure pro-inflammatory cytokines in maternal and fetal blood samples, and they will examine collected placental tissues for the presence of infection. Microbiologic, histologic and molecular methods will be applied in order to ascertain the presence of infection.

Regional and National Significance
The four specific aims of this proposal are:

1. To evaluate the causal connection between epidural, intrapartum maternal fever and infection in labor.
2. To evaluate the causal connection of epidural analgesia with cytokine levels and to determine the relation between cytokine levels and epidural-related fever.
3. To evaluate whether epidural-related fever during labor predicts histologic chorioamnionitis.
4. To evaluate the association of epidural-related fever and cytokine levels with neonatal outcome.

The aims of this proposed trial are original. The investigators plan to use new techniques (bacterial DNA PCR analysis along with the more traditional culture approach) to help determine infection status. Elucidation of the mechanisms for the now well documented association between epidural use and maternal fever, and the relation of this fever to adverse neonatal outcomes is an important and original specific aim. It is important to note here that the most innovative and significant aim (from the standpoint of public health significance) is the fourth of the four aims specified by the investigators. As such, this very large and logistically complex trial is geared more towards replicating (albeit using a technically more rigorous study design) earlier observations of the association between epidural use and intrapartum fever. The most compelling aim (Aim 4) will only have adequate statistical power for the least clinically important neonatal outcome. Specifically, the proposal as designed (with an estimated 121 febrile mothers and 380 afebrile mothers) will have 98% power for low 1 minute Apgar. Less than adequate power will be available for bag & mask resuscitation (42%), need for oxygen in nursery (45%) and hypotonia (75%). Power for seizure is not provided.

Results from observational studies indicate an association between epidural and fever. Epidural-related fever is associated with adverse infant outcomes including hypotonia and seizures. Given that labor pain management is achieved with the use of epidural in over half of all deliveries the topic of this research is of very high public health significance. The investigators make this point in a quite compelling manner. They note that of the 2 million women each year receive epidural for pain relief during labor, and that based on their preliminary data, 54,000 infants develop an adverse outcome associated with that fever annually. They further estimate that 4,800 infants per annum experience seizures associated with this fever. The investigators’ preliminary reports and these estimates serve to bolster the importance of specific aim no. 4. Therefore, it is puzzling that this application does not appear to have been optimally designed (i.e., limited power for the most compelling neonatal outcomes, and no power presented for seizures) for this important specific aim.

Scientific and Technical Merit
The investigators propose a 4-year randomized trail of 1,500 term nulliparous women, (recruited in the third trimester) from two medical centers. This is a revised proposal. Overall, the investigators have been responsive to the reviewers concerns. First, as noted above, they provide a very compelling argument noting the high stakes involved given the ubiquity of the exposure and its adverse consequence on neonatal outcomes. Second, they provide more discussion in support of their study design. Specifically, they provide details and justification for the use of labor support for those women assigned to the
no-epidural group. Briefly, women assigned to the epidural group will be free to request an epidural at any time. Women assigned to the no-epidural group will be asked to avoid epidural. In order to decrease the likelihood of crossover of women in the no-epidural group to the epidural group, the investigators will provide subjects randomized to the no-epidural group with a labor support person to help them cope with the pain of labor.

This point of the design represents one of the most important concerns of this otherwise technically outstanding trial. Specifically, there is a major concern that this study will not be feasible. The very high use of epidural in the US (around 60-70%, and 64% at the major study site during a recent clinical trial) would suggest that the demand for epidural in this population will be high. The investigators report that their earlier experience suggest that labor-support may reduce epidural demand by 10%. This is interesting, but does not provide a sufficiently strong rationale in support of the argument that labor support as an efficacious means of impacting the potentially high cross-over rate. In summary, enthusiasm for this reviewer is reduced as a function of persistent concerns about the feasibility of executing such a study in large urban tertiary centers in the US (where epidural demand and use are likely to be near universal).

Third, in response to the earlier review, the investigators have amended the pace and duration of data collection and the revised budget is now 30% less than the earlier budget. Other relatively minor issues were addressed and points of clarification were provided. It is important to note here that the in response to questions raised about the emphasis on short term versus long term neonatal outcomes, the investigators noted that like their preliminary studies/analyses, the present study will also be limited to those outcomes ascertainable during the first 48 hours of delivery. This truncation of the "relevant" observation period seems conceptually overly narrow and reinforces the impression that assessment of potential adverse infant outcomes is not central to their proposal. This observation is somewhat disappointing. It would appear that the investigators may miss an opportunity to both confirm and expand upon their preliminary findings. Even if longer term follow-up were not feasible given the realities of budgetary constraints, the investigators may want to at least consider options, such as co-sponsorships/funding, to complement their infant outcome ascertainment plan.

Overall, this is a very well written proposal. Given the clear primary focus on specific aim number 1, technically, the choice of study design is well justified and is appropriate. The design, is however, not optimal (e.g., under-powered and overly narrow) for specific aim number 4. The proposal has a very large number of impressive strengths. These include: 1) a highly experienced investigative team led by a very capable epidemiologist; 2) compelling preliminary data; 3) the large and obviously cooperative population is a plus, but the historical and present high use of epidural makes this almost moot; 4) an exceptionally well developed conceptual model and analytical plan; and 5) well demonstrated track record of successfully executing, analyzing and publishing results from a trial of similar complexity. This is truly an outstanding and accomplished group of investigators. The proposal is written with great care and attention to details. There is a very high degree of confidence that the data collected will be of high quality and that the data will be well analyzed and carefully interpreted.

In spite of the many strengths, concerns about the feasibility (impact of labor support in limiting a likely high cross-over rate is likely to be low) and the relatively underdeveloped and under powered 4th specific aim serves to limit enthusiasm for this technically strong application.

**Evaluator 3**

**Scientific and Technical Merit**

This is a revised application in which changes were made on study duration (4 years vs 5) and budget (Total direct Cost of $2,343,353 compared to $2,501,903 previously ) In response to reviewers’ concerns the investigators have clarified several issues such as significance of the project by focusing on the adverse infant outcomes, especially in those who develop seizures. They justify that in order to prevent such adverse outcomes, it is necessary to understand the etiology. Given that approximately half of the 4 millions births in the US are under epidural analgesia,an estimate of 300,000 women will undergo fever evaluation and 54,000 infants might have adverse events related to intrapartum fever (18%) and/ or seizures (4,800 infants).

Clarifications were made to the crossover concerns and the use of labor support for those randomized to "no epidural". Furthermore the ethical issues of consent were further delineated as well as the recruitment process.
This is a well-written proposal that will establish whether epidural analgesia causes fever and whether epidural related fever is due to infection in term pregnancies. This knowledge might help clinicians to discern whether fever work up is necessary for specific patients. It will not reduce the infant morbidity as it relates to fever and/or seizure unless the mechanisms for the fever might be related to specific drugs or to specific medications that could be intervened or blocked. It is still a very expensive undertaking.
ETS and Smoking Control in Families: A WIC Trial

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Project Number R40MC00093


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Summary

Statement of the Problem

Babies’ exposure to environmental tobacco smoke (ETS) is a significant problem because ETS is an etiologic factor in lower respiratory disease including otitis media, asthma, and bronchitis, and is associated with an increased risk of sudden infant death syndrome (SIDS).

Research Questions or Hypotheses

This study tests a behavioral counseling intervention designed to reduce ETS exposure among babies under age 1. Specific aims are to (1) determine the effects of clinic-based behavioral counseling on ETS exposure among babies of low socioeconomic status (SES), as measured by mothers’ reports and babies’ urine cotinine analyses; (2) validate parent-reported ETS exposure measures using urine cotinine assays and environmental nicotine monitors; (3) determine the effects of participation on the mothers’ smoking rate and the proportion of mothers who quit smoking; (4) explore health outcome...
measures associated with decreased ETS exposure; and (5) identify possible determinants of ETS exposure.

**Study Design and Methods**

A two-group repeated measures design with random assignment will be used. After baseline measures are collected, mothers and babies will be assigned at random to the experimental counseling or "usual care" control group. Clinic personnel (health educators, registered nurses, and medical assistants) will serve as counselors for the experimental group, conducting three face-to-face and four telephone sessions over 6 months. Counseling will incorporate contingency contracting and problem-solving negotiations.

**Population and Sampling Plan**

A total of 150 English-speaking and Spanish-speaking mothers will be recruited from patients seen for well-baby visits through the California Department of Health Services' Child Health and Disability Prevention Program (CHDP) at North County Health Services and East County Community Health Services, two of the largest community clinic systems in San Diego County. Outcome measures will be obtained from both groups at 3 months (midintervention), at 6 months (posttest), and at 12 and 18 months (followup).

**Analysis Plan**

Differential change in ETS exposure between experimental and control groups will be evaluated using repeated measures analyses of mothers' reports of ETS exposure and babies' urine cotinine results. The group by time interaction in each model will be assessed. Hierarchical multiple regression analyses will be used to explore correlates of ETS exposure and health. If effective, this intervention could be incorporated into CHDP-funded well-baby care throughout the State of California and in other well-baby care settings across the country.

**Pre-Award Evaluation**

*Evaluator 1*

**Originality and Importance**

A major feature of the proposed intervention is that it can be applied in a "real world" setting. Moreover, the intervention will be tested within the context of such a setting. The investigators have the cooperation of one of the largest community health systems in San Diego County to undertake the work. In addition, they have developed contingency plans if they find that there are not enough subjects in the clinics.

**Regional and National Significance**

The problem of infant exposure to environmental tobacco smoke (ETS) is significant. ETS exposure may be an etiologic factor in the rates of respiratory disease in children who live in households with adults who smoke. An intervention to reduce this exposure that can be implemented as part of routine pediatric care may have widespread application and would be of national and regional significance.

**Scientific and Technical Merit**

The proposed analyses are a natural extension of the previous work of the investigators. They have several years of experience in studies of ETS exposure and clinical trials of preventive interventions. The research team is very strong in terms of both research and clinical background. The proposal is also well-written. Another strength of the proposal is its use of validation measures for parental reports of ETS exposure. The investigators will use the Centers for Disease Control and Prevention (CDC) laboratories to analyze the urine cotinine levels of infants. These laboratories have the most sensitive tests available for urine cotinine. The study design appears to be appropriate to answering the study questions, and the investigators are aware of the potential limitations of their work. The objectives of the study are clearly stated and linked to the study hypotheses. The study hypotheses are also clearly specified, and a rationale and a list of variables are provided for each. Power calculations are presented for each hypothesis. These indicate that, given the proposed sample size, the investigators will have adequate
power to test the hypotheses.

Although the proposed studies have many strengths, they also have a number of weaknesses. First, it is unclear why the investigators need to do the two studies simultaneously. The natural study to pursue first is the one in the white population that addresses whether counseling by telephone has an effect on reducing ETS exposure among healthy infants. The investigators are introducing two new elements to their previous work: The telephone contact and the healthy population. It is not clear that face-to-face counseling would have an effect on children who are free of respiratory disease. The second study is predicated on the evidence from the first study. Moreover, the second study needs a separate rationale and a set of retention methods and counseling approaches that differ from the first study.

A second weakness of the proposed study is that other investigators may not be able to replicate the intervention. The proposal contains a lengthy discussion of the counseling and what it might involve, but presents no clear guidelines for counseling. More standardization of the intervention appears to be needed before it can be replicable.

A third weakness is that although the investigators state they are using social learning theory to guide the intervention and the data collection, they never indicate which theory or how it directly relates to the interventions. The literature review provides a graphical representation of the relationships among variables, but the proposal does not mention these relationships again.

The investigators may be overly optimistic about the success of their followup of subjects. They project counseling points that coincide with well-child visits, but they do not indicate what they will do if a mother does not bring in her child for a visit at the proposed times. A 15-percent attrition rate over the course of the 18-month followup seems very low.

The investigators propose to use a biomarker to validate the ETS exposure data reported by the parents, but the biomarker may not be a valid measure of exposure. Is there a reason to estimate biomarker levels if they are of questionable validity? One measure, environmental nicotine levels, will only be estimated for 20 percent of the sample due to the cost of measuring these levels. It is likely that either the data on morbidity will not be useful or the sample size will be too small to detect differences in the incidence of more severe lower respiratory illnesses. Thus, it is not clear whether the study will obtain valid data on outcomes for the entire sample.

Power calculations predominate in the analysis plan. The plan is difficult to follow because it is too succinctly written, does not clearly indicate the independent variables for the analysis, and suggests methods (such as correlation for the determinants of ETS exposure) that may not be the best approaches. The inclusion of a dummy variable for group membership may not account for differences in the effect of the independent variables on ETS exposure between the intervention and control groups.

The literature review primarily includes the previous work of the investigators. The investigators indicate that very little work has been conducted on reducing ETS exposure in children. However, there have been a number of clinical trials on smoking cessation among pregnant women that may provide information about the best strategies for intervention. Some acknowledgment of this literature would seem appropriate. One important finding in these studies is that, despite higher quit rates in the experimental group, the effect of the intervention on infant birthweight was small.

The behavioral counseling program for nonsmoking Latino mothers is described as being culturally tailored. In this study, counseling will be directed toward the mother to reduce the child's exposure to the father's tobacco smoke. Although the program will be delivered in Spanish or English (according to the family's preference), the potential for marital/family conflict poses a serious threat to the participants' well-being and their ability to remain in the study. What counseling and retention procedures will be implemented in the event of increased marital problems? Will the nature of these marital conflicts and their resolution be documented? In what ways will conflict-resolution counseling be culturally tailored? In addition, many Latinas live in extended families, which create complex intervention situations. Will counselors whose professional expertise is limited to OB/GYN and birth control be sufficiently prepared to address complex extended-family issues? Although the proposal contains evidence that Latino mothers are likely to get fathers to cooperate, the data presented are based on a relatively small number of families. To reduce infant ETS exposure in this group, it would be worth considering ways in which the father and other household members might be actively involved in the intervention. Direct and personal involvement by fathers may also decrease the potential for conflicts with the mothers.

Clearly, the use of independent measures of ETS exposure is a strength of this study. However, as the principal investigator suggests, a potential weakness of the study design is the lack of an "attention control" group. If the present study shows a significant decrease in ETS exposure levels, how will the reactivity threat be handled?

It is not clear how the attrition rate was estimated. The investigators' previous experience is limited to working with parents of children with respiratory disease and face-to-face (as opposed to phone counseling) interventions. In this proposed study, participants and their infants have characteristics that may increase the attrition rates considerably beyond the estimates. The dropout rate among controls could be lower because of fewer study demands.
The study timeline appears to give the investigators sufficient time to recruit the sample, collect the data, and analyze it. The problem of infant exposure to ETS is a significant one. Exposure may be an etiological factor in the rate of respiratory disease in children who live in households with adults who smoke. An intervention to reduce exposure that can be implemented as part of routine pediatric care may have widespread application. Unfortunately, the investigators have not made a good argument for doing both studies. The recommendation is for approval of Study 1 only, with the stipulation that prior to funding the investigators comply with the following conditions:

1. Support the estimated rate of attrition given in the application protocol;
2. Address the possibility that participation in the study may lead to spousal and/or family conflict, and specify the measures that will be taken to address this problem if it occurs; and
3. Submit a data analysis plan and revised budget that is restricted to the activities proposed for Study 1 only.
Evaluation of Hawaii's Healthy Start Program - Phase Two

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Johns Hopkins University

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Project Number R40MC00123


Costs

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Year 2010 Objectives
15.33

Study Design
Experimental

Time Design
Longitudinal

Care Emphasis
Interventional

Population Focus
Adolescents, Parents/Families/Mothers/Fathers

Race/Ethnic Focus
Asians-Filipinos, Asians-Japanese, Hawaiian Natives, Pacific Islanders

Priority Research Issues

Summary

Statement of the Problem

Hawaii's Healthy Start Program (HSP) is a well-established outreach program that provides community-based screening to identify newborns at environmental risk for child abuse and neglect. HSP also provides for home visiting by paraprofessionals to promote healthy family functioning and child development through role modeling, education, and linkage with pediatric primary care and other needed community resources during the child's first 3–5 years of life. Nationally, home visiting programs (in general) and HSP (in particular) receive strong endorsement. Efforts to establish community-based home visiting programs, however, have been impeded by several unresolved issues: (1) The mixed results of past evaluations, (2) the limited study of nonnurse home visiting, (3) the evaluation of demonstration projects rather than established programs, (4) the little research on the types of families most likely to benefit, (5) the uncertain cost benefits of home visiting, and (6) the lack of information on the impact of home visitation on the fathers' role in parenting. These issues render evaluation findings essential for informed policy and program development.
Research Questions or Hypotheses

As described in the abstract titled "Evaluation of Hawaii's Healthy Start Program," which is in this publication, Phase One of the evaluation addresses the following four questions:
1. How closely does program implementation mirror program design?
2. How successful is the program in achieving intended benefits for children and families?
3. How does fidelity of implementation influence program achievement of intended benefits?
4. How do achieved benefits compare to direct and indirect program costs?

Phase Two of the evaluation addresses two additional questions:
1. How does the HSP affect paternal functioning and maternal perceptions of it?
2. How does the HSP affect the concordance of fathers' and mothers' parenting attitudes and beliefs?

Study Design and Methods

This ongoing, community-based, randomized trial is the largest, most rigorous study of the HSP model. The study's goals are to measure program process, assess program impact on family functioning and on child health and development, relate process to outcome, and determine cost benefits. In the original study, family functioning is operationally defined in terms of maternal parenting attitudes, beliefs, practices and self-perception, life course, and psychological well-being.

From November 1994 through December 1995, we recruited 684 at-risk families of newborns. We randomly assigned them to HSP or control groups, and we are monitoring them until the infants are 3 years old. We collected baseline and annual followup data through HSP record review, structured maternal interview, and several strategies that focused on the index child: Observation of the home environment and mother-child interaction, child developmental testing, review of pediatric medical records, analysis of health-care-use files, and review of Child Protective Service records.

Although not part of the original workplan, we collected detailed information on fathers through maternal interviews during baseline and annual followup assessments. Thus, we have longitudinal data on several aspects of the father's role as follows: (1) His relationship with the mother; (2) his prenatal involvement; (3) the mother's desires and expectations for his involvement in parenting during the child's first 3 years of life; (4) her report of his accessibility, engagement in child rearing, and sharing of parenting responsibilities during the child's first 2 years of life; and (5) her report of his educational and vocational course, substance use, and approaches to resolving conflicts with her.

As noted earlier, the HSP aims to improve family functioning. To this end, services are offered to both parents and to extended family members, not just to the mother. Phase Two allows us to assess HSP effects more fully by measuring impact directly on both parents, not just the mother.

Phase Two involves interviews with fathers and direct observation of father-child interaction. Measures were selected on the basis of demonstrated validity and reliability, appropriateness for the Hawaiian population, objective assessment, and prior use in studies of home visiting.

Parenting behaviors are measured in several ways. Abidin's Parenting Stress Index assesses parental distress, parent-child dysfunctional interaction, and the parent's perception of the child's temperament. Using Lamb's typology of accessibility, engagement, and responsibility as domains of parenting, we developed items to measure the father's desire, expectations, and reported behavior in each area. Observed parent-child interaction is measured by using the teaching scale of the Nursing Child Assessment Satellite Training Scales. Caldwell's observational Home Observation for Measurement of the Environment Scale is used to measure the home environment. Parent employment and education interview items are drawn from existing national surveys.

Psychological well-being is measured using the short form of the Rand Mental Health Inventory (MHI). The MHI focuses on two aspects of general mental health: Anxiety and depression. Substance use, stages of use, treatment, and consequences of use are measured using several existing scales, including quantity and frequency of consumption, symptoms, and consequences of use items drawn from the Addiction Severity Index; the AUDIT, CAGE, S-MAST, and T-ACE; and Prochaska and DiClemente's Stages of Change Model (e.g., contemplation to stop or modify use, action to seek formal or informal treatment, maintenance of nonuse or relapse).

Population and Sampling Plan

The target population is families of newborns at environmental risk for special health needs. The accessible population was families of newborns on Oahu who were identified as being at risk during study recruitment. A family was eligible for the HSP if the family (1) lived in an HSP catchment area, (2) was assessed as being at risk, and (3) was not already known to
Child Protective Services. A family was eligible for the evaluation if the following applied: (1) The family was assessed eligible for the HSP, (2) the mother did not need a translator (less than 3 percent need a translator), (3) the family was assessed at the time of the infant's birth (less than 20 percent are prenatal referrals), and (4) the family had never been enrolled in the HSP. About half of the study parents were married or living together at the time of the index birth. Phase Two is limited to these families because the HSP targets services to these fathers. Early identification (EID) assessment and study recruitment activities were integrated. Families were recruited by EID workers by using the usual HSP protocol to identify at-risk families of newborns at each hospital on Oahu. By protocol, all families in HSP target areas were screened and assessed. If the family was at risk, the EID worker described the HSP and the evaluation and asked for a signed informed consent. After obtaining consent, the EID worker called the study fieldwork office to learn the family's group assignment and then shared this information with the parents. The fieldwork director made the assignment by adding the family's name to a log with preassigned study numbers. Subsequently, a study interviewer, who was unaware of the group assignment, conducted the baseline maternal interview at the hospital. The intent-to-treat model is our main approach for assessing program effectiveness, but the study is designed to assess program efficacy as well. By design, we assigned a larger proportion of subjects to the HSP group to compensate partially for sample losses from program attrition and to increase statistical power to assess family and agency influences on engagement. All study families are followed for 3 years, regardless of whether they stay in the HSP. Program effectiveness is assessed by using the intent-to-treat model (i.e., outcomes are measured with regard to family assignment to the HSP, regardless of the intensity of services a family receives through the HSP). However, to measure program efficacy (impact under ideal conditions) and dose-response effects, we used a group-allocation ratio weighted toward the experimental group. Families are followed from the infant's birth through his or her third birthday, with baseline and annual data collected (for intervention and main control groups) for key outcome variable indicators. The paternal assessments are conducted in conjunction with the final maternal and child followup assessments.

**Analysis Plan**

HSP's "Impact on Paternal Functioning and Maternal Perceptions of It: Phase Two" allows us to test two hypotheses of HSP's effects on both parents' assessments of the father's role. For each of these outcomes, the null hypothesis of no differences among members of the HSP and the control groups is tested. The outcome variables that are measured are of three basic types: Binary (e.g., any involvement by the father in child-rearing responsibility), counts (e.g., the number of pediatric visits in which the father participated), and indexes or scales (e.g., the father's Center for Epidemiologic Studies depression scale score, measures of father-child interaction). For each study group, the scale variables are analyzed to determine appropriate transformations and groupings. The methodology used is that of exploratory data analysis in the context described by Hoaglin, Mosteller, and Tukey. Internal consistency of composite scores for scaled indexes is investigated using Cronbach's alpha.

The techniques of generalized linear models are used to investigate the relationships between each basic outcome and the covariates. Depending on the nature of the outcome measure, logistic, log-linear, or linear regression is used. For HSP's "Impact on Concordance of Fathers' and Mothers' Parenting Attitudes and Beliefs," we will measure concordance by the kappa statistic and the intraclass correlation coefficient and their associated 95 percent confidence intervals.

**Pre-Award Evaluation**

**Evaluator 1**

**Originality and Importance**

The proposal addresses a timely and important topic. The number of vulnerable families appears to be increasing in the United States, but the best means by which to address their needs remains uncertain. The Healthy Start Program is a widely replicated program that attempts to meet the needs of at-risk families, and is especially noteworthy because of the central place that evaluation has assumed since the program's inception. The randomized trial currently being conducted with support from the MCHB reflects an unusual and innovative attempt to evaluate the 'real-world' implementation of a government-supported social program. The trial will provide extremely important information about the effectiveness of home visiting programs, such as the Healthy Start Program.

The proposal currently under consideration will expand the clinical trial by providing additional data pertaining to fathers,
thereby allowing an assessment of the program's impact on both parents, not just the mother. The proposal will also provide comparative data from not at-risk families.

The proposal addresses several issues listed as part of the MCHB research agenda, including 3.7.2, the differentiation of maternal and paternal care giving roles, 4.4.1, the evolution of the father-child relationship and its affect on mother-child and father-mother relationships, and 5.6.1, the role that minority fathers play in promoting their children's health and development. More generally, the Healthy Start Program embodies the Healthy People 2000 guiding philosophy and specific recommendations.

**Regional and National Significance**

The number of at-risk families in the United States continues to grow. The problems that they face have assumed national significance, because of the burden they place on public agencies and the health care system. If a home visiting program could promote better functioning and improve the health status of parents and their children, and especially if it did so with an attendant savings in the social costs that they would otherwise incur, it would warrant widespread implementation. The proposed research has the potential to influence policy and programs designed to meet the needs of at-risk families.

**Scientific and Technical Merit**

This is a well-written proposal that has a number of strengths. The statement of the problem is clear and concise. The review of the literature is comprehensive without being discursive. Concepts and working definitions are well explicated. The study's design and methodology are described in adequate detail, and the study's hypotheses are linked closely to the variables to be measured.

The proposal also has several shortcomings. First, the preliminary results are somewhat discouraging. The retention rate for participants in the Healthy Start Program was somewhat lower than expected, with only 50% of the families still active at 1 year. Moreover, the effects of the intervention have been clinically significant for only a few outcome measures, and the effect sizes for those measures have been modest, so that their clinical significance is uncertain. The low retention rate and modest effects of the intervention, at least based on the first year of data, raise concerns about the value of the expanded proposal that are not addressed by the researchers.

The proposal also suffers from structural flaws that result in occasional failures to distinguish clearly between the current study and the proposed expansion. For instance, the hypotheses that are specific to the expanded proposal are described as part of the statement of the problem. They are presented separately from the central hypotheses guiding the overall program evaluation. The two sets of hypotheses are not linked or integrated very well. Similar gaps appear elsewhere in the proposal. As a consequence, the relationship between the larger study and the proposed expansion, as well as the differences between them, is not always clear.

Several measurement issues are of concern. First, the use of the Stanford Binet Intelligence Scale to assess developmental status is fraught with problems in young children, especially those who are at-risk. The scale has a very restricted range of items for younger, lower-functioning children, and can therefore result in significant floor effects. Second, the researchers suggest that they will administer the HOME independently with mothers and fathers. The HOME, however, was not constructed to provide separate ratings for different parents. Indeed, several of the scales on the HOME do not reflect parental behavior, and would presumably provide exactly the same scores. Thus, there is a lack of independence in the resulting measurements.

The researchers also provide relatively little rationale for the recruitment of a sample of not at-risk families. They do not indicate how they plan to contact the families, many of whom presumably will have moved or otherwise be lost to follow up in the interval since they were screened. They do not provide any support for their anticipated rate of participation, and apparently have made no preliminary attempts to contact not at-risk families to ascertain their willingness to participate. The specific variables and measures that will be assessed in the not at-risk families are also unclear. The researchers do not indicate whether all of the outcome measures and dependent variables that are being collected with regard to the at-risk
participants will be available for the not-at-risk families. In any case, data regarding variables such as the adequacy of health care and the use of community resources would be obtained retrospectively rather than prospectively, and would therefore be of significantly less quality than the data collected in the original cohort.

Finally, the description of data analysis is relatively sketchy, and is not presented in a fashion that makes clear precisely how the specific sub-hypotheses presented will be tested. Instead, the description is often guided more by the general study hypotheses. For instance, the researchers mention longitudinal data analyses, although the data that will be collected as part of the expanded proposal and used to address its specific hypotheses is largely cross-sectional, so that the relevance of their comments is unclear. Similarly, the researchers characterize the statistical power of the analyses based on the total sample size. They do not discuss the power of the analyses that will be conducted using the data collected specifically as part of the expanded proposal. The power of those analyses will be less than that described because data collection will be restricted to parents who were married or living together at the time of study enrollment, and hence will include only about 50% of the current sample.

The proposed study will be conducted under the auspices of the Johns Hopkins School of Medicine, in collaboration with the Hawaii Medical Association and the Hawaii State Health Department. The history of cooperation between these institutions is one of the strengths of the proposal.

Overall, the research team is well suited to the conduct of the project. The principle investigator is currently an Associate Professor in the Department of Pediatrics at Johns Hopkins University School of Medicine. She is an experienced investigator with numerous publications listed in her Biographical Sketch, although there are relatively few for which she is the primary author. She will be joined by two co-principal investigators who will oversee the fieldwork activities subcontracted to the Hawaii Medical Association and coordinate program evaluation activities as they involve the Healthy Start Program facilities and the Hawaii State Health Department. The study will also have several collaborators at the Johns Hopkins University, including the project's health economist, and statistician, as well as a psychological expert.

The budget is rather large for a 2-year addition to an ongoing project. In general, workload projections are not presented to justify personnel needs. It is not clear why the principle investigator is requesting support for an additional 25% time during the first year, when both the current and expanded proposal will be in effect. It also is not easy to determine exactly why personnel costs at the Johns Hopkins site double in year 2. The salaries for interviewers at the Hawaii site are rather high, and it is not clear why they are paid more than research assistants. The request for funding for both an administrative assistant and a secretary at the Johns Hopkins site is not well justified, particularly when they are in addition to a full-time project director. Administrative and secretarial support should ordinarily be provided by the university.

Human subjects protections appear to be adequate, and IRB approval has been obtained.

Evaluator 2

Originality and Importance
This application requests funding for an expansion of a MCHB-funded study of the effectiveness of Hawaii's Healthy Start Program. The researchers plan to expand the sample and add to the variables assessed in the Wave 3 of family follow-up. The proposed expansion would focus on the MCHB research priorities related to studying the role that fathers play in the health, growth, and development of children and identifying factors that support or undermine fathering for different groups in different circumstances. The researchers wish to assess the extent to which fathers become engaged in the Healthy Start Program, the family and community factors influencing their level of engagement, and the program's impact on their role as parents. The currently funded study is a large, rigorous investigation of the effectiveness of the Healthy Start Program model.

Regional and National Significance
The researchers argue that much is still to be learned about home visitation, including the effectiveness of paraprofessional visitors, the effectiveness of programs that have gone to scale, the types of families that benefit most, and the effect of
visitation on the father. Although not part of the funded work plan, the researchers have been collecting information on fathers through maternal interviews at baseline and in the Waves 2 & 3 follow-up. Maternal reports are available on the following: the father's relationship with the mother, his prenatal involvement, the mother's desires and expectations for his involvement in parenting in the child's first three years, his accessibility, engagement in child rearing and sharing of responsibilities in the child's first two years of life, and his educational/vocational course, substance use and approaches to resolving conflicts with her. The broad objectives of the expansion are 1) to determine how personal, familial and cultural factors influence paternal engagement in home visitation, 2) to assess the impact of home visitation in supporting effective fathering, and 3) to determine how the father's engagement in visitation influences program effects for the mother, child, and family.

Scientific and Technical Merit
The aims of the expansion form two clusters. These will be addressed separately. The first cluster relates to an expansion of the data protocol for existing study families, adding measures of paternal engagement in the program, interviews with and observations of fathers, and expansion of maternal interviews to better measure their perceptions of fathers parenting attitudes, beliefs, and competence. Parents are either married or living together in about half of the study families (373 intervention families and 311 controls). The father component of the study would be based on Lamb's topology of accessibility, engagement, and responsibility. The expanded data protocol is exciting and important because it would allow researchers to collect data directly from fathers, including observations of father-child interaction. This is an important addition to the study, which will substantially increase the contribution of the research to our knowledge.

The second expansion cluster involves recruiting a new sample of not at-risk families to provide normative information on fathers in Asian/Pacific islander populations. This component of the expansion is less compelling. Hawaii Healthy Start services are provided to both parents and to the extended family. The rationale for this component of the expansion is sound, but the description of the sample and data collection/analysis strategies are not well developed. It would seem that this attempt to obtain normative data is a study in its own right and should be submitted, and evaluated, as a separate research project, rather than as an add-on to the existing trial. Enthusiasm for this component of the expansion is low.

The existing study is making good progress.

This is a strong research team.

IRB approval has been received. There are no human subjects concerns.
Factors Associated with Nutritional Intake in Adolescents

Grantee  
University of Minnesota

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Project Number  R40MC00125

Project Period  10/1/1997-9/29/2001

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Summary

Statement of the Problem

Dietary patterns developed during adolescence may contribute to obesity and eating disorders and may increase the risk of several important chronic diseases later in life. Therefore, a number of Nutrition Health Status and Risk Reduction Objectives described in *Healthy People 2000: Midcourse Review and 1995 Revisions* have relevance for youth. These objectives include the following: Increased consumption of fruits and vegetables; increased consumption of calcium-rich foods; decreased consumption of fat; the use of sound dietary practices and physical activity; and decreased prevalence of overweight. Existing data strongly suggest that these objectives will not be reached among adolescents by the year 2000. Furthermore, the prevalence of overweight has increased significantly, particularly among minority youth and among youth from low socioeconomic backgrounds. To address these growing problems, it is essential to identify the groups of adolescents that need to be targeted for intervention and to identify the factors that need to be addressed in the interventions. However, there are large gaps in our understanding of the factors associated with nutritional intake, physical activity, and weight status among adolescents.
Research Questions or Hypotheses

Following are the main research questions to be addressed:
1. Are adolescents meeting the *Healthy People 2000* Nutrition Health Status and Risk Reduction objectives? Which groups of adolescents are at greatest risk for not meeting these objectives and thus need to be targeted for intervention?
2. What are the direct and indirect overall contributions of socioenvironmental, personal, and behavioral factors to the explained variance in nutritional intake and weight gain status? Are similar associations found among adolescents from different socioeconomic, age, gender, and racial/ethnic groups?
3. Which specific socioenvironmental, personal, and behavioral measures are associated with the targeted behaviors outlined in the *Healthy People 2000* Nutrition Health Status and Risk Reduction objectives? Are similar associations found among adolescents from different socioeconomic, age, gender, and racial/ethnic groups?

Study Design and Methods

The study will include three separate but integrated components: (1) Focus groups with 150 adolescents; (2) survey completion and anthropometric assessments of 5,500 adolescents in grades 7 and 10; and (3) parental telephone interviews with 900 parents of the adolescent respondents.

Population and Sampling Plan

Those eligible to participate are students in grades 7 and 10 who attend schools in St. Paul with at least 25 students in each of those grades. Students will be drawn from 14 schools with 7th- and 10th-grade classes. These grades were selected in part because mandated health education training occurs in these grades. It is estimated that 90 percent of the eligible students will participate. Based on school enrollment data, the sample is likely to include five racial/ethnic groups: African Americans, whites, Native Americans, Asian American/Pacific Islanders, and Hispanics. Telephone interviews of approximately 900 parents of the surveyed students will be conducted after the in-class surveys. These parents will be selected by a randomization procedure.

Analysis Plan

The proportion of adolescents meeting the *Healthy People 2000* objectives (e.g., percentage of overweight adolescents) will be analyzed with chi-square tests. Logistic regressions will be used to examine independent associations between sociodemographic variables and outcome measures. Questions concerning mean levels of dietary intake (e.g., daily servings of fruits and vegetables) will be addressed with t-tests. Analysis of covariance will be used to compare means among subgroups of the population. Structural equation modeling (SEM) will be used to test models describing the relationships between socioenvironmental, personal, and behavioral factors and each outcome measure. Hierarchical regression will be used to identify specific constructs (from within the socioenvironmental, personal, and behavioral factors) associated with body mass index and with nutritional behaviors targeted in the *Healthy People 2000* objectives.

Pre-Award Evaluation

Evaluator 1

Originality and Importance

This study aims to identify socioenvironmental, personal, and behavioral factors associated with nutritional intake and weight status among adolescents, as outlined in the *Healthy People 2000* nutrition objectives. The findings will lead to the development of more effective interventions aimed at improved eating behaviors among youth. This is an important, well-designed study. The details of implementation are explicitly articulated, the goals of the research are consistent with the data to be collected, the researchers are experienced in the areas of investigation, the contributing colleagues are appropriately trained for their roles, and there is indication that the necessary collaborations will occur.
**Regional and National Significance**

The need to identify and understand the factors associated with nutritional intake in adolescents is an issue of national significance that should be addressed. This review makes clear that the proposed study is a logical next step that will advance the state of knowledge related to adolescent nutrition. The materials generated from this study will permit examination of a wide array of issues related to beliefs and practices of adolescents concerning diet and exercise/physical activity.

**Scientific and Technical Merit**

This revised application was reviewed at the November 1996 review cycle, at which time action was deferred pending additional information. The application proposes a three-stage study of the factors associated with nutrient intake and body weight in adolescents. The investigators have responded carefully to comments by the study section. Initially, the investigators plan to draft a questionnaire and a set of questions for use in focus groups. These materials will then be examined and assessed by an established advisory board at the University of Minnesota; the board includes 10-15 adolescent members. The revised materials will be used in the next step of the research.

During the subsequent stage of the study, 150 adolescents will participate in tape-recorded focus group sessions lasting approximately 1 hour. The participants in this phase represent three 7th grade and three 10th grade health education classes selected from one junior and one senior high school in St. Paul, MN. Guided by the questions developed in the earlier stage of the study, students in the focus group sessions will describe and discuss their food choices, physical activities, and the factors they believe may influence their consumption of specific healthful foods or their level of physical activity. These open discussions will be followed by a period of debate, in which half of the participants will take roles as "resistors" and the others will attempt to convince them to change behaviors; the students will then change roles. The same groups of students will also complete the draft questionnaire.

The data from the focus group sessions will be coded and analyzed for themes related to factors affecting nutrient intake and physical activity; factors enhancing activity and the consumption of more healthful foods; and the benefits and barriers related to these behaviors. Coding reliability will be tested on a subset of transcripts. The findings will be used in modifying the student survey and in a parental telephone interview for the next stage of the project. Test-retest reliability of the survey will be determined by repeating the process 1 week after initially administering the survey.

After these developmental sections of the study are completed, the revised materials will be used in surveying approximately 5,500 adolescents, who will also have weight and height measurements recorded. These students will be recruited from 7th and 10th grade classes in 14 schools, and an estimated 90 percent of the eligible students are expected to participate. Based on school enrollment data, the researchers anticipate the formation of five ethnic groups: American Indian/Alaska Native, Asian American/Pacific Islander, Hispanic, African American, and white.

The issue of informed consent remains a concern. In the revised application, as in the previous versions, a letter of consent is to be "sent home to all parents . . . and returned to the school with their child" if they do not want the child to participate. Presumably, the letter is to be delivered by the student, but that is not specified. This is problematic because failure to deliver the letter could result in student participation without true parental consent. Participating students complete a consent form at school. If parents of participating students are later contacted to participate in the parental interview component of the study, they may be unaware and justifiably disturbed that their child participated in the study without their consent.

Therefore, the research review committee recommends that the letter of consent be mailed directly to the parents' home. A stamped, return-addressed postcard should be provided so that parents who decline participation can indicate this easily. Furthermore, since the Hmong subsample does not speak English, the mailed consent form probably should be stated in English on one side and in Hmong on the other, unless the Hmong parents can otherwise be identified.

The recommendation is for approval with the following conditions: (1) The informed consent letter for parents should be mailed directly to the home; (2) the mailing should include a stamped, return-addressed postcard; and (3) the budget should be reduced by 15 percent.
**Fetal Antecedents of Infant Outcome**

**Grantee**  
The Johns Hopkins University

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**Project Number**  
R40MC00180

**Project Period**  
1/1/2000-12/31/2002

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**Year 2010 Objectives**  
No Stated Healthy People Objectives

**Study Design**  
Observational

**Time Design**  
Longitudinal

**Care Emphasis**  
Noninterventional

**Population Focus**  
Infants, Pregnant women (not otherwise identified as adolescents)

**Race/Ethnic Focus**  
No Stated Race, Ethnic Focus

**Priority Research Issues**

**Summary**

*Statement of the Problem*

The period before birth has long been recognized as the progenitor of postnatal development. Recent models of the potential for antenatal programming of adult diseases and conditions have contributed to a resurgence in interest in the fetal period in the biomedical community. In addition, the focus of inquiry into the origins of severe neurologic deficits, such as cerebral palsy, has shifted in the last few years from the intrapartum to the antenatal period. Yet relatively little is known about what constitutes normal development prior to birth, whether prenatal development can be successfully measured, and whether predictive validity to later developmental outcomes can be established from the fetal period. Ultimately, documentation of normal fetal ontogeny, and the factors which influence it, will allow detection of atypical antenatal development in fetuses at-risk for postnatal developmental morbidity.

*Research Questions or Hypotheses*

The broad conceptual orientation of this research is that fetal neurobehavioral development reflects maturation of the central
nervous system during gestation and establishes origins of individual differences in autonomic functioning. Constraints on development may be provided by fetal factors, such as fetal sex, and maternal factors, including psychologic distress, which affect the intrauterine milieu. This project is oriented toward answering the two following research questions:

1. What is the validity of measures of fetal neurobehavioral development in predicting postnatal development and behavior through the first 2 years of life? We predict that individual differences in the rate of development, behavior, and temperament are established prior to birth and that there will be continuity in prenatal to postnatal function.

2. What are the effects of maternal stress on infant development? We predict that maternal stress will be associated with reductions in cognitive and motor development, and impairment of regulatory processes, including attention, as a result of disruption to the homeostasis of the developing hypothalamic-pituitary axis.

Study Design and Methods

This project includes only the infant follow-up portion of a larger study in which pregnant women are assessed at six gestational ages: 20, 24, 28, 32, 36, and 38 weeks, and their infants receive a standard neurobehavioral assessment at 6 weeks postpartum. During each antenatal visit, measures of fetal function (e.g., heart rate, motor activity, and their interrelation) and maternal physiology (e.g., heart rate, skin conductance response and level, and respiration) are collected. Maternal-fetal data are digitized using a computerized system during undisturbed baseline conditions as well as periods of induced maternal arousal (i.e., cognitive and emotional challenges). During each visit, women complete a battery of self-reported questionnaires regarding their levels of anxiety, mood, depression, and perceived stress. The MCHB-funded project begins with an infant follow-up assessment at 16 months based on a maternal telephone interview. The interview includes: 1) the Sleep Habits Inventory for Toddlers; 2) the Infant/Toddler Symptom Checklist designed to ascertain symptoms of regulatory difficulties; 3) a motor milestone scale; and 4) a physical activity scale.

Data collection at two years of age involves a laboratory visit. Toddler heart rate patterns, including vagal tone, are measured from ECG monitoring. The Bayley Scales of Infant Development II are administered (MDI, PDI, and Infant Behavior Record). Attention, behavioral regulation, and maternal-child interaction are assessed during two observational situations: a shape sorting task and joint book reading. The entire session is videotaped for behavioral coding. Mothers also complete a series of psychosocial questionnaires.

Population and Sampling Plan

The sample for this study is 120, stratified by parity (nulliparous vs multiparous) and fetal sex. During pregnancy, participants are volunteers recruited from the local community. Subject participation is restricted to non-smoking women with singleton, uncomplicated pregnancies who are at least 20 years of age. Given the gestational age-based nature of the study, accurate ascertainment of fetal gestational age is imperative. Exclusion criteria, determined through self-report and review of prenatal and intrapartum medical records, include maternal medical (e.g., hypertension) or behavioral (e.g., documented substance use) risk factors and fetal conditions which are known to affect fetal development and outcome. In general, the sample includes well-educated, employed women; approximately 20% are racial/ethnic minorities.

Analysis Plan

This project generates complex data which requires a series of analytic approaches tailored to the specific hypothesis being tested. The hypotheses can be broadly categorized into the following two categories: Fetus-Infant and Mother-Fetus-Infant. Four statistical techniques will be utilized: 1) exploratory and bivariate analysis to describe the simple relationships; 2) simple and multiple linear regression, in order to predict to the 16 and 2 year outcomes from single and multiple fetal and maternal measures; 3) individual growth curve modeling, to determine whether the rate and patterning of prenatal development predicts outcomes independently from level, and 4) structural equations modeling (SEM), to model fetal neural integrity, the underlying latent variable of interest. With respect to the first question, both within domain (e.g., activity level during the fetal period to activity level during infancy) and cross-domain (e.g., fetal behavioral state to infant attentional performance) predictive relations will be analyzed. With respect to the second, it is predicted that the physiologic data collected from pregnant women during both undisturbed and evoked conditions will be more potent predictors to infant outcome than paper and pencil reports of psychological stress.

Pre-Award Evaluation
Evaluator 1

Originality and Importance
No statement of originality and importance.

Regional and National Significance
No statement of regional and national significance.

Scientific and Technical Merit
Hypotheses are fully developed and tied to the complex processes of the conceptual model provided in the proposal. Developmental assessments of the infants include an array of factors that reflect broader developmental notions of influence related to fetal neurobehavioral function, and the data analytic scheme is tied directly to the hypothesized relations that are discussed.

It is interesting from a basic science perspective to link fetal neurobehavioral functioning with later infant developmental functioning. The notion of continuity from fetal status through later childhood is entirely sensible. Given the constructs that are to be assessed in the proposal, most of which address attributes with strong biological components (e.g., regulatory behavior, motor development), it would be more surprising to find a lack of continuity than continuity between fetal neurobehavioral functioning and subsequent infant regulatory behavior. It would be helpful to know whether there is meaningful application of the ability to characterize fetal neurobehavioral status. The basic science aspects are clear, but the concepts of the applied aspects are not developed within the proposal.

One strength of this application is that a large portion of the overall project, the antenatal assessment and the six week post-birth assessment, are all funded by an NIH grant. Therefore, the current proposal only seeks support for the 12-month maternal report and an 18-month infant mother lab session. The cohort 2 study of 40 to 50 infant home assessments is also included. Whether or not this merits four years of support will be addressed later, but it seems a lengthy period.

Another conceptual issue involves the choice of the 12 and 18-month measurement periods. There is no developmental argument provided for the choice of these periods and the information that is collected within them. Why are regulatory, developmental, and interaction indices collected in depth at 18 months, and maternal report data on child behavioral symptoms, sleep habits, and motor milestones collected at 12 months? Infant regulatory abilities are well developed by age 12 months, and can be easily measured by methods similar. The choice to use 18 months may be sensible, but there is a long latency between observational assessments (6 weeks to 18 months) which is not optimal in longitudinal assessments of early developmental continuities. Some developmental rationale for these choices would have been helpful.

The inclusion of a data collection for cohort 2, entirely separate from that occurring with the cohort 1 data, presents questions. Cohort 2 is first, a small sample (and there may well not be sufficient power to demonstrate predictions despite the power analysis offered), but more importantly does include the same measurements protocols available in cohort 1. The fetal assessments are fewer and from somewhat different periods, and there are no assessments of the mediators collected in cohort 1 that form the basis of the full developmental model being investigated. In fact, it is quite simply the combination of the fetal neurobehavioral data and the developmental-contextual mediators together predicting links to children's later functioning that provide the strength of this proposal. The cohort 2 assessment cannot duplicate this wealth, and will be of limited value comparatively.

In regard to the observational measurements, there is a lack of detail that is unfortunate when these measurements are critical to the assessment plan at 18 months. For example, are the interval data to be collected scored as frequencies within the interval or simply as present or not? Is there any indication of the "degree" to which these behaviors occur (e.g., negative affect can vary widely; what qualifies as negative affect?). Are there child behaviors scored outside the attention scoring? None are listed in the maternal-child interaction description. The power analysis provided makes its assumptions on the basis of 5 variable inclusions in the regressions. Given the wealth of data that may be involved to address the complex...
mediational and/or maturational aspects of the proposal, 5 variables seems rather optimistic.

The principle investigator has a strong scholarly record in the area of the proposed work, and is very well qualified to conduct the proposed research.

The sample acquisition process, and the complexity and frequency of the fetal assessments require that adequate time be given to acquire a sample so there are not too many data collections ongoing at any one time. However, the timeline provided suggests that data collection is complete by the end of the third month in Year 4. That leaves only data analysis (slated for 4 months) and report preparation (slated for 5 months). Yet, the year 4 budget is nearly $5k greater than any other budget. This is not sensible.

Evaluator 2

Originality and Importance
The present project’s goal to link in-utero behavior to later developmental outcomes is a problem worthy of pursuit. So much of antenatal development may be predicated upon in-utero development such that potential developmental problems during infancy and childhood may be addressed before birth. While such knowledge has the potential for misuse, it may also provide the information needed to create early interventions geared towards addressing in-utero problems immediately after birth.

Regional and National Significance
The proposal is well written and well conceived. There is a rich fetal data set and the initial findings appear to support many of the hypotheses posed. The literature reviewed is broad and makes some interesting assumptions about how fetal movement may be indicative of neurological development. It is still yet to be seen if these links are born out by the data, but the questions posed in the proposal go beyond what is known at present. The outcomes of such a study would be a major contribution to the field.

Scientific and Technical Merit
A major question has to do with the logic between the fetal data and some of the cognitive outcomes posed. It seems reasonable to suggest that changes in fetal movement patterns over the course of gestation may be indicative of increasing neural integration. Therefore, it also seems reasonable to predict that such patterns should relate to measures taken between 6 weeks and 18 months, especially since all of these measures are motor dependent. That is, the early cognitive measures, like the motor milestone measures, assess motor behavior and coordination. Since similar factors are being linked between the fetal and the infancy data, one would expect to see a relationship if one existed. Such a relationship is harder to justify in the 5 year old data, specifically the cognitive assessment to be made. At 5 years old, the intelligence instruments move from being motor-based to being verbally based. From my reading of the literature, the relationship between infant measures and verbal measures is not that strong. Indeed, so many other environmental factors come to be better predictors of performance on such tests than earlier mental performance. Just look at how the gap between Blacks and Whites on intelligence tests begin to diverge once the measures change from motor to verbal. The possibility that fetal behaviors relating to such culturally latent measures at age 5 seems questionable to me. Using the HOME is good given its relationship with verbal IQ measure. However, one questions the validity of the hypothesized link in this particular instance.
Growth and Development Longitudinal Follow-up: Phase 2

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Project Number R40MC00241

Project Period 8/1/2001-7/31/2005

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Year 2010 Objectives
No Stated Healthy People Objectives

Study Design
Experimental

Time Design
Longitudinal

Care Emphasis
Interventional

Population Focus
Adolescents

Race/Ethnic Focus
African-American

Priority Research Issues

Summary

Statement of the Problem

Pediatric obesity is a serious public health problem that is increasing in prevalence, particularly among minority children from low-income families. Data on the prevalence of obesity in the United States come from the National Health and Nutrition Examination Survey (NHANES-III), a nationally representative survey conducted from 1989-1991. Using criteria of overweight (BMI > 85th percentile) and obesity (BMI > 95th percentile), 22% of children were overweight and 11% were obese. Thus, over 6 million children were heavy enough to be endangering their health. Although obesity is a chronic disease that is influenced by genetic, metabolic, and physiologic factors, there are environmental and psychological factors that contribute to obesity and therefore can be the focus of prevention efforts. Effective goals of prevention are to increase activity (reduce sedentary activities) and to decrease consumption of high fat foods – factors that have been associated with obesity.

Research Questions or Hypotheses
The dependent variables represent measures of: body fat (BMI and BIA), diet (percent fat and servings of fruits and vegetables), and physical activity (self-report and activity monitor). The outcome measures (body fat, diet, and physical activity) will be predicted by a longitudinal model including child characteristics (growth history, gender, self-esteem, and self-efficacy) and family characteristics (BMI, parenting style, support).

1. Specific relationships:
1a) A history of high BMI during childhood will increase the likelihood of high body fat during adolescence (high BMI and high BIA).
1b) The relation between self-esteem and obesity may vary by age and gender. When self-esteem is measured during childhood (self-esteem is measured at ages 6 and 8), it will not be associated with body size. However, in keeping with Strauss (2000), among boys, low self-esteem at age 13 will be associated with high BMI. There is not enough evidence to predict a relationship between self-esteem at age 13 and BMI for girls.
1c) Adolescents with a high self-efficacy for physical activity and dietary control will be more likely to engage in physical activity and follow dietary recommendations than those with low self-efficacy. In turn, adolescents with high self-efficacy will be less likely to have high BMI and BIA.
1d) Adolescents whose parents are overweight or obese are more likely to have high body fat during adolescence.
1e) Adolescents whose parents are authoritative (high controlling, high nurturance) are more likely to be physically active and to follow dietary recommendations and less likely to have high body fat, compared to adolescents whose parents are authoritarian (high controlling, low nurturance) or low controlling, regardless of nurturance.
1f) Adolescents who report that their parents are supportive of physical activity will engage in more physical activity and adolescents who report that their parents are supportive of dietary recommendations will be more likely to follow dietary recommendations.
1g) Adolescents who endorse the value of physical activity and dietary control and an average body size will be more active, follow dietary recommendations, and have less body fat, compared with those who do not endorse these values.
2) The relationships among individual, family, and cultural level factors and the dependent variables will vary by children’s history as FTT or nonFTT; rates of obesity will be higher among children in the nonFTT group.
3) Adolescents who receive the intervention will demonstrate a reduction in % body fat, a reduction in percent of calories from fat, an increase in fruits and vegetables consumed, and an increase in activity, compared to adolescents in the control group.
4) Adolescents’ response to prevention will be moderated by the State of Change. Adolescents in the Action or Maintenance Stages are more likely to demonstrate a reduction in body fat, reduction in percent calories from fat, and an increase in activity than adolescents in the Precontemplative, Contemplative, or Preparation Stages.

Study Design and Methods

In the Formative Phase we will recruit an Advisory Group of adolescents who live in the same communities as the study participants. We will use ethnographic interviews and focus groups to identify the ethnotheories of the adolescents regarding body size, diet, and activity. We will use data from the ethnotheories to develop the 12-session intervention and to produce a 15-minute videotape that will be incorporated into the intervention.

In the Intervention Phase we will conduct a randomized controlled trial of the intervention. The intervention will be conducted by Personal Trainers (undergraduate students) and will include membership in the local YMCA. Evaluations will be conducted at baseline, at the close of intervention and one year after the close of intervention.

Outcome measures include:
1) Body Composition: (a) Body Mass Index, and (b) Body Impedance, and (c) DXA
2) Physical Activity: (a) Direct measure - minimitters, and (b) Self Administered Physical Activity Checklist (Sallis, 1993)
3) Dietary Intake: (a) Youth/Adolescent Questionnaire (Rockett et al., 1997), and (b) Food for Life Survey (Havas et al., 1997)

Intervening Measures include:
1) Demographics
2) State of change, self efficacy, and decisional balance
3) Self esteem (Rosenberg, 1965)
4) Depression (Beck, 1960)
5) Body perception – silhouettes
6) Body self esteem (Mendelson, 1995)
7) Attitudes about dieting and activity (Crandall, 1994)
8) Children’s version of Eating Attitudes Inventory (Garner et al., 1982)
9) Caregiver/Peer Support – An Authoritarian Index (Jackson, 1998)
10) Child Feeding Questionnaire (Birch et al., 1998)

Population Description and Sampling Plan

The sample was recruited when the youth were < 2 years of age. All participants were born at term with birth weight appropriate for gestational age and no congenital problems, disabilities, or chronic illnesses. Within the first two years of life the children in the FTT group experienced a deceleration in weight gain, resulting in their weight-for-height or weight-for-age dropping to below the 5th percentile. The children in the Comparison group experienced adequate growth during the first two years of life with both weight-for-height and weight-for-age above the 10th percentile, based on national growth charts. Most children are from African American families (>95%) and reside in the low-income communities of West Baltimore. They are predominantly from single parent families who have limited education and are supported through public assistance. The sample is balanced for gender. During the course of this investigation the children will range from 12-15 years of age.

Analysis Plan

Hypothesis 1 addresses the determinants of body fat, dietary choice, and physical activity and will be analyzed using multiple regression. We will use hierarchial linear modeling (HLM) to examine the effects of developmental-ecological variables on changes in children’s growth from infancy through early adolescence. Hypothesis 2 addresses the relationship between children’s growth history (FTT vs. nonFTT) and outcomes during early adolescence. We will use multivariate regression analyses to examine the moderating and mediating effects of the intervening variables on the relationship between growth history and body fat, dietary practices, and physical activity. Hypothesis 3 examines whether adolescents who were in the intervention group are more likely to experience reductions in body fat and dietary fat and increases in fruits and vegetables consumed and in physical activity. We will use multiple regression analysis. The final hypothesis examines the moderating effects of stage of change to determine if response to intervention varies by the individual’s readiness to change. We will use regression analysis with body fat, dietary pattern, and physical activity as outcome variables. The moderating effects of stage of change on the response to the intervention will be examined by making an interaction term between stage of change and intervention status.

Pre-Award Evaluation

Evaluator 1

Originality and Importance
The PI makes the case that identifying factors that cause obesity is a current area of interest in the US due to the alarming increases in child and adolescent rates of obesity and in being overweight. Interestingly, though, in their sample only 19% of the FTT group is listed as being overweight, a number not too far from what is expected. This may have negative implications for the representativeness of their sample. Nevertheless, the originality of the intervention and the use of an existing sample on which much developmental data has already been obtained gives this proposal an important opportunity to contribute to the literature regarding obesity in youth.

Regional and National Significance
The successful implementation of a program for reducing the percentage of over-weight people would clearly have both regional and national significance.

Scientific and Technical Merit
The problem conceptualization was succinctly stated, specifically regarding the need for a controlled clinical intervention that is well informed by theory and is multifaceted in implementation. The PI does a good job in integrating what is known with
specific ideas for intervention and elucidating what further knowledge can be gained.

The review of the literature seems complete, including work done by the PI and the research team regarding the study of FTT children. One question that does arise is the PI's review of the self-esteem literature regarding African-American (AA) females. The PI correctly states that the literature relating self-esteem and weight problems in AA females suggests no relationships. The PI suggests that this may mean that weight is not an important priority in their lives, but another explanation has been suggested in the literature. That is, the typical measurement of self-esteem may not be valid for AA females; supporting evidence in education also shows an inconsistent relationship between self-esteem and achievement in AA females. How would the PI address this possibility? Also, there is some possibility that the PI exaggerates the relationship between FTT, obesity, and their causal influences. It seems that, for example, there is a real and psychologically important difference between mothers who are neglectful and mothers who are controlling. Is there literature that would suggest a stronger relationship than the PI's speculation on this issue?

The hypotheses listed are adequately stated, although some are fairly obvious and their inclusion diminishes the careful thought that was put into this study. For example, it is hypothesized that a history of high BMI in childhood will increase the likelihood of a high BNII in adolescence. This is the foundation of the whole proposal. If the children that were overweight at age 8 are not likely to be overweight now, then there is no real reason to continue to follow this group. One takes it that the PI does not really intend this to be an issue that is still debatable.

The explanation of concepts, particularly, the components of the intervention, were more than adequate. However, it was not clear to what extent the keeping of a personal notebook and 24-hour diet recalls is a part of the intervention, or a part of the method for evaluating the effectiveness of the intervention. In either case, one suspects that the PI will have difficulty in getting adolescents to actually engage enthusiastically in this behavior. What evidence exists that this component will be useful or successful?

In general, the measurement section was adequate, but a few questions remain. Continuing from before, +0 what extent is there evidence that adolescents can complete the 24-diet recall form with any degree of reliability or completeness? Second, the PI will collect adolescent perceptions of caregiver attempts to sabotage their efforts to meet their healthy lifestyle goals. Why not get caregiver reports as well to get the other side of the story? Also, the PI will measure the stages of change readiness (TTM) that are reported by both the target adolescent and the primary caregiver. Why not include a measure that also indicates the processes of change that is used by both as an additional source of information regarding the nature of the intervention?

Finally, the use of the Harter to measure self-esteem in AA females has been specifically targeted for possible validity issues due to its response format. Would it be possible to include a second measure to obviate this possibility of measurement bias?

The study design is clear, although this reviewer worries that the attrition from this long-standing sample is higher than the PI suggests. As understood, this sample has been out the study for about 5 years. Does the PI indeed know that the n=190 is still available and willing to participate in the study?

The data analysis plan is complete and adequate for the questions proposed. The only issue is that guarantee in inter-rater reliability by letting coders discuss until consensus is reached is not a fair assessment of reliability.

The timeline is adequate for the study.

The PI has adequate access to resources to complete the project successfully.

The budget could stand considerable paring.

There are no human subject concerns.

Evaluator 2
Scientific and Technical Merit

The proposal has considerable strengths. As a longitudinal study, the project will benefit from a strong base of previous information on the children, allowing exploration of a variety of possible pathways of influence in the development of childhood obesity. In addition, as the investigators point out, the research team itself is already established and has the capability to carry out this new project with little extra preparation time. The relevant literature is thoughtfully discussed and its contribution to the proposed work is clearly specified. The intervention (a combination of home visiting and an instructional video to be developed specifically for this purpose) is modeled on a similar intervention already used successfully by the investigators in another context. The proposal contains detailed plans for analyzing the quantitative data, and a considerably more elaborated plan for dealing with the textual material generated by the focus groups than is often seen. The project is notable for its recognition that the entire family should be included in the intervention, in contrast to many youth programs. There are also a number of creative and even heartwarming details, such as presenting home visitors as "personal trainers," having a "small grant program" by which study participants can apply for funds to cover sports equipment or fees related to activities, providing "personal notebooks" for the study participants to track their progress and other aspects of their lives, and having a "dinner club" at which participants cook, serve and share a meal.

Three concerns can be raised about the proposed study. First, the investigators' emphasis on the issues of parental control over eating, based on research by Birch, may neglect other equally or more important aspects of the children's environment related to eating. Keeping closer track of what actually happens each day through such measures as logs kept by the children or their parents could provide valuable additional information about how eating fits into the child’s developmental niche. Secondly, one is puzzled by the investigators' emphasis on the consumption of high-fat foods as the crux of weight control issues, especially since there has recently been a good deal of public discussion about how Americans may be misled in believing that bodily fatness derives solely from fatty foods. Finally, although one is impressed by the investigators’ evident knowledge of anthropological approaches to parental ideas, it would be good to know what kinds of ideas they expect to hear in the focus groups. Judging from their review of the literature, it would seem likely that one idea will be that fatness, at least in girls, is not viewed negatively in this population. If that is the case, then one is faced with an interesting dilemma: how to be culturally sensitive and relevant without simply agreeing with a point of view that may not support good health and that, in any case, runs counter to the thrust of the project. One would imagine that the investigators may already have given this issue some thought, but it would be interesting to know how they plan to deal with it.

Evaluator 3

Originality Importance

This is a well-written grant that addresses an important issue affecting the life and wellness of many citizens. The PI and her colleagues have designed a project which will allow them to further evaluate the unique longitudinal population that they have been following for many years. A major strength of this project is this longitudinal study of an at-risk population - a perspective and opportunity rarely available in research. Additionally, the investigators are able to use information that they have gathered from previous experience and expand upon already established relationships with the study participants.

Regional and National Significance

Obesity and lack of physical activity contribute significantly to the morbidity and mortality associated with the chronic diseases affecting citizens, especially African Americans today. Especially alarming are the high rates of cardiovascular disease, diabetes, and heart disease which are all negatively affected by overweight and inactivity. Unfortunately very little information exists about effective interventions that prevent obesity particularly in light of numerous genetic and environmental factors associated with this condition. As described, this study will help to identify those factors that both protect against/prevent as well as contribute to obesity in this population. In addition, the planned prevention activities will allow some assessment of interventions and their probability of success. The investigators propose to have two phases; an informative phase involving ethnographic evaluation and assessment of factors associated with over-weight and then an intervention phase where information collected from the first phase along with proven effective methods are combined to develop and deliver interventions to adolescents in the study population.

Scientific and Technical Merit

The investigators listed clearly have the experience and expertise to conduct this study. Additionally, their long-time
working relationship and collaboration further ensures the success of this project. The prime variable that exists is related to the as yet unidentified graduate student who will be a primary player in this study, if funded. While the PI has had previous successful studies with similar construction it is worthy of mention and attention.

The fundamental theories and constructs supporting the foundation of this study are impressive and represent a significant strength of this project. The research plan's attention to these constructs greatly strengthens this proposal. Attention to this is evident throughout for example in the formative phase when good attention is paid to obtaining and incorporating appropriate ethnographic information in the intervention. Evidence of attention to these constructs is clear throughout the proposal.

Another strong feature of this proposal is the prior experience this group has had with similar study designs and interventions. This experience is evident in the selection of strategies, like home visits, and attention to adolescents and assurance of choice for adolescents which are incorporated into this study.

Use of this population which has previously been studied and provides longitudinal data is a strength of this proposal. Originally infants selected were FTT and non FTT and similar with regard to other demographic factors. This therefore should provide for a representative sample but one wonders if there has been distortion or selective criteria associated with families who have chosen to remain in the study throughout its course. Are there factors making this a unique population or is it representative of the community as a whole and therefore more generalizable.

This study is divided into two phases; formative and intervention. One appreciates the attention paid to the formative phase. Careful and sound approach to the interview as well as the use of standardized recording and transcription methods allow the capturing of qualitative as well as quantitative information.

The data methods and analysis described in the grant appear reasonable. This reviewer has not had much direct experience with HLM, but reviews of this method are consistent with description provided.

I was further impressed by the careful exploration of each of the variable and factors contributing to this study. Each aspect of the study and measurement are carefully examined and described. Attention is paid to possible problems inherent in each of the study methods employed, i.e. 24 hour food recall, self reporting of physical activity.

This is an expensive study that could stand considerable trimming. Travel budget appears generous. There is one inconsistency with regard to Ms. Kerr's position - in text noted to spend 30% on this project yet is budgeted for 100% on the table.
**Summary**

**Statement of the Problem**

Organ transplantation has transformed a number of previously fatal childhood illnesses into chronic conditions. In exchange for survival, children must commit to a lifetime of immunosuppressive medications; they then become vulnerable to the side effects of these medications and to infections. Long-term adherence to medications and other medical followup care is extremely challenging for these children and their parents; this is further complicated when families have substantial obstacles to care. Such obstacles include restricted or insufficient coverage by health insurance, lack of transportation for medical appointments, and inadequate fluency in English.

These obstacles to care are common within culturally and socioeconomically diverse patient populations and are addressed at most transplant centers through additional support that is provided by a combination of social workers and nurse coordinators or case managers. However, concern about costs in the current, highly competitive health care market has eroded the availability of many concrete supportive services. There is growing evidence that such cutbacks may prove to be shortsighted. Reduction in psychosocial support services may lead to increases in more costly medical service use. For example, researchers have demonstrated that use of a case manager on a kidney transplant service can decrease medical utilization (e.g., a shorter length of hospitalization). Cutbacks in such services can result in a loss of these cost savings.
A complete psychosocial assessment of the child and parents is routinely included in the pretransplant evaluation of potential organ recipients. If specific family psychosocial factors can be identified throughout the course of treatment as predictors of long-term health care utilization, targeted psychosocial interventions might result in cost savings. Clinicians note that adherence appears to diminish over time, particularly after the first 2 years posttransplant. The prevention of a single, significant rejection episode represents considerable financial savings (hospital and medication costs), as well as preservation of the donor organ, which is a scarce resource. Such preventative interventions could also result in substantial savings in terms of human suffering and future years of life for the child.

**Research Questions or Hypotheses**

This study would provide the basis for the development of supportive psychosocial interventions for pediatric kidney-transplant, heart-transplant, and liver-transplant recipients who are identified as high risk. This could affect cost savings by reducing medical services utilization while maintaining or improving functional outcome. The primary objectives of this study are:

1. To identify nonmedical factors that predict high utilization of medical and psychosocial services for pediatric kidney-transplant, heart-transplant, and liver-transplant recipients in the second, third, and fourth years posttransplant;
2. To identify nonmedical factors that predict poor functional outcome for pediatric kidney-transplant, heart-transplant, and liver-transplant recipients and their parents in the second, third, and fourth years posttransplant; and
3. To develop an assessment instrument that could be used to predict medical and psychosocial service needs of pediatric kidney-transplant, heart-transplant, and liver-transplant candidates.

**Study Design and Methods**

This study is conceived as a longitudinal study that uses multivariate statistical techniques to determine the amount of variation in treatment costs and outcomes accounted for by parent or family psychosocial indicators. Subjects and their families will be enrolled in the study at 12 months posttransplant and tracked for the subsequent 36 months. A research team member in a face-to-face or telephone interview will administer questions in either English or Spanish. This will require approximately 60 minutes per family assessment. A research assistant will be available at all times to answer questions about the questionnaires. At the completion of each of the three assessment points of the study, the parent will receive $40 for participation (a total of up to $120 for participation in the entire study).

1. **Psychosocial predictors (independent variables):** All of the psychosocial predictor variables will be assessed by self-report data from the organ recipient's mother. If the child does not live with his or her mother, data will be collected from the primary caregiving adult. These measures will be administered at entry into the study and 24 and 36 months after.
   a. Concrete resources will be assessed by using a brief checklist that has been designed for this study and will be administered verbally. The checklist, which has strong face validity, is designed to be similar to the social work assessment that is a part of each pretransplant assessment. The items will be totaled to result in a numerical concrete resources score.
   b. The Social Support Survey that was created for the Medical Outcomes Study will be used; this 26-item self-report measure assesses emotional or informational, tangible, affectionate, and positive social interaction for adults.
   c. Socioeconomic status (SES) will be represented by the widely used Hollingshead-Redlich two-factor rating formula that is based on the parents level of education and occupational status.
   d. Acculturation will be assessed by using a standardized measure titled the Marin Short Acculturation Scale for Hispanics that is designed for use with Spanish-speaking immigrants. These four questions briefly assess acculturation by evaluating the degree to which the individual prefers the use of Spanish or English in various areas of life.
   e. Information regarding type of insurance is readily available. For purposes of data analysis, all payers will be categorized as (1) MediCal or (2) other. (We recognize that all renal-transplant patients will also be eligible for Federal medicare.) This data may provide an opportunity to separate the effect of insurance type from the effect of SES or concrete resources. The most current type of insurance will be used in each assessment period.

2. **Treatment outcome:** Treatment outcome will be assessed by the following:
   a. Child functional outcome: The Child Health Questionnaire measure, which is available in a 50-item parent-report version, will be used for all subjects. This is fully applicable for children ages 5 years and older. Parents of younger children will complete only the portions that are applicable to their children. Additionally, at 24, 36, and 48 months posttransplant, the teacher questionnaire will be mailed to the index patient's classroom or homeroom teacher and returned in a postage-paid envelope.
b. Parent functional outcome: A widely used self-report measure will be used to assess parent functional outcome. The Psychosocial Adjustment to Illness Scale is a 46-item self-report instrument that was initially designed to assess the adaptation of adult patients to major or chronic medical conditions. Additional measures include the State Trait Anxiety Inventory, the Beck Depression Inventory II, the Postraumatic Stress Diagnostic Scale, and the Impact on Family Scale.

c. Medical service utilization costs: This variable will be based on the need of hospitalizations, emergency care, and major medical procedures by the index patient in the second through fourth years posttransplant. These needs will include (but not be limited to) additional surgical procedures, radiographic and imaging evaluations, and endoscopies. Utilization information will be obtained from Current Procedural Terminology codes on payers’ billing records and converted to dollar amounts using conversion figures for medicare cost data.

d. Patient compliance: Patient compliance will be assessed by the treatment team through a brief questionnaire that has been developed for this study.

Population and Sampling Plan

All pediatric patients (ages 1–18 years at the time of transplant) who receive liver, heart, or kidney transplants and who survive for more than 24 months posttransplant will be eligible for inclusion in the study. We anticipate that approximately 150 families will agree to participate in the study. Patients are expected to range in age from 3 to 20 years at the time of entry into the study. Based on the overall pediatric transplant experience at this center, it is anticipated that the sample will be closely divided evenly between males and females. The racial/ethnic distribution of the sample will reflect the general treatment population of the Mattel Children's Hospital at the University of California, Los Angeles, which is approximately 60 percent non-Hispanic white, 30 percent Hispanic, and 10 percent a mix of African-American, Asian, and other racial/ethnic groups. Only families in which the primary caregiving parent is fluent in English or Spanish will be eligible for participation. We anticipate that less than 1 percent of the otherwise eligible subjects will be excluded on the basis of this criterion. Given the age, gender, and racial/ethnic diversity of this sample, the findings of the proposed study will be generalizable to other pediatric solid-organ transplant populations.

Analysis Plan

The primary goal of this research is to assess the relationship between key predictors (concrete resources, social support, SES, acculturation, and insurance status) and outcome variables (medical and psychosocial utilization costs and patient and parent functional outcomes). Several potential confounding factors (type of organ transplanted, patient age at transplant, type of illness, and severity of complications during the first 2 years posttransplant) will be controlled for. The measurement of outcomes at three points in time enables us to investigate (1) the average outcome across all three points in time, (2) a linear contrast that captures the degree to which outcomes are trending upward or downward across all three points in time, and (3) a quadratic contrast that captures the extent to which changes across the three points in time are nonlinear. Because the primary outcome variables in this study are being measured with composite instruments that can be thought of as producing measures on an underlying continuous scale, multiple linear regression analyses can be used. The primary tests of significance for the study can be framed as multiple regression analyses. For each of the four primary outcomes (medical service and psychosocial utilization costs and patient and parent functional status), a group of social and psychological factors are included as predictors in a model with other potential confounding factors that are intended to control for background differences among subjects. The latter predictors are type of transplant (heart, liver, or kidney), age group (categorized as 0–5, 6–11, and 12–18 years old), type of illness (congenital vs. acquired), and severity of complications during the first 2 years posttransplant (mild, moderate, or severe). For each outcome variable, we plan three tests—one for each contrast of interest (average outcome and linear and quadratic trends in outcome across three points in time). The primary test of interest for each contrast will be to see whether the predictors of interest (concrete resources, social support, SES, acculturation, and insurance status) collectively predict a substantial amount of variability in the outcome of interest. A multiple regression F-test can control for the confounding factors noted above.

Pre-Award Evaluation

Evaluator 1

Originality and Importance
The goal of this study is to identify posttransplant psychosocial factors that predict increased medical and psychosocial health care utilization or poor functional outcomes. Investigators hope to demonstrate the link between psychosocial services and improved functional outcomes for children with organ transplants. By defining the predictive factors of interest, investigators seek to develop a standardized psychosocial screening instrument to identify families at risk, as well as supportive or compensatory psychosocial interventions for these posttransplant families.

**Regional and National Significance**
The systematic assessment of psychosocial predictors of utilization and functional outcomes among children and adolescents with organ transplants is a crucial and growing area of research. Reviewers judged the research topic to have both regional and national significance.

**Scientific and Technical Merit**
The project's focus on families from diverse demographic backgrounds and on the risk factors that are amenable to preventative interventions suggests that findings will be generalizable and have practical significance for organ recipients, their parents, and health care providers. The principal investigator and research team are highly qualified to conduct the research.

Although this revised proposal has considerable strengths, a number of concerns still need to be addressed. If one of the goals of this study is to provide posttransplantation data on populations from diverse cultural and economic backgrounds, the small number of participating Hispanic, African-American, and Asian-American transplant recipients and their families may not constitute an adequate sample size. Although the power analysis suggests that a sample of 118 participants would be sufficient to detect statistical differences, and the investigator hopes to recruit a total of 150 participants, the anticipated sample size with respect to racial/ethnic populations raises additional questions. If the sample size is inadequate, the proposed multivariate analyses would not be possible and the generalizability of the findings would then be compromised. This problem is further compounded by the fact that the attrition estimates may be overly optimistic. Retention may be especially difficult among families of low socioeconomic status who have transplant recipients not yet enrolled in school. One possible strategy would be to oversample members of these groups to ensure sufficient numbers.

The specific variable, ethnic group membership, does not appear in any of the variable lists. How will the cultural differences between groups be factored into the data analysis plan?

Additional questions involve ratings of functional outcome. Teacher ratings of a recipient's functional status will be obtained at 24, 36, and 48 months. Presumably, these data are intended for cross-validation. The proposal makes no reference as to how this will be accomplished or how these data will be used. If there is disagreement between parents and teachers as to the functional status of the recipient, how will this be resolved? The proposal states that each parent will complete ratings of both the recipient's and the parent's functional outcome. In cases in which both parents cannot complete ratings, will the mother be selected as the informant? How will the data from two-parent households be compared with the data from single-parent households?

Although the data analysis strategy states that the longitudinal design enables the investigator to capture outcome trends and nonlinear changes, it is not clear how the causal relationships between the predictors and outcome variables will be ascertained. In the study design diagram, it is suggested that predictor variables "cause" functional outcomes. However, the current literature on social support recognizes that the distress of poor outcomes can also have a negative impact on adequacy of support. Given the fact that the data will be available to assess the bi-directional nature of support and outcomes, it seems appropriate to address this issue as part of the overall scope of the project. Exploring causal relationships more precisely seems especially important because this study is intended to provide the groundwork for future psychosocial interventions.

Although one of the major purposes of the study is to develop a standardized psychosocial screening instrument to identify families at risk, there is no direct description of the procedure to be used in developing such an instrument. How will the validity of this instrument be demonstrated? How will sensitivity and specificity be established? This issue was raised in the original review and remains a concern.

The cultural differences between the groups to be studied were only superficially addressed in the original application. The treatment population at the University of California, Los Angeles (UCLA) Medical Center includes a large Spanish-speaking subsample. The reviewers commented that cultural differences needed to be addressed in the study's conceptual framework, research questions/hypotheses, study measures and methodology, and data analysis. To assist with these issues, Dr. Carole Browner, an anthropologist with expertise in working with Spanish-speaking populations, served as a consultant for the revised application. The Marin Short Acculturation Scale has been added, and measures have now been selected based on...
their use with Spanish-speaking populations. Inclusion of this population is a strength of the research, since so little is known about pediatric transplant predictors and outcomes for this group of families.
The revised application, although considerably improved, still needs refinement. However, given the potential significance of the study, approval is recommended, with the following stipulations prior to funding: (1) Dr. Browner is to be hired as a paid consultant to the study; (2) analyses are to be restricted to the use of descriptive approaches with confidence intervals estimation; and (3) concerns raised in this summary review statement are to be clarified.
Improved Prenatal Down Syndrome Screening: PAIRED Testing

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Project Number  R40MC00195

Project Period  2/1/2001-1/31/2004

Costs

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Summary

Statement of the Problem

Each year in the United States, more than 2 million pregnant women are screened during pregnancy for increased risk of having a baby with Down syndrome. Down syndrome is the most common of the major chromosomal disorders that are compatible with life, having a prevalence of about 1:650 live births. The condition creates ongoing medical and societal challenges for families with affected members. Down syndrome can be reliably diagnosed in pregnancy by chromosomal analysis of fetal cells obtained by amniocentesis, but this procedure is expensive and carries a risk of fetal loss. For this reason, screening tests using serum obtained from maternal blood have been developed to identify women at a high enough risk to justify amniocentesis. Currently, the most widely used test is the triple test, which measures three substances in maternal serum in the second trimester of pregnancy. The triple test can detect 70-75% of Down syndrome cases by identifying 7-8% of the pregnancy population (screen positives) at sufficient risk to warrant an offer of amniocentesis. However, the down side of this screening is that almost all women called screen positive are false positives, i.e., almost all women referred for amniocentesis do not have a baby with Down syndrome. False positives cause psychological distress, cost to the health care system for expensive diagnostic procedures, and the potential loss of unaffected fetuses attributable to second trimester amniocentesis. Reducing the number of women with false positive test results would be an important
contribution for both patients and the health care system. The current grant is an intervention study to implement a new method of screening for Down syndrome that uses two serum samples (Paired Testing). This method, called the Integrated Serum Test (IST), has the potential to reduce the false positive rate from the current 7-8% to only 2-3% while still maintaining a high detection rate.

Research Questions or Hypotheses

The goals of the study are to establish that the IST can be successfully performed in a variety of primary care settings through a centralized administrative program, and that the false positive rate (essentially equivalent to the number of women with a screen positive test result) can be reduced to 2-3%. These goals will be addressed by answering the following questions:
1) Will health care practices now providing second trimester prenatal screening for Down syndrome agree to offer the IST?
2) Will women receiving prenatal care in the first trimester agree to IST screening?
3) Will women agreeing to the IST in the first trimester submit a second trimester serum sample?
4) Will the predicted reduction in the false positive rate be achieved?
5) Will a high percentage of screen positive women opt for diagnostic testing?
6) Is the Down syndrome detection rate consistent with expectations based on modeling?
7) Will the IST screening be cost effective as compared to the current standard of care (triple test)?

Study Design and Methods

The study design is an intervention trial to develop, test, and validate the improved approach to serum screening for fetal Down syndrome that is projected to reduce the number of women with false positive test results from 7-8% to 2-3%. With this method, measurements from five substances found in maternal serum are combined (the IST) to identify women at sufficient risk in the second trimester to warrant offering amniocentesis. The study population will be women in Maine receiving first trimester prenatal care. After informed consent, a blood sample will be drawn and sent to the laboratory for measurement of one component of the IST. A second blood sample will be drawn in the second trimester for measurement of the four other components of the IST. After computer matching, results of all tests will then be mathematically combined to give a single risk for Down syndrome. Women with high risks (screen positives) will be managed according to current medical practice.

Population Description and Sampling Plan

All 11,000 women in Maine presenting for prenatal care in the first trimester of pregnancy (7-13 weeks of gestation) are potential candidates for being offered the IST. Two-thirds of eligible pregnant women undergo traditional second trimester screening for Down syndrome. If this same rate holds in the first trimester, then 7,000 women might agree to being screened with the IST each year. However, because of the investigational nature of the testing requiring informed consent it is projected that only half of the 7,000 women will actually agree to be tested. Therefore, over the course of the two-year enrollment period it is conservatively projected that a total of 7,000 women will be tested. The population of Maine is approximately 97% white, with 1% or less of Native Americans, African Americans, and Hispanics. Approximately 50% of the population has an educational level of greater than 12 years, 38% have 12 years, and 12% have less than 12 years of education.

Analysis Plan

The following analyses will be performed to document the success of the IST screening approach:
1) Percent of women opting for the IST in the first trimester;
2) Percent of enrolled women providing a second trimester serum sample;
3) Percent of women with false positive screening results using the IST;
4) Percent of women with false positive screening results if the triple test had been used instead of the IST;
5) Down syndrome cases detected; and
6) Cost effectiveness of the IST as determined by comparing the savings resulting from the reduction in costs of amniocentesis/karyotypes with the increased cost for serum testing.
Pre-Award Evaluation

Evaluator 1

Originality and Importance
As initially noted, this is an important and well written proposal by an internationally recognized team of investigators who have made significant contributions in this area of study to the literature.

Regional and National Significance
The revised proposal seeks to integrate creatively first and second trimester Down syndrome screening results to minimize health risk, psychological stress and unnecessary cost by reducing the number of false positive screens.

Scientific and Technical Merit
The investigators have provided a thoughtful, critical and detailed response to the reviewers’ comments. There is a point by point comprehensive and detailed response to all questions raised in the critiques forwarded by each of the reviewers.

In the initial review, the scientific and technical merit was questioned as a result of the Wald et. al., August 1999 NEJM publication (341:461-7) reporting on improvement in detection and false positive rates utilizing the Integrated Test.

In responding to the above concern, the investigators clearly detail how the proposed PAIRED serum test parallels the Wald test (Wald, N et.al., NEJM. 1999; 341-7). The investigators note how their proposed test, except for the inclusion of nuchal translucency measurements is identical to the "integrated test" described by Professor Wald.

The applicants acknowledge that the Integrated Test combining the best first and second trimester serum markers with a first trimester ultrasound measurement of nuchal translucency (NT) thickness to produce a single Down syndrome risk estimate may yield the best results. Yet, even if superior, it is unlikely that NT measurements can be performed in primary care settings. Thus, they have chosen to study the variant of the Integrated Test that does not include NT (Integrated Serum Test). It is also noted that the Integrated Serum Testing builds on the existing infrastructure developed for the current standard of care (the Triple Test) that is proved to an estimated 2.1 million pregnancies annually. The only additional requirement is the collection of a blood sample at a time when other blood drawing is generally performed.

The applicants note that the Integrated Serum Test is not a competitor but a step on the road to the full Integrated Test. If successfully implemented, it can be introduced immediately and would lead to important improvement in patient care. Because of the ease of collecting a first trimester serum, the Integrated Serum Test could be offered to women in both urban and rural areas in the U.S., while the measurement of NT would be restricted to trained sonographers in high-risk perinatal centers.

The investigators acknowledge that the use of the term PAIRED serum test to describe the proposed method caused some confusion. The test they propose to use as noted is identical to a variant of the "Integrated Test" as described by Professor Wald. Accordingly, following discussions with Professor Wald, they have decided to change the name of the testing protocol from the PAIRED Serum Test to the Integrated Serum Test throughout this response and in the future. Professor Wald has written a letter supporting their proposed approach to implementing the serum variant of Integrated Testing.

The psychological impact of the proposed study was a point of reviewer concern. The applicants had emphasized throughout the protocol that the psychological impact of false positive test results would be a significant problem. Yet, there was no monitoring or tracking of the psychological impact of the proposed screening program. Since there are delays between the first trimester blood sample and the second trimester results the delay may increase a woman’s anxiety and the level of stress.

Based on the reviewers’ comments, the investigators have contacted Barbara Bernhardt, M.S., Co-Director of the Johns Hopkins University/National Center for Human Genome Research Institute Graduate Genetic Counseling Training Program, who has extensive experience in assessing ethical, legal and social implications of genetic testing. After reviewing the
project protocol and the MCHB reviewers' comments, she recommended that the most appropriate and cost effective approach would be a patient satisfaction survey at 24 weeks of gestation in a sample of the study population. Such a survey would be sufficient to identify important negative factors that might be associated with the Integrated Serum Test as compared to routine second trimester testing. The study plan now calls for a survey instrument to be developed and piloted. This survey will then be administered, on a random basis, to women who receive negative screening results (40 randomly selected women opting for the Integrated Serum Test and 40 matched women undergoing traditional second trimester testing). Matching will be on maternal age, number of years of education and expected date of delivery. The 80 women will be sent a questionnaire, with a follow-up reminder for those not responding. The final content of the questionnaire will be developed and interpreted with the assistance of Ms. Bernhardt.

The applicants also stated, in response to a parallel concern regarding early and late test induced stress, that it will be made clear to women who agree to be screened that no interpretative tests will be done on any serum sample until the second trimester. The first trimester serum is forwarded to the screening laboratory and frozen until the corresponding second trimester serum is received. If the second trimester sample is not received, the first trimester serum will not be analyzed. It will be emphasized in the patient educational material that the results of the Integrated Serum Test will be reported in the second trimester in exactly the same manner as would have been the case for traditional second trimester screening. The Integrated Serum Test is not unique, but merely a refinement to existing prenatal screening protocols.

The proposal did not sufficiently address other possible lines of development and detection tests. That is a state of technology review, that may have a bearing on this proposal.

The applicants have expanded the proposal's discussion of competing technologies including graphics in Section 2, pages 2 and 3. A comparison of the screening performance of the proposed Integrated Serum Test with existing and emerging screening methodologies has been included and satisfactorily identifies details and explains comparison methods.

As maternal age increases, both the false positive and detection rates increase. How will this affect the false positive rate?

The applicants note when using a fixed risk cut-off, the reviewer is correct that as maternal age increases the false positive and detection rates increase for any method of screening that utilizes maternal age. However, the benefit of an improved method of screening remains regardless of the age distribution of the screened population. For example, consider a group of 35 year old women. Using the current 'triple markers', the detection and false positive rates are 71% and 13%, respectively; using the proposed Integrated Serum Test, the detection rate would increase to 79%, while the false positive rate would be reduced to 4.2% (using a risk cut-off of 1:100). Were only older women to accept the Integrated Serum Test, a significant reduction would still occur.

Participation rates, access, and demographics could produce other experience if tested in other states.

Although it is possible that a successful Integrated Serum Test program in Maine may not be directly transferable to other populations, this has not been their experience. FBR implemented one of the first neural tube defect screening programs in the United States in Maine in 1977, implemented Down syndrome screening using AFP in 1986, implemented the triple test for Down syndrome in 1990, implemented trisomy 18 screening in 1993, and implemented quad testing for Down syndrome in 1999. All have been, or are being, successfully duplicated, with few, if any, modifications, throughout the U.S. The initial review raised the question that the PAIRED serum test is expected to reduce the false positive rate to as low as 2.1% with little effect on the detection rate. Yet, currently being studied is the addition of the dimeric inhibin A measurements (DIA) in the second trimester resulting in a four marker test. This fourth marker can add 8 to 10% to the detection rate without appreciably reducing the current false positive rate. Is the 5% improvement in detection rate with the four marker test as important a consideration as the decrease in false positive rate with the PAIRED test?

The investigators responded by stating that the objective of this grant is to offer a screening test that will significantly reduce the false positive rate while maintaining the detection rate now achievable by triple testing. The psychological impact of false positive test results are a significant down side to population based screening and may, eventually, result in lower screening uptake rates. A study published since the submission of this grant found that anxiety caused by a false positive screening result reduces participation in maternal serum screening in the next pregnancy. The authors conclude that reducing
the false positive rate will alleviate maternal anxiety and probably lead to more stable participation in screening programs. 

The earlier critique noted that the PAIRED Serum Test (now called the Integrated Serum Test), like the Triple test, is more likely to assign a high risk for Down syndrome if the pregnancy is incorrectly dated further along than it really is. Will more reclassification occur in the PAIRED study resulting in a shift in screen positive and false positives?

The response notes that the majority of pregnancies in Maine (65%) are dated by ultrasound examination by the second trimester and reclassification in these pregnancies is not an issue. First trimester marker PAPP-A levels increase as gestational age advances, and will, along with the second trimester markers, identify LMP dated pregnancies whose gestational age is overestimated. Evaluating the impact of adding this additional marker to the false positive rate is one of the aims of the study. However, the effect may not be very large since most of the incorrectly dated pregnancies are already being identified using existing second trimester markers.

Reviewers also noted that seven of the hypotheses are directed at studying the compliance and behavior of providers and patients. The study design includes reference to developing and validating physician and patient education materials. Nevertheless, there is no outline of the specific steps to be taken and the validation methods to be used.

Test linkage and sample marking were considered potential problems by the reviewers.

The patient record system, in place at the FBR for the last 25 years, has algorithms that link patient samples and patient records, track missing samples, track overdue samples, produce lists of outstanding or uncompleted tests, and produce monthly reports of tests performed by test type. These algorithms and protocols have been developed and validated as an integral part of the patient record system over many years. The linking algorithms take a hierarchical approach to matching samples that have been extensively validated for both the patient population that we serve and for several large nationwide collaborative studies that we have successfully conducted. This protocol will be modified to include items specific to the Integrated Serum Test.

The interviewer noted there was no information on how the sample will be forwarded to assure timeliness and how it will be monitored.

The applicants note as pointed out in Section 1 a and 1 b, page 2, the only sequential component of the Integrated serum test is obtaining sera at two points in pregnancy. The calculation of a final Down syndrome risk uses all the data and occurs only in the second trimester of pregnancy. That single risk will be used in exactly the same fashion as current used for second trimester screening. The Integrated Serum Test risk will, however, provide more accurate risks, resulting in many fewer women being classified as screen positive.
The reviewers noted that the steps to be taken to ascertain the cost information are not specified. The definition of patient education and the elements contained are not provided. The variation in educational efforts are not discussed.

The main component of cost effectiveness of the Integrated Serum Test as compared to the current Triple Test will be to compare the additional ongoing costs (education, sample collection and transport), and added laboratory costs with the savings due to the reduced number of ultrasound studies, amniocenteses and karyotyping. In addition, the one-time costs associated with developing, validating, and printing patient and physician brochures, enrolling physician practices, and other activities will be quantified.

The initial review noted that the plan for data analysis is almost entirely descriptive and limited in scope. Given the complex nature of the model, the multiple laboratory tests and the indices of risk to be derived and the cut off points established to determine risk a, more comprehensive plan to guide analysis may be helpful. Moreover, seven of the hypotheses are directed at studying the compliance and behavior of providers and patients. The study design includes reference to developing and validating physician and patient education materials. Furthermore, cost effectiveness and psychological impact are to be studied. Yet, the analysis section remains unrevised and the specific response to the critique fails to address this critical component of the study.

The budgeted personnel support appeared a bit "light" for the investigator, biostatistician and data coordinator.

The estimates of percent of time correspond to the average commitment over the course of a year. For example, the 10% of time allotted to the P.I. corresponds to 200 hours a year, and it is anticipated that most of this time allocation will be expended when the study is being implemented and diminish once the program is underway. If personnel require extra time, it will be donated to the Maternal and child Health Bureau. The budget has been increased to pay for a consultant to assist the FBR in assessing ethical, legal and social indications of Integrated Serum Testing.

Based on suggestions from the reviewers, additional funds are requested to study and assess a woman’s satisfaction with the Integrated Serum Test, including questions concerning anxiety as compared to matched women receiving only routine second trimester screening.

A draft of the informed consent document was not included.

The IRB-approved consent form is included in the revised document and is satisfactory.

An adequately detailed schedule is presented. It is realistic and appropriately conforms to the general outline of the protocol.

No other funds are reported being sought nor is there overlap with any other project. The Principal Investigator is currently supported by one NIH grant to study screening and treating of Hypothyroidism in pregnancy.

The P.I., Dr. Knight, received his PhD in Physiology and Biochemistry from Rutgers University in 1968 and his MS in Biology from Harvard University in 1964. Since 1978 he has held the following posts: Director, Prenatal Screening Laboratory, Foundation for Blood Research, Scarborough, Maine; Director, Interlaboratory Comparison Program for Acetylcholinesterase; Scientific Advisory Staff, Maine Medical Center, Portland, Maine; Adjunct Associate Professor of Biology, University of Southern Maine, Portland, Maine. Dr. Knight has authored or co-authored seven referred publications in the past two years almost all of which touch upon an aspect of pregnancy screening or Down syndrome. Dr. James Haddow received his MD degree from Tufts University in 1961. He is Associate Medical Staff, Maine Medical Center, Department of Research with privileges in Pediatrics since 1974 and is Vice-President/Medical Director, Foundation for Blood Research. Dr. Haddow has been principal author on a number of referred journal articles over the past two years, several with Dr. Knight as co-author that report on Down syndrome and pregnancy testing.

Mr. Palomaki is the team biostatistician. He received his B.S. in 1973 in Physics and Math from the University of New Hampshire. He has joined Drs. Haddow and Knight as co-author in several of the above referenced publications.
Edward Kloza received his MS in Genetic Counseling in 1975 from Rutgers University and has been at the Foundation for Blood Research since 1979. He was field coordinator for Primary Obstetric genetic risk assessment in Maine.

The Principal Investigator and the research staff of the Foundation for Blood Research have played a leading role in developing the methods currently used for prenatal screening in the United States, including being co-developers of the widely used triple test for Down syndrome screening. In addition, FBR staff has extensive experience in implementing population based prenatal screening programs as new methods of prenatal screening become available. Another important activity has been to conduct large collaborative epidemiologic studies in both the first and second trimester that have confirmed the screening performance of various proposed prenatal screening methods, such as the one outlined in this proposal. In addition to playing a central role in the development of prenatal screening in the United States, the research staff has had a major impact on setting standards for implementing and assuring the quality of such screening.

The Foundation for Blood Research has established arrangements with all physician practices in the State of Maine for transporting second trimester screening test using the FBR courier, second party couriers or express mail. This means that the practices are visited daily, and first trimester samples can be transported to the FBR laboratory using these same resources.

Total direct costs for the three year study were initially $431,430. As a result of the reviewer and committee comments to address maternal anxiety Ms. Barbara Bernhardt, Co-Director of the Johns Hopkins University National Center for Human Genome Research, is being added to the project as a consultant and will impact the budget as follows:

During year one, Ms. Bernhardt will receive a $1000 consulting fee for assisting in developing And piloting a maternal anxiety and satisfaction survey. During year two, Ms. Bernhardt will receive a $500 consulting fee for oversight during the administration of the survey. An additional $1000 will be required for tracking the women, printing, distributing, collecting the survey and posting reminders. During year three, Ms. Bernhardt will receive a $1000 consulting fee for aiding in the interpretation of the survey results and helping to write the final summary concerning the survey. Total direct costs are $4000. The applicant states if the committee decides that this additional component is worthwhile, modified budget pages will be prepared.

The first year request is for $147,787. The P.I., Dr. Knight indicates effort and support at 10%, Project Advisor, Dr. Haddow requests 5% support and Biostatistician, Palomaki is budgeted for 10% of salary. Fifty percent and 80% is budgeted for the Study Coordinator, Mr. Kloza and Diedre Foster, the Laboratory Technician respectively; with 10% to 20% support for processor, programmer and data coordinator. The budgeted personnel support appears a bit light for the investigator, biostatistician and data coordinator. Equipment, supplies and other expenses appear appropriate and justifiable.

The Foundation for Blood Research is now adequately described in the addendum to this application. The Prenatal Screening Laboratory at the Foundation for Blood Research is described as routinely providing multiple serum marker testing for over 30,000 women annually. The laboratory will utilize a Diagnostic Products Corporation Immunlite 2000 random access automated machine to measure AFP, _E3 and hCG. PAPP-A and DIA are microtitre plate assays. An ELIZA reader, washer and multichannel pipettes are available for these assays, as well as a Packard Multiprobe (a robotic liquid handling system). There are adequate computer resources to manage the PAIRED serum test interpretation and reporting.

IRB approval would appear to be pending. A draft of the informed consent document is now included.

Dr. John Williams III, Co-Director, Reproductive Genetics and Associate Professor of Obstetrics and Gynecology UCLA School of Medicine, was an additional outside reviewer whose opinion and recommendation was solicited at the request of the Study Section. Dr. Williams III summarized his review as follows: "In summary, Professor Wald's paper demonstrates (in theory) that pairing of first and second trimester maternal serum samples can improve Down syndrome screening by increasing the detection rate and lowering the false positive rate. Dr. Knight's project will determine whether paired or integrated first and second trimester screening actually can be done on a large scale in a clinical practice setting. A reduction in false positive rate from 5% to 1% would decrease the number of invasive diagnostic procedures such as chorionic villus sampling and amniocentesis by 80%. A reduction of this magnitude in invasive testing represents a substantial savings in terms of fiscal cost and unaffected pregnancies. It is on this basis that I recommend that Project R40 MC 00195-01 be
considered for funding."

Evaluator 2

Originality and Importance
This proposal seeks to decrease the false positive rate in prenatal screening for Down syndrome by using maternal serum samples collected during the first and second trimesters of pregnancy. The aim to decrease false positive rates without compromising the sensitivity of currently available screening tests is one of high public health importance. Reduction of false positive screen results will likely result in a considerable diminution of maternal anxiety associated with an incorrect positive screening test. Of equal importance, a reduction of the false positive rates stands to reduce substantially the risk of iatrogenic fetal loss (associated with amniocentesis) and prenatal care costs.

Regional and National Significance
The regional and national public health significance of this research is high.

Scientific and Technical Merit
This is a clearly written application, though as noted in the previous review, there was an inadequate description of several key facets of the proposed study design. Subsequent to the previous review, the investigators have provided a detailed response to the many questions and concerns raised in that review.

Overall, the investigators have been responsive to the concerns raised, and the additional information serves to raise the level of enthusiasm for the proposed study. Several of the major modifications proposed for the research are presented below:

1) The investigators plan to add a study aim directed towards evaluating maternal anxiety and satisfaction with the Integrated Serum Test (IST). The addition of Ms. Bernhardt, who has extensive research experience in assessing ethical, legal and social implications of genetic testing serves to strengthen the investigative team and increase the likelihood that the planned survey will be executed in a manner that provides meaningful results. It is disappointing, however, that the investigators provide only a cursory overview of the research approach to be taken in designing this survey. For instance, it is notable that the investigators provide no justification for the sample size of 80 subjects in the anxiety/satisfaction survey. This pattern of providing only a cursory or superficial discussion of key study procedures is pervasive throughout the proposal (as noted many times by previous reviewers).

2) The investigators (in their response) now provide a more comprehensive discussion of the other Down syndrome screening test and estimates of their performance. This information has been helpful in assessing the contributions results from this study are likely to make in this rapidly evolving area of prenatal diagnosis.

3) The investigators now provide a more detailed outline of the steps to be taken in developing and validating physician and patient educational materials.

It is important to note here that the investigative team at FBRI has over 25 years of experience in conducting these types of studies (this is stated many times through the proposal and in the response document). They are also recognized leaders in the field of prenatal diagnosis protocol development. However, the cursory manner in which the research plan was originally proposed, raises considerable concerns about the adequacy of the investigators’ plans for implementing and operationalizing data/specimen quality control procedures that assure the creation of a high quality database to be used for testing their specific aims. There were, for instance, considerable concerns about the likelihood of erroneous linkage of first and second trimester samples. Though the investigators address this concern in their response document, a clearly articulated plan for assuring that such errors are kept to a minimum would provide some assurances that data quality is regarded as a high priority by the investigative team.

The budget and time line are reasonable for a project of this scope. The additional requested funds to support the maternal
anxiety and satisfaction survey activities is reasonable, though again it is disappointing that a clear justification for the sample size of 80 individuals is not provided.

The protection of human subjects appears to be adequate.

**Evaluator 3**

*Scientific and Technical Merit*

This is a resubmission of a deferred proposal from the June review cycle. The name of the proposed test: PAIRED SERUM TEST, has been changed to INTEGRATED SERUM TEST to avoid confusion. Furthermore, the principal investigator is excluding the ultrasound measurement of nuchal translucency from the original package, stating valid arguments to do so. The question raised by the study section regarding potential maternal anxiety will be studied by adding a consultant who will advise in the area of assessing the woman’s satisfaction with the procedure. The survey instrument will be developed and piloted, and then administered randomly to women undergoing this new testing and compared to women undergoing the traditional 2nd trimester testing.

The principal investigator has answered all other questions satisfactorily and has demonstrated his knowledge and commitment to this area of research.

The informed consent as submitted is appropriate. However it is suggested that the last sentence be modified to read: "I understand the discomforts, inconveniences, risks and potential benefits of this study"
Improving Anemia Screening in Inner-City Children

Grantee
Boston Medical Center

Investigator
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(414) 3679 fax
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Project Number  R40MC00207

Project Period  8/1/2000-7/31/2002

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Summary

Statement of the Problem
Anemia and iron deficiency continue to be common in inner-city children. However, widely practiced screening and treatment strategies remain unproven.

Research Questions or Hypotheses
We are seeking to determine:
1) The clinical effectiveness of iron therapy for anemic children and non-anemic children with abnormal red cell indices;
2) The predictive value of supplemental tests [red cell distribution width (RDW), mean corpuscular volume (MCV), and erythrocyte protoporphyrin (EP)] in children with low-normal hemoglobin (Hb) levels; and
3) The best screening strategies for children with repeated normal Hb.

Study Design and Methods
Data have been obtained for children <5 years old from an inner-city primary care laboratory database (1/95-7/01). Results include a CBC (Hb, RDW and MCV), lead (Pb) and EP. Children with CBC, Pb and EP at 8-15 months of age followed by a second set before age 30 months have been included. Medical records of the selected children will be reviewed to determine presence of iron therapy between initial and follow-up testing.

**Population Description and Sampling Plan**

The study population consists of children <5 years old from an inner-city primary care clinic who have had a CBC, Pb and EP at 8-15 months of age followed by a second set before age 30 months (n=1150). Children with sickle cell anemia or elevated Pb levels (≥10µg/dL) will be excluded. Nearly all of the patients attending this clinic are poor and from minority ethnic groups. The data collected of this study population could be explored in secondary analysis to address gender, racial, and or ethnic health issues.

**Analysis Plan**

Children included in the study will be divided into six groups based on their Hb level and the presence of abnormal red cell indices at 8-15 months of age. Hb will be categorized as anemic (Hb<11g/dL), low-normal (11≤Hb<12g/dL) and high-normal (Hb≥12g/dL). Red cell indices will be considered abnormal if RDW>14.5%, MCV<70fL or EP>35µg/dL. The lab results and presence of iron treatment between the initial and follow-up tests will be used to determine the clinical effectiveness of iron therapy and the best screening strategies for iron deficiency anemia. We will also use survival analysis to determine whether children with one or more normal Hb results in the first two years of life need additional screening.

**Pre-Award Evaluation**

**Evaluator 1**

**Originality and Importance**

Practitioners are given conflicting information about anemia screening in children. The AAP and CDC recommend annual screening for the first five years of life, while the Institute of Medicine, Bright Futures RepoM and US Preventive Services Task Force recommend screening high-risk infants only once in early infancy. Better evidence is needed to guide clinicians toward the most efficient use of laboratory screening tests.

**Regional and National Significance**

Iron deficiency anemia is the most common nutritional deficiency in US children. If initial screening could predict those who will develop anemia and should begin prophylactic iron therapy, anemia prevalence may be reduced from its current 10-30% level to the goal of 3% set by the Healthy People 2000 report. Secondly, the actual clinical effectiveness of our current practice of prescribing iron therapy will be studied.

Although this data is from one institution, the population is a high-risk group from multiple ethnic cultures. The information gained will most likely be applicable to other high risk, low socioeconomic groups.

**Scientific and Technical Merit**

The proposal is clearly and succinctly written. The investigators clearly state their hypotheses and their sample size and analysis plan for each. Objective entry criteria and operational definitions are given. Pilot data indicates that there should be sufficient children who are anemic or have low-normal values at initial screen and also have a repeat screen >6 months later.

The use of longitudinal data collected on a high-risk population is an inexpensive and quick method to gain information. Unfortunately, it suffers from all the usual problems of retrospective data collection. Is there a bias of who is re-screened for anemia? What is the current practice standard of the clinic? Is yearly screening recommended? What proportion of children had at least two screens and what are the differences between those who were and were not re-screened?

The investigator has experience with chart reviews from this clinic, but no data is given for the capture rate of finding the
chart. Even if 90% of charts are found, what percentage will have information regarding treatment? A pilot study would be helpful. What experience does the investigator have with trying to call parents of patients from this clinic? Some may not have been at the clinic since the last Hgb level done over seven years ago! Again, pilot data are needed. Are hemoglobin levels obtained 6 months apart or 40 months apart comparable? Do all children also have MCV and RDW data or was a simple Hgb recorded for some?

In addition to the problems stated above, the investigators point out that they must rely on the iron parameters generated from a CBC to diagnose IDA instead of specific biochemical markers of iron status, such as ferritin, iron levels, and TIBC. Although these may be excellent proxies for IDA, are they available on all children who were screened in the clinic? Will there be sufficient numbers to answer aim #2?

It is not clear why direct immunization doses is an entry criteria. If it is to ensure longevity in the clinic, does getting three shots on the same visit count?

The third objective, assessment of clinical effectiveness of iron therapy for anemia may be difficult to assess with this database. Even if the chart states that the child was prescribed iron, it is doubtful that a telephone call will add information. Parents may not remember or be truthful about compliance if they can be reached. The percentage of parents that can be contacted may be very low.

Despite these limitations, the proposed project should add much needed information. Using this information, prospective interventional studies or prospective evaluation of recommended screening practices could be designed.

**Evaluator 2**

**Scientific and Technical Merit**

The importance of evaluating Iron Deficiency QD) is well documented. This proposal points to both the higher incidence in children of minority ethnicity and those living in low income families are at higher risk of ID and its component Iron deficiency anemia (IDA). The importance of screening and evaluating interventions in this longitudinal based study is highly relevant to the research mission of MCHB as well as the implications for the IDA screening concerns of the US Preventive Services Task Force.

The proposal will use an existing medical record review and laboratory database to evaluate currently recommended IDA screening practices, the use of supplemental tests and to determine clinical effectiveness of iron therapy. The Investigators state the perceived weakness of using an existing data based principally the lack of full range of iron parameters from a complete blood count.

**Study Design**

The sample (described below) children will be followed through a retrospective analysis of the ARCH reporting systems and immunization tracking system (to define enrollment date).

The four major hypotheses (p. 19-) while rather general have several subparts that are clarified further the analysis. However words like "we predict that a substantial number of children" are not quite up to the measure of a statement of epidemiological significance or definitive criteria for testing. The intent of the descriptive study and the preliminary evaluation of predictive and treatment assessments are clear, although it is difficult to track the explicit criteria to be used.

**Data and Measures**

A major advantage of Us study is the availability of the data flow since the 1992 period for some screening and the complete data results on all subjects commencing in 1994. The total data base is contains information on over 1500 children essentially followed form birth to 48 months of life ( p. 18).

The description of completeness of follow-up, the use of person months concepts in the analysis, and further explication of anticipated loss to follow up would help to strengthen the proposal from an analytical standpoint.
The sample, among other criteria, is based on the classification of probable IDA described by Hgb and MCV, and RDW criteria. The sample is based on the number of children followed in the database and the latter eligibility criteria. Hence there is no power calculations presumably since the sample is fixed. (p. 24.) Preliminary demographics of the database presented demonstrate that an array of demographic ethnic-racial composition, primarily poor, and a substantial number of children with families with no insurance will be found in the database. The population in the sample is highly relevant to the study tenants.

Analysis
The analysis plan presented does not clearly track the hypotheses stated. (p. 22) and mirrors the vague statement of several of the hypotheses. The specific analysis techniques, comparisons, Chi Square tests, and logistic regressions are appropriate. The illustrations provided are primarily based on relative risk and confidence interval. The study would benefit from further explication of the use of the words "substantial" in the general hypotheses to be tested.

More detail on the generalized regression analysis to supplement the use of confidence intervals would also be useful. However if such models still await development then that too would have been helpful (p. 26) for example, it is not clear what is meant by saying that there is a passing reference to longitudinal or clustered data.

The illustrations are based in part on earlier pilot studies. In concert with the exploratory nature of the data, the stated lack of preliminary or complementary studies (for example assessing the clinical guidelines, the study would contribute to the literature and indicate future directions consistent with the general aims of the study.

Budget
Proposed budget is consistent with the exploratory nature of the study, and in the need to clean and compile the final database for the analysis.

In summary, this is a good study but with areas of weakness in the precision of the hypotheses to be tested, and the concomitant analysis. It is not clear how longitudinal and multivariate models will be used.
**Increasing Safety Seat Use Among Preschoolers**

**Grantee**  
Children’s Hospital Medical Center Research Foundation

**Investigator**  
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**Project Number**  
R40MC00116

**Project Period**  
10/1/1998-9/30/2001

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**Year 2010 Objectives**

15.20

**Study Design**

Quasi Experimental

**Time Design**

Mixed

**Care Emphasis**

Interventional

**Population Focus**

Preschool-age children, Adolescents, Parents/Families/Mothers/Fathers

**Race/Ethnic Focus**

African Americans

**Priority Research Issues**

**Summary**

**Statement of the Problem**

Crash-related fatalities remain the leading cause of injury and death for children between the ages of 1 and 4 years. The arguments for use of a child safety seat (CSS) for all preschool children are compelling. Risk of death or serious injury can be decreased approximately 71 percent by use of a CSS. However, usage rates among preschool children are very low; the rates range from 6 to 43 percent. Preschool children who are restrained in safety belts are at risk for severe or fatal head, intestinal, and spinal injuries. Minority and disadvantaged children are at particularly high risk for injuries resulting from car crashes. Use of a CSS is very low in this population, and crash-related fatality rates are twice as high among low-income children. High rates of misuse have been observed among the small number of preschool children who do ride in a safety seat, which may degrade the protective effect of the seat. Several injury-prevention approaches have addressed low CSS usage. However, legislation and short-term educational, incentive, and give-away programs have not been successful in increasing CSS usage among preschoolers.

The intervention is a preschool passenger safety curriculum coordinated with a parent educational program that will be implemented in nine preschools and child care centers in Hamilton County, OH, throughout the 1999–2000 school year. The children's curriculum is taught by the classroom teacher, who incorporates the passenger safety messages and activities into all areas of the classroom. The parent intervention, which is based on the tenets of the Health Belief Model and Social
Learning Theory, will provide modeling and positive reinforcement to increase parental competence in dealing with CSS-related issues. The parent program will address the barriers to consistent CSS usage identified by three focus groups that will comprise parents of preschoolers; the focus groups will be conducted during spring 1999. The parent program will also disseminate to other parents the behaviors and activities identified by focus group participants as facilitators to CSS usage.

**Research Questions or Hypotheses**

This study will address the following hypotheses:
1. A multidimensional child passenger safety program based on the principles of Social Learning Theory and integrated into the curriculum throughout the school year will result in increased usage of safety seats among preschool children;
2. CSS usage will demonstrate a larger increase among families with less income and lower parental educational attainment when perceived barriers to usage are addressed;
3. Use of safety belts will increase significantly among parents as a result of the program; and
4. Specific educational messages developed for parents and children will result in significantly more children riding in a rear seat position in vehicles equipped with passenger-side air bags.

**Study Design and Methods**

The purpose of this study is to evaluate the effectiveness of an innovative, preschool-based child passenger safety program to increase the prevalence of CSS usage and the rates of correct installation and proper harnessing of the child. Two secondary objectives are to increase the use of safety belts among parents and to increase the percentage of children riding in the back seat of vehicles equipped with passenger-side air bags. Tertiary objectives include increased parental and teacher awareness, attitudes, and knowledge related to child passenger issues and self-reported motor-vehicle restraint use. A quasi-experimental, pretest-posttest control group design will be used to evaluate the intervention. Injury prevention efforts may have an impact along a continuum that progresses from awareness of risk, knowledge of how to prevent or minimize injury, and, ultimately, to behavioral change. The program evaluation includes assessment of all three areas in order to determine the impact of the program on each.

Behavioral change (i.e., using a CSS, wearing a safety belt, positioning a child in a rear seat) is the ultimate goal of the program. Measurement of program effectiveness on the primary and secondary objectives will be assessed through direct observation during the arrival times for children at both the intervention and control schools. Observation and a brief driver interview will be conducted by blinded interviewers from the University of Cincinnati Institute for Policy Research. Observation will be conducted in the fall before the introduction of the program and again in the spring.

Measurement of the tertiary objectives will be conducted through questionnaires administered to parents and teachers before the introduction of the program and again in the spring. These questionnaires will assess awareness of and attitudes toward personal use of restraints, safety seats for children, and other injury-prevention devices. The questionnaires will also measure knowledge of specific CSS issues and knowledge of State law related to child passenger safety.

Additional measures include weight and height information for each child. These measures will be taken in the classroom, and suggestions for selection of an appropriate safety seat will be provided to the parent.

Process measures for the program will include monthly teacher activity diaries. Because program materials and activities will be employed in the classroom at the discretion of the teacher, it is not feasible to accurately observe the degree of compliance with the program in all intervention school classrooms throughout the school year. To obtain some estimate of the degree of implementation, each month the teachers will complete a diary that describes how often specific materials were available in their classrooms and how often they conducted program-related activities.

**Population and Sampling Plan**

Preschools were obtained from a list of all licensed preschools and child care centers operating in Hamilton County. They were stratified into high-tuition, middle-tuition, and low-tuition level groups. Within each tuition tertile, schools were randomly selected and contacted until the demographic and sample size requirements for that stratum were met. Each parking situation was assessed to ensure that observation could be safely conducted at the school. Schools that agreed to participate and that met the study criteria were allocated to the intervention or control group through a coin toss. Seventeen
schools are participating in the study, nine as intervention sites and eight as control schools. The estimated total number of children enrolled for September 1999 is about 1,400. There are approximately 500 African-American children and 900 white children. African-American children are overrepresented in the sample to permit analysis of socioeconomic interactions within race. With an alpha of \( p=0.05 \), the statistical power to detect a difference in CSS usage from preprogram to postprogram levels is greater than 90 percent.

**Analysis Plan**

Because child-specific information (age, standing and sitting heights, weight) will be linked to observation data, the unit of analysis is the individual passenger. However, within tuition tertiles, preschools were randomly assigned to intervention or control status. To control for the potential violation to independence introduced by using the school as the unit of randomization, the general estimating-equation-logistic approach will be used for the following primary outcome variables: CSS usage, parental safety belt usage, and rear seating. Covariates will be considered for inclusion in the equation by using a modified stepwise procedure. Key variables (study group, tuition tertile, school, and race) will be forced into the model. Questionnaire data will be analyzed by using frequency counts, univariate analysis, and Mantel-Haenszel chi-square techniques.

**Pre-Award Evaluation**

**Evaluator 1**

**Originality and Importance**

This study is important in two respects. Its objective is of intrinsic interest to anyone interested in improving children's health. Perhaps more importantly, the study's approach has relevance to a more generic problem: how can one increase the use of relatively inexpensive interventions that clearly benefit both individual users as well as society as a whole? The study is an example of how the use of rigorous quantitative methods can be used to assess interventions that might be considered "soft" or "hard to pin down."

This study's subject area - prevention of child injury, child death, and increasing the use of safety belts - is an issue of major scientific importance, which clearly falls in an area of critical importance for the MCHB Research Program and is in synchrony with the Healthy People 2000 goals.

**Regional and National Significance**

The study is significant, particularly from a methodological standpoint. If successful, it could be a model for 1) the incorporation of rigorous quantitative approaches to the measurement of community-based interventions, 2) improving the overall quality of community-based interventions, and 3) increasing the links between researchers and the ultimate beneficiary of their work - the community.

**Scientific and Technical Merit**

This proposed study has several strengths. The authors have performed a thorough review of the literature. This thoroughness is evidenced in that their study design clearly incorporates others' work and is grounded in a coherent conceptual framework (Health Belief Model and Social Learning Theory). The authors also have a fairly clean analytic design with very clear delineation of independent and dependent variables. Moreover, their key outcome variables are readily quantifiable and it is reasonable to anticipate that final data analyses can be straightforward.

Additional strengths of this project deserve special mention. The first is that the authors have conducted and learned from a pilot study. Their pilot study is important in that 1) it shows that it is possible to make an impact on this problem, 2) it identified key outcome variables which have guided the design of this proposed study, and 3) it identified key factors that need to be considered if one is to increase use of car seats. In particular, the pilot study highlights the importance of an intervention that does not separate parental use of seat belts with the use of child safety seats's in pre-schoolers.
The second major strength of this project is that the authors clearly demonstrate knowledge of how to reach their target populations. The educational materials they provide in the appendix are of very high quality and evidence a very thoughtful team. Material provided by the authors also evidences that this team is comfortable working outside a strictly theoretical environment.

The major remaining problem with the revised proposal relates to the process whereby this project's findings become generalizable. While it is true that they now describe various schemes that will attempt to "tease out" the relative contribution of specific project components (e.g., educational videos), the actual mechanism for this involves a rather weak design (asking teachers and parents what they thought worked the best). There is scant description of how this rich body of data will be transformed into an "inexpensive, self-contained module." In fairness to these investigators, this problem is not fatal.

The locale for this study is ideal. The population is readily available and recruitable. The investigators also demonstrate that they do have access to leaders in the community and that they have performed an extensive amount of preparatory work (e.g., identifying centers that will need to be randomized and established links with local community leaders).

The principle investigator is highly qualified to lead this study. He has conducted significant research in many of the areas required. These include pediatric trauma, as well as injury prevention. He has also used the prestige of his position and research to "leverage" community interest, which is important for this study. Dr. Zins is a psychologist who is also well qualified and who has published extensively in areas relevant to this project. Dr. Rivara is a political scientist with experience in survey research, data management, questionnaire development, and opinion polling. He is a valuable member of this team. The addition of Dr. Tuchfarber significantly improves the team's analytic capability. Susan Laurence will be the project coordinator and will be responsible for the day to day management of this project. Kathryn Clark will provide administrative support and consultation for the project. She is also well qualified to perform this task. Data collection for the key outcome measures will be performed by professional interviewers who will be hired on a contract basis.

Some of the key data collection for this study does need to be performed by individuals at a high level of training (Zins, Rivara, Tuchfarber). The other costs listed are appropriate; they form part of the "nuts and bolts" of this project where contact with centers and families is concerned. The key issue with this project's budget is teasing out which project analytic costs are intrinsic to the project and which are for the poorly defined process whereby study findings will be transformed into an "inexpensive, self-contained module" suitable for national dissemination.

Protection of the rights of human subjects in this study is adequate.

**Evaluator 2**

*Originality and Importance*

This proposal is designed to assess the prevalence and reasons of inadequate use of age-appropriate restraint devices for preschool children in automobiles. The project includes development of an injury prevention program to increase use of child safety seats and booster seats, particularly among high risk, disadvantaged families. It also includes evaluation of the effectiveness of the program by comparing changes in the use of child safety seats among parents whose children attend control preschools with those attending preschools participating in the injury prevention program. The prevention of injuries among preschool age children is an important research priority of MCHB and the Healthy People 2000 directive.

*Regional and National Significance*

Inappropriate and/or lack of use of child safety seats among preschool children is widespread and well documented in the 1990s despite mortality and injury statistics for this age group due to automobile collisions without use of appropriate restraining devices. The problem is worse among the disadvantaged and minority children. Why this injury prevention strategy is ineffectively used by large numbers of parents despite federal efforts to encourage the use of child safety seats remains unclear. This projects proposes to identify barriers and facilitators of child safety seat use, determine the prevalence of inappropriate and lack of use of child safety seats, and develop an effective community-based program that increases use of
child safety seats and booster seats among preschool children and the use of seat belts among parents. The project will also evaluate the effectiveness of this injury prevention program. Each facet of this program can be generalized to other communities nationally and therefore has national significance.

**Scientific and Technical Merit**

The literature is clearly cited and provides compelling figures describing the magnitude of the problem and the potential number of lives that could be saved and injuries reduced. It includes direct observations made by the principal investigator in his community. It also includes explanations as to why adult restraint devices are not effective for preschool children. The reasons why previous injury prevention programs in this area have not worked are also cited.

The concepts explained are the Health Belief Model for why people practice prevention behaviors and the Social Learning Theory as a means to help people change behaviors. The specific principles of these theories are cited and provide rationale for the structure of the proposed injury prevention program.

The hypotheses are clear and measurable although the techniques to measure effects of the intervention are largely through parental self-reporting. Outcome variables are use of child safety seats for the children, seat best for the parents, and rear seat child safety seats positioning. Whether the program increases child safety seat use more among families of lower socioeconomic status will also be measured. The test measurements will be self-reporting behaviors through interviews and surveys and actual use of restraining devices by drivers and children arriving at preschools. Use of restraint devices per preschool is the unit of analysis; schools will agree to receive the intervention or act as controls.

The fact that the author has completed a pilot of the project and subsequently refined the content of the education program adds considerable strength to the current proposal. The use of focus groups has been improved with resubmission of this proposal. A mechanism for setting priorities regarding parent-based barriers and facilitators of child safety seats use is inherently selective, i.e. the modifications/suggestions that can be included in the prevention program. However, a mechanism for identifying the order of importance of parent issues is now in place. An additional strength of the methodology is the stratification of focus groups by socioeconomic status. However it is unclear how components among the three focus groups will be prioritized among groups, particularly if increasing child safety seats use among lower socioeconomic families is a priority of the project. Whose input is most important?

The data based on direct observation of child safety seats use by parents arriving at school by car with children is strengthened by the prior training of the observers and assessment of inter-observer variability during training sessions. Observers will be blinded to the allocation of the school in the intervention or control group. It is unclear if the interviewees will be blinded to the observations recorded by the interviewers. Secondary outcomes will be measured with parent surveys using a pretest-post-test design to discern differences due to the intervention and changes will be compared between groups of parents from control and intervention groups of schools. Poor response rate to parent surveys may still represent a limitation of the design despite additional incentives to schools for parents to participate.

The frequency of carpooling and its impact on the utility of observation data remain problematic. It will be helpful to know the frequency of car pooling for each school and between groups of schools in the intervention and control groups. How will parent survey responses and parent behaviors be correlated using child safety seats? Is child safety seats use proportional to number of children in the car, i.e. are there enough child safety seats in the car? This data should also be reported and perhaps a separate description of use of child safety seats and booster seats as a function of car pooling is in order. Finally, it would be interesting if the education intervention had a differential effect on car pooling parents vs. single driver parents.

The educational intervention has multiple components for both parents and children using a variety of methods (e.g., videos, newsletters, parent education sessions, and classroom role-playing). No single component will be judged for effectiveness as the project is now written. Focus groups among the schools that experienced the most improvement in use might be helpful to further evaluate the intervention's educational components.

How will the investigators alter their approach if the parent participation (as measured by frequency of video checkout?) is particularly low in certain schools after 6 months?
Enrollment of schools will be done with number of children per school and tuition for school in mind in order to assure balanced representation of socioeconomic groups in both the control and intervention groups. No attrition of schools is anticipated. Number of schools and students to be enrolled exceeds power calculations to assess an increase in child safety seats by 50%. Data will be analyzed by linear regression techniques accounting to three tiers of tuition and two racial groups balanced among control and intervention groups of schools. Changes in survey responses pre- and post-intervention will be tested with a chi-square procedure.

The time schedule seems appropriate. Analysis of the initial focus group input will need tight time controls in order to refine the educational program and initiate it at the onset of the school year. There are no collaborative financial arrangements.

The investigators are most qualified to conduct this project given their previous publications regarding injury prevention and the previous experience of the team in conducting a pilot project in Cincinnati. Resources are adequate for feasible completion of the study. The project has been approved by the Children’s Hospital Medical Center Institutional Review Board.
Infant Functional Status and Discharge Management

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Project Number R40MC00236

Project Period 9/1/2001-8/31/2004

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Summary

Statement of the Problem

Timing the hospital discharge of a preterm infant after a neonatal intensive care stay is a complex and difficult decision. This study will elucidate the medical and economic consequences of decisions concerning the discharge of premature infants. The American Academy of Pediatrics (AAP) guidelines for Discharge of the High-Risk Infant emphasize the need to base such guidelines on review and analysis of evidence since pressures from cost-containment and fixed definitions of medical necessity on hospital length of stay may influence clinical decisions. However, the literature provides scant quantitative data that would assist a clinician to make this decision. In this study we will develop a physiologic model based on a combination of infant functional status variables that identifies the best timing of discharge such that rehospitalizations and subsequent economic costs are minimized. In particular, we wish to understand how functional status at discharge, as defined by dimensions of feeding maturity, thermal and respiratory stability, influences readmission rates and the overall resource utilization (both inpatient and outpatient) after a defined point in a hospitalization corresponding to minimal acceptable maturity for discharge. Thus, our study aims to aid in the development of more appropriate guidelines that should better account for the costs and benefits associated with decisions concerning discharge management.
Research Questions or Hypotheses

The study addresses two types of hypotheses: economic/outcomes hypotheses and physiologic hypotheses.

Economic and Outcomes Hypotheses: In terms of economic hypotheses, we posit that infants can be discharged too soon, leading to increased total costs due to more resource utilization after discharge. Adjusting for all "baseline" data prior to the earliest point in time that a baby may be discharged, there should be discharges at later points in time for which the total cost of treatment will be less.

Infants discharged too soon may also lead to increased medical events and readmission rates. Adjusting for all variables prior to the earliest point in time that a baby may be discharged, there may be a maturity level, after which discharged infants will have decreased readmission rates as compared to those discharged prior to that point.

Physiologic Hypotheses: The study addresses two physiologic hypotheses. The first one, the relative weighting hypothesis, states that specific physiologic parameters have greater influence on outcome than others. We will report the relative importance of each milestone, adjusting for all other milestones in the analysis. We would hypothesize that achieving some physiologic states of maturity would have greater impact on outcome than other states.

The second physiologic hypothesis, the "timing" hypothesis, states that adjusting for baseline variables, there exists an optimal discharge point such that expected costs, and the risks of readmission, are minimized. Furthermore, we will explore whether subsequent resource utilization and outcomes is a function of time from achieving physiologic stability to discharge.

Study Design and Methods

This study uses a retrospective observational longitudinal cohort design. The 1400 infants from 1998-2000 will be randomly selected for a detailed chart review and for economic and outcomes modeling. The administrative and clinical data from the Division of Research Perinatal Research Unit (DOR PRU) will serve as a sampling frame, and detailed chart review from primary hospitalization will provide the basis for model construction in this dataset. Outcomes (resource utilization and readmission) will be collected from the Kaiser Permanente Medical Care Program (KPMCP) administrative and clinical databases for up to a 6-month discharge period. The actual outcomes statistics will be defined for a period starting when the infant achieves a minimal maturity level and extending for 6 months from that date.

This study design has numerous strengths. (1) The structure of the cost accounting, starting from the point of minimal physical maturity to a 6-month period, provides an improved methodology for comparing costs across hospital discharge algorithms. This structure requires the input from experts in neonatal development and clinical management. Hence, the second strength, (2) is the strength of the team. The proposed study will bring together experts in the clinical management of premature babies, experts in economics and cost effectiveness, and experts in pediatric managed care. Finally, (3) the third strength relates to the unique data set, which we will be able to collect with the input of the largest HMO in California. All three strengths aid in making this a workable project.

Population Description and Sampling Plan

This study specifically focuses on the care of newborns. No ethnic or racial group is excluded. The population in this study consists of inborn infants admitted to one of 6 level III intensive care nurseries (the KPMCP medical centers at Hayward, Oakland/Alta Bates, Sacramento, San Francisco, Santa Clara, and Walnut Creek). These 6 units capture approximately 95% of intensive care admissions in the KPMCP’s Northern California Region. High-risk deliveries from other KPMCP facilities are referred to one of these 6 medical centers. Consequently, this is an enriched database, which has relatively more low birth weight and premature infants than the general KPMCP population. We are restricting our population to those infants 1) having gestational age ≤ 34 weeks; 2) birth weight less than or equal to 1800 gms; and 3) not having life-threatening (major) congenital anomalies or chromosomal abnormalities.

The data for this study will be collected from two sources: the DOR PRU database systems which consist of several databases located on the mainframe of the DOR PRU at KPMCP and by tracking the infant after discharge from the Neonatal Intensive Care Unit (NICU) and identifying and collecting all the resources utilized which are not already in the DOR PRU. We do not have patient level socioeconomic status data. However, we do know that the KPMCP covers approximately 30% of the population in Northern California and that it is demographically similar to the general middle-class California population (the very poor and very wealthy are under-represented).

Analysis Plan
In general, all hypotheses will be tested using regression models. In particular, contrast statistics on regression coefficients will be used to test all hypotheses. The advantage to this approach is that the methodology incorporates the flexibility and ease of regression modeling, and the statistics associated with comparisons of regression coefficients. After data collection is complete, we will develop predictive models of cost and readmission. Models will be developed on a random half sample of the entire data set. Variables that are clinically relevant and statistically significant, using univariate tests at the 0.15 level will be included in the initial multivariate models. We will explore residual plots for both the linear and logistic models, and Cox regressions. Once development is complete, models will be validated on the second half sample. Validation will include studying the correlation of outcomes derived from the validation model applied to the development data set, versus the development model using the development data set. Differences in estimated coefficients between the development and validation models will be tested using a dummy variable interaction model, using the random split as a dummy variable interacted with all other coefficients. After validation, the final models will combine samples when reporting final results.

**Pre-Award Evaluation**

**Evaluator 1**

*Originality and Importance*

This proposal shows considerable originality. The study, if successful, will result in a novel approach to characterizing quantitatively the maturity of premature infants, and assist in standardizing approaches to planning for their discharge. Other work has examined one or more of these issues, like apnea, but none has attempted to consider all together. Moreover, the study addresses a significant issue. Shortening the length of stay of premature infants not only reduces hospital costs for children, but also reunites the family sooner. However, this may increase the risk of subsequent health problems due to the continuing vulnerability of these infants. Current approaches are formulaic and experiential without a firm empiric basis. The more rigorous approach planned in this proposal would be a major advance.

*Regional and National Significance*

The study clearly has regional significance to the California area. The study is likely to have national significance if the methods prove generalizable. However, the specific results may or may not be generalizable as California is well known to have different patterns of hospital use. The results are likely to understate the savings in areas with higher hospital use. Also, they will restrict their sample to those remaining in the system, but provide no information on how representative these are of a whole cohort of births.

In response the investigators point out that at least theirs is a regional study not based on a single institution. In addition, while the methods may need to be tailored to individual regions, the methodological advance should be generalizable.

*Scientific and Technical Merit*

The proposal has major scientific and technical strengths. One of these is the setting at Kaiser with the capacity to link records and follow children through a computerized system. Much of the information will be abstracted from these automated systems.

The second area of strength is a clear conceptualization of the problem. This generates both a comprehensive consideration of outcomes, as well as a novel approach to measuring physiologic maturity, and assessing its role in discharge decisions.

Their approach to considering the economic consequences of discharge is thoughtful and one which should eliminate the biases of other approaches which they note. They have clearly incorporated notions derived from standards for cost-effectiveness analyses, although they are not performing one. The discussion is somewhat truncated on the definition of costs, and to what extent Kaiser "costs" are comparable to other systems. Moreover, the costs being captured are those to the Kaiser medical care system, and do not reflect out of plan use. In addition, no consideration is given to indirect and opportunity costs.

In response, they report that previous studies indicate little or no out of plan use, but that their results may underestimate
costs if KP is a more efficient provider.

The study design is a longitudinal, cohort study covering several hospitals, and represents another area of strength. The variables to be collected are clearly described, and plans to maintain data quality are thorough.

The data analytic plans are very sophisticated. They are carefully linked to the hypotheses.

**Evaluator 2**

*Originality and Importance*
This proposal addresses a very important problem—lack of objective data suitable for discharge planning of premature infants—in a creative and promising way. The problem is important for resource utilization (premature infants are heavy users of medical resources, both in the neonatal period and often over the lifetime), and for health outcomes.

*Regional and National Significance*
The most creative aspect of the proposal is the idea of defining functional status at the earliest point at which any clinicians would consider discharge, and then measuring medical costs for six months from this point, comparing costs and outcomes with other possible points of discharge. The investigators do a good job of explaining the rationale for this approach.

*Scientific and Technical Merit*
The team of investigators and the KPMCP data set, which provides access to high quality clinical and hospital cost data, as well as data on outpatient medical costs following the initial hospital stay. Responses to reviewer comments indicating that 80% of infants are still members of KPMCP eight months after discharge, and that out-of-plan use is minimal further testify to the strength of the data set. Responses to questions about generalizability outside of California and lack of data on indirect costs (such as opportunity costs of parent’s time in caring for infants discharged early) seem acceptable.

A question was raised about how infant deaths would be handled. The investigators’ response is reasonable. It appears that deaths are sufficiently rare that this should not be a serious problem for the analysis. Since the proposed adjustments for costs of deaths are rather arbitrary, the primary approach should probably be not to adjust costs, but to note in interpreting the results whether there are differences in deaths associated with different discharge strategies.

A question about cost data not fully addressed in the responses is how well the "per diem cost for bed and nursing and physician services" (which is likely to be an important component of hospital costs) accounts for differences in the marginal cost of different levels of care.

How the definitions of different possible points of discharge (M1, M2, M3,...) will be established is still not entirely clear. The proposal and response refer to using a half sample of the entire data set to develop models. It would appear that for purposes of this study, the different M’s should be defined either by clinical judgments about appropriate points of discharge prior to doing the study, or by examination of the empirical distribution of when discharges actually occur, or some combination. The first approach could be taken without reference to the data from this study, and it is unclear why the second approach could not use all of the data rather than a half-sample.

It seems inappropriate to use empirical data on costs and outcomes from the study in defining the M’s. That approach would introduce spurious correlation between the M’s, which should be independent variables, and random variation not explained by the model, creating problems for hypothesis testing. M2, for example might, turn out to be MOPT according to some criterion, but this should be determined after the fact, it should not be used to define M2.

In summary, this is an innovative and important project with an excellent team of researchers and access to a unique and very appropriate dataset. Reviewers concerns have been adequately addressed. Further clarification of how functional status associated with possible discharge points will be determined would be helpful.

**Evaluator 3**
Originality Importance
This proposed research has many innovative qualities. The topic of research is of extremely high significance. The investigators are proposing a new construct that should be able to motivate and rationalize how discharge timing is addressed in neonatology.

Regional and National Significance
The regional and national significance of the proposed research is considerable. The investigators now acknowledge the potential limitations in generalizability.

Scientific and Technical Merit
This has many considerable strengths.

The investigative team is strengthened with the addition of Professor of Statistics, Dr. Paul Rosenbaum. The investigators also provide a more complete justification for the inclusion of Drs. Medoff-Cooper, Bakewell-Sachs, and Botas. Their respective areas of expertise and the role each will play on the proposed investigation is now well described and clearly justified.

It was noted that the investigators did not elaborate on indirect and opportunity costs. It is now indicated that such costs would have to be addressed in future prospective studies.

The investigators, in response to concerns and questions related to Mmin (the period when the caregiver with the lowest threshold will allow discharge), have been further defined the operational and conceptual definition of this important covariate. Though the response is not supported empirically, the response is thoughtful and suggests that the team is well equipped to adjust their approach, should experience indicate a benefit.

In response to concerns about how infant death will be handled in the economic model, the investigators now state that they will conduct what amounts to be a series of sensitive analyses. Specifically, they will consider a number of different scenarios when modeling their data; and subsequently report how these scenarios result in different interpretations. This seems a reasonable approach, as a range of estimates will likely reflect the uncertainty inherent in this research.

The investigators have provided additional elaboration of their analytical plan. Specifically, they will model seasonal variation where appropriate. Additionally, they will adjust for physiological variables associated with patient status.

All in all, this revised proposal is much improved. The investigators have addressed all the concerns, and where appropriate have modified the protocol.

In summary, this is a very interesting and innovative proposal. The investigators have been highly responsive to all comments and concerns raised in the previous review. The revised proposal is strong, and the research team is strengthened with the addition of a senior statistician.
Infant Temperament: Neonatal–5 years in Rural Appalachia

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Project Number  R40MC00091


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Summary

Statement of the Problem

The lack of cross-sectional and longitudinal data on individual differences in developmental trajectories in the rural Appalachian population has hampered efforts to design culturally relevant interventions for this population. More information is needed on the strengths of this rural population to disentangle the role of poverty versus culture in examining variables of interest. It is important to learn more about protective factors that promote good outcomes in rural families of low socioeconomic status (SES) as well as to understand whether risks identified in infancy and preschool have effects once children enter school.

Research Questions or Hypotheses

Two research questions will be addressed by this study. First, what continuity is there from certain temperament and mother-infant relationship qualities in infancy to preschool behavior problems and early school adjustment? Second, how do...
concurrent environmental factors such as poverty and low parental education levels, cultural values regarding education and achievement, and individual differences in temperament and mother-child relations interact to influence early school adjustment and performance?

The following hypotheses will be tested:

1. Difficult temperament is a risk factor when combined with a less optimal or less supportive caregiving environment. Children who showed continuity in high negative emotionality during the first year will be higher on preschool behavior problems and less sociable, positive, and persistent at age 4 if their mothers also had one or more of the following characteristics: Higher scores on negative personality traits, lower sensitivity during interaction, and low social support.

2. A positive, socially responsive temperament and a secure relationship with the primary caregiver are protective factors against global risk conditions such as poverty. Children who remain high or increase in positive emotionality/social responsiveness during the first year and those who have secure attachments to their mothers at 15 months will be lower on preschool behavior problems, higher on persistence and problem solving, and more likely to remain securely attached at age four.

3. The major child outcome variables from each age in this study (15-month attachment and verbal communications skills, 4-year behavior problems, attachment, temperament, and verbal skills, 5-year measures of social and cognitive functioning) will contribute significantly to variation in kindergarten adjustment. Continuity in positive factors and more optimal characteristics beyond infancy will best predict good school adjustment.

4. Parental expectations/aspirations will interact with child and family characteristics to influence school adjustment. Higher parental aspirations for the child and higher value placed on education, in combination with strengths such as child positive/social temperament, high social support, and stable, satisfying parental relationships are expected to predict higher teacher-rated adjustment in kindergarten.

Study Design and Methods

This is a continuation of a previously funded project on infant temperament. This project will conduct assessments at the age of 4 years, immediately before entry into kindergarten, and during the kindergarten year. At the age of 4 years, the laboratory assessment includes child free play with the mother and a stranger (a preschool version of the strange situation), a clean-up task, two puzzles of increasing difficulty, and the PLS–3 scale of language development. Mothers will repeat social support and relationship satisfaction measures that were given prenatally and will also complete measures of child-rearing values and attitude toward spanking. Before entry into kindergarten, the child and both parents will engage in free play and clean up; then the parents will be interviewed on aspirations and expectations for the child and their feelings about education while the child repeats the PLS–3 and plays counting, sorting, and completion games and is given a resistance-to-temptation task. During the spring of the child's kindergarten year, the kindergarten teacher will complete the classroom behavior inventory with scales that measure both social behavior and academic performance.

Child variables to be assessed include the following: Standard measures of attachment and behavior problems (age 4 years); a number of ratings of temperament and social functioning such as positive and negative emotionality, sociability, persistence, focused attention, and compliance (ages 4 and 5 years); concepts and language skills needed for school (ages 4 and 5 years); and a standardized measure of classroom functioning (kindergarten). For parents, variables to be assessed include the following: Repeated measures of family demographics, maternal social support, and relationship satisfaction (age 4 years); parenting attitudes (age 4 years); ratings of parent-child interaction (ages 4 and 5 years); and attitudes toward education and hopes and expectations for the child (age 5 years).

Population and Sampling Plan

This longitudinal sample will consist of 95 rural Appalachian, white, mother-child pairs with children 4 years old (all of those who completed the first phase of the project). The mean age of the mothers is 27 years, and the majority are married (68 percent) or living with a partner (10 percent). The mothers' and fathers' average level of education is 10.8 years; 46 percent of the parents are not high school graduates. About 70 percent of the families report annual incomes of less than $10,000 and receive public assistance. The children are 53 percent male, and 72 percent are second-born or later. It is estimated that 85 mother-child pairs will be retained through the kindergarten data collection.

Analysis Plan
Multiple regression and path analyses will be used to determine which child and caregiving environment variables best predict behavior problems, temperament, cognitive functioning, and school adjustment. At each age, the outcome measures are expected to relate to individual differences in prior child temperament, attachment, and cognitive functioning, and relate to concurrent mother-child interaction and characteristics of the caregiving environment in a process model that reflects both direct and indirect influence. Discriminant function analysis will also be used to identify predictors that best distinguish groups who are secure and insecure in attachment, high and low in behavior problems, and problematic vs. functioning satisfactorily in cognitive measures. The goals of data analysis are twofold. First, the study aims to increase understanding of the developmental processes that lead to more and less optimal socioemotional functioning and adjustment in both family and school contexts for rural, low SES children. Second, the study aims to identify specific risk and protective factors in this population. Achieving both of these goals will lead to increased ability for early identification of children who may be at risk in order to provide appropriate, culturally relevant, intervention programs.

Pre-Award Evaluation

Evaluator 1

Originality and Importance
This well-written and well-designed research proposal will provide more information on an understudied, high-risk group of Appalachian women and their infants. The observations already obtained by the study, combined with a lack of cross-sectional and longitudinal data on individual differences in the developmental trajectories of this population, argue for continuation of the study. As the investigators acknowledge, additional information is required before culturally relevant interventions can be designed for those at risk.

Regional and National Significance
There is little current research on the Appalachian population. The project will assist the MCH community in better understanding the developmental trajectories of this population and will provide additional information about designing culturally relevant interventions. Therefore, the project has regional and national significance.

Scientific and Technical Merit
As in the prior application, the design and methods are well-described and appear appropriate for longitudinal followup of this population. Although the mothers in this sample are socioeconomically disadvantaged and have low self-esteem, they do not have lower maternal self-efficacy than mothers in a comparison sample. The investigator has attempted to remedy the deficiencies of the previous proposal. Specifically, the literature review and description of the conceptual framework (as well as hypotheses and analyses) attempt to view the strengths of the rural Appalachian culture and disentangle poverty and culture in examining the variables of interest. The investigator attempts to include fathers in this revised proposal. Specifically, at the 5-year data point, fathers and mothers will be assessed in the structured-task interaction situation. However, details of paternal involvement (i.e., anticipated numbers) are not provided, and the consent form has not been revised to reflect the inclusion of fathers. In this revision, sample size estimates based on a power analysis are provided. The original submission proposed a sample size of 175, but no details were provided for the final sample size of 121 in phase 1. This revision provides the rationale. The original proposal was based on 1989–90 figures for the number of prenatal patients in Lincoln County. Since that time, the population has declined, resulting in fewer births. Seventy percent of eligible women were recruited in phase 1; however, 111 of 121 women had infants who met study criteria. Attrition due to mobility and other factors accounts for the additional loss of subjects and the projected sample size of 100 at the beginning of phase 2, when the infants will be 3.5 years of age. Based on the same estimate of attrition, 85 infants are expected to be included at 5 years. However, estimates of attrition are not extended to the kindergarten data point. It is probable that less than 80 subjects will be available to study at this data point.

The conceptual framework is a synthesis of attachment and risk/resiliency theories, and suggests selected variables to be included. Within this framework, the investigators perhaps have focused more on methodological rigor than cultural relevance. A paradigm that takes into account culture as well as parenting and other developmental processes may be more informative. Additionally, since attrition is expected to reduce the power needed for multivariate analytic techniques,
qualitative approaches to examining major phenomena should be considered. The principal investigator has published several articles in this area. She is well-qualified to conduct this study as proposed. The addition of team members, as suggested in the 1994 review, adds to the proposal. The budget appears to be appropriate. This is a modest budget for a 5-year study; personnel costs are the major line items. This is a clear and well-written application. The research methods are sound and the conceptualization is compelling. The investigator has responded to concerns noted in the initial review, and the revised application is stronger as a result. The recommendation is for approval.
Intergenerational Pathways to Competence in Minority Families

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Project Number R40MC00254

Project Period 9/1/2001-8/31/2005

Year 2010 Objectives
1.14, 7.1, 7.3

Study Design
Experimental

Time Design
Longitudinal

Care Emphasis
Interventional

Population Focus
Infants, Toddlers, Preschool-age children,
School-age children, Adolescents,
Parents/Families/Mothers/Fathers

Race/Ethnic Focus
African-American

Priority Research Issues

Summary

Statement of the Problem

The purpose of this work is to examine the extent to which continued benefits of intensive early childhood educational intervention for individuals reared in poverty can be seen in adulthood. The study is relevant to maternal and child health issues because of the pervasive negative effects of poverty on all aspects of adult adaptation: educational, vocational, socioemotional adjustment, and health. Because the studies involved are randomized clinical trials of intensive early childhood intervention, they provide one of the best controlled-studies of long-term benefits of massive ecological intervention. Treated individuals received full-time educational childcare from early infancy. Control individuals were reared in the natural ecology of the local community. Two controlled clinical trials of early intervention will be followed up: the Abecedarian Project (ABC) and the Carolina Approach to Responsive Education (CARE). These two studies were contiguous trials drawing from the same community. Child participants were born between 1972 and 1980 and thus, when followed up now, will range in age from 30 to 26 years. Because assignment to treatment and control conditions was random in both studies, it is possible to attribute long-term benefits to the treatment with greater confidence. The findings thus address the long-term benefits, in terms of better life success, to be derived from providing high quality childcare for children of the poor.
Research Questions or Hypotheses

1) Adults who received early educational childcare are expected to demonstrate higher educational attainment, more vocational success, greater self-sufficiency, reduced criminal involvement, and reduced substance use compared to adults who did not have the early childcare educational intervention.
2) Average IQ, earlier academic skills, childhood behavioral adjustment, and earlier educational attainment are expected to mediate the effect of early childcare educational intervention on adult functioning.
3) In addition to early childcare treatment, the moderating effects of factors associated with risk are expected to predict longitudinally to adult functioning (including family instability in childhood, the quality of the early home environment, early behavior problems, criminal involvement, substance use, and poor mental health.
4) Several factors may constitute either risk or protection against risk depending on the level experienced. For example, a poor early home environment might serve as a risk factor, whereas a high quality early home environment might protect against risk. Hypothesized predictors for specific outcomes include: (a) Adult vocational success will be predicted by maternal IQ, own average IQ, earlier academic skills, educational attainment, and perceived racism; (b) Parenting skills will be predicted by maternal attitudes, the quality of the early home environment, childhood behavioral adjustment, and concurrent stress and social support; (c) Marital success will be predicted by early family composition, maternal attitudes, and early behavioral adjustment; (d) Mental health will be predicted by early childhood behavior, the early home environment, perceived racism, concurrent stress and social support; and (e) Substance abuse will be predicted by parental substance abuse, maternal mental health, own IQ, concurrent stress, and social support.
5) Children born to parents who received early childhood educational intervention will show greater academic abilities (or readiness skills) and lower levels of behavior problems than children born to parents that did not receive the early childcare intervention.
6) The adult participant’s childhood and adolescent history of academic and behavioral problems will be related to behavior problems and academic functioning in the offspring.

Study Design and Methods

The study is best characterized as an experimental clinical trial with individuals randomly assigned to the early childhood treatment conditions. Outcomes will be compared among groups with relevant covariates controlled as appropriate. Current methods will include interviews (young adult interviews for CARE participants initially) then adult interviews to establish current demographic status (education, work, family) and psychological assessments of mental health, risk taking, parenting efficacy (if relevant), self-concept, and perceptions of racism. Children will have academic assessments and parents will have home visits and complete questionnaires about their children.

Populations Description and Sampling Plan

Up to 170 adults (105 from ABC (51 males, 54 females) and 65 from CARE (39 males, 26 females)) might take part. The number and gender of potential offspring is indeterminate at this point. Eligibility was based on a high-risk index of sociodemographic variables, used for both ABC and CARE. As noted below, the participants are primarily African American, but data are not available to make cross-ethnic comparisons.

Analysis Plan

To learn if those adults with early childhood treatment attain higher levels of education and vocational status regression analyses (multivariate analyses of covariance for continuous outcomes and logistic regressions for categorical outcomes). A once-assigned, always analyzed approach will be used. Repeated measures longitudinal analyses using mixed model methods will test whether the preschool intervention significantly relates to more positive outcomes across time and/or different rates of change over time. Planned group comparisons and the use of covariates as appropriate will be used to examine the extent to which early treatment is related to adult outcomes. Other questions that may be addressed by the data set include issues related to parenting, ethnic issues and the like. Descriptive, correlational approaches will be used as appropriate.
Pre-Award Evaluation

Evaluator 1

Originality and Importance
This is a generally clearly written proposal that addresses some unique and intriguing questions. One of the major strengths of this proposed work is that it will draw upon a long-term longitudinal data set that has been well followed and well examined over the years. There is a wealth of early data that will no doubt contribute in meaningful ways to our understanding of the long term effects of early intervention, but of even greater potential interest are the many possibilities to explore various facets of intergenerational transmission of competence or maladaptation in high risk low-income populations. There is indeed much to be admired in the proposal. The topic of interest is clearly thoughtful and timely, and the issues are of particular salience to the field and to MCH research initiatives. The investigative teams have been involved with these study cohorts since the inception of the Abecedarian and CARE projects, and have built a strong research system that provides confidence that the participants can be found and will actually participate in the work. It seems likely that important information will emerge about both the long-term effects of early intervention and the potential for such to affect intergenerational processes.

Although the strengths are notable, there are several weaknesses to the proposal as it currently exists. The conceptual modeling, as well as the hypotheses that are presented, really do not offer much new in the way of developmental prediction. Granted, the pure notion that the long-term effects of early intervention can be addressed is in and of itself rather notable, but the investigators note that the study is really best described as a descriptive correlational study designed to test theory-driven regression models to explain adult outcomes (p. 57). There is a wealth of longitudinal data that address like issues and the predictions that are made are likely to result in easy confirmations (e.g. on p. 46 ... adult vocational success will be predicted by maternal IQ, adults IQ, earlier academic skills, educational attainment, and perceived racism). In that example, every one of these A predictors has a wealth of previous research that shows similar findings, so what is the unique aspect to this proposed investigation? The lone exception may be the perceived racism factor, but there is little development within the proposal that allows for some understanding of why or how racism will function in that capacity. Are these many predictor factors additive in their effect? Multiplicative? Equally weighted? At this point, more compelling conceptualizations seem necessary than those that are offered. And although the title suggests that the project will focus on the pathways to competence in minority families, there is far too little development of the issues involved in such a focus. Another major concern with the proposal is the undeveloped nature of the methods. The investigators suggest that an array of measures will be given, and such an array is presented. However, the investigators that these are not necessarily the measures that will be given. In fact, the actual measures will be chosen later based on some pilot testing. This is not a sufficient strategy. Most of the constructs of interest have measures available, and at the very least there needs to be a cogent discussion of the issues involved in the measurement protocol to justify the need to pilot test prior to final selection. Specific measurements need to be identified and chosen that offer adequate reliability and validity. The tables of measures presented (Tables 2 and 3) are of little help in general, as the information offered in the tables varies greatly measure to measure. Some measures offer information as to reliability, but often there is no telling what kind of reliability is being presented. Other times, there is no reliability information whatsoever. Sometimes, the appropriateness of the measure for African American populations is discussed, sometimes, not. These tables need to be complete and coherent across categories if they are to be helpful in making a strong case for the use of any one tool.

The sampling plan presents several interesting issues as well. First, little data is presented on the samples and their composition, even though data have been collected on the samples across time. But it would be helpful to know the equivalence of these samples at the time they were enrolled in the two intervention studies. And, what were the equivalences at the age 12 data collection? Do they represent a single intervention group that can be collapsed across cohorts? Also, the sampling plan presents a challenge that is difficult to understand as well. This is a four year study, and the CARE sample will have a data collection at age 21-22. They will also provide data at 26-30 similar to the Abecedarian group. However, this strategy will only be possible at the very outside of the 22 year olds age, and the very inside of the 26-30 year old age. Otherwise, it will not be possible to accomplish both within the time frame. And even then, the edges will need to be blurred to accomplish this within the proposed 4-year time period.

The proposed study involves two basic data collections: one a 2 hour telephone survey that will be accomplished with the 60
CARE participants (at age 21-22), and the other the 160 home and lab visits that will be done when the participants are 26-30. If the 60 telephone surveys are conducted in the first six months of year 1 (as suggested), then that represents 2.5 - 3 surveys per week (or approximately 5 - 6 hours). Then, across the next three years (or so), 160 participants will be seen for the 26-30 age assessment. That is approximately 53 participants per year; or roughly slightly more than one per week. Assuming the six hour period of time suggested for each of these data collections is true and correct, this is a very small data collection effort for the number of years allotted and for the size the project staff being proposed.

Evaluator 2

Originality and Importance
This study is unique in its examination of multiple generations and in its use of data gathered over approximately 25 years of the lives of individuals (largely African-American) who lived in low-income families and received early education services. Findings from the proposed study will yield important information about the long-term effects of intensive early education on the participants themselves and on their children.

Regional and National Significance
The investigation is relevant to MCHB Priority VI, Longitudinal Studies of Health and Normative Development in Minority Children, Children with Special Health Needs and Children of Low SES, Rural Migrant, and Homeless Backgrounds. The findings from this study will have important implications for the health and development of children growing up in low-income families.

Scientific and Technical Merit
The investigator has a unique opportunity to study the long-term outcomes of participants in two similar early education projects, the Abecedarian Project and Project CARE. Both of these projects were located in North Carolina and enrolled participants from low-income families. Families were randomly assigned to "treatment" or comparison groups. Follow-up studies of the individuals (at 21 years of age) in the Abecedarian Project have been conducted, and published findings indicate long-term advantages (in cognitive performance, academic skills, educational attainment and delayed childbearing) for those individuals, especially females, who received intensive early education through a full-time educational daycare program. A similar follow-up of Project CARE participants (at age 21 years) is proposed here with a plan for additional data collection from both samples when participants reach 26 -30 years of age. Further, the cognitive and socioemotional functioning of children of participants (3 years of age and older) in both samples will be studied.

The original studies were both randomized clinical trials but the current follow-up is described as a "descriptive, correlational study designed to test theory-driven regression models to explain adult outcomes" (p. 57). The "treatment" is considered one of the potential moderators of outcome. Nevertheless, the two major research questions (p.59) focus on the effects of the "treatment" on participants and their offspring. If "treatment" is central to this investigation (and I assume it is), then it would be important to know the comparability of the intervention (Abecedarian and Project CARE) and sample sizes for each of the various intervention groups. According to Wassik et al. (1990) no group in Project CARE served as a replication of the Abecedarian intervention although one group (n=15) received both educational child care and family support. Do the investigators intend to combine that group with the Abecedarian child care group in analyses? Will that provide sufficient sample size to conduct the proposed analyses on both early education participants and their offspring? I realize that a power analysis was conducted for a total expected sample size of 150 to 166, but I wonder how that sample breaks down into the various intervention groups. Adding sample size estimates to the cells represented by the various intervention groups in Figure 1 would aid in understanding whether sufficient power exists to study the effects of these various approaches on the young adults. On page 59 the investigator suggests a 3 group analysis (child care, parent education, control) will be conducted, but how will the investigator determine in which group to place each of the various intervention models (e.g., child care and family support, only family support, only school age, etc.). Further, will there be sufficient power to conduct the proposed analyses using data from the offspring? From comments made in the analysis section, I assume the estimated sample size of 100 for the offspring includes sibling groups.

Two important design features exist in this proposal. One involves the age of the participants at the time of the proposed follow-up. The age 26-30 data collection point for the full sample seems reasonable (although age 26 may still be too transitional) in terms of questions of stability related to the participants’ economical and psychological well-being and
approach to parenting. The age 21 follow-up conducted on the Abecedarian sample was perhaps too early in the life of the young adults to investigate adult indicators of financial stability and economic well-being. In that regard, I wonder how the investigator plans to use the data gathered from Project CARE participants at age 21. Will these data be added to the Abecedarian data set? I doubt if there will be sufficient power to analyze them separately. Finally, I wonder where the age 21 data "fit" in the conceptual framework (Figure 2).

A second important design feature involves the investigation of the effects of the family context created by these young adults on their children. The conceptual model (Figure 2) incorporates outcomes for both the young adults and their children. Although the model includes potentially valuable constructs such as perceived racism and discrimination, the model requires fuller discussion especially related to the rationale for the inclusion of various constructs as mediators or moderators.

The proposed data analysis plan for the adult (aged 26-30) outcomes appears reasonable but is somewhat vague. For example, the inclusion of gender as a covariate is perplexing. Also, how will the investigator make decisions about the construction of composite variables? An even more important issue concerns the application of HLM analyses to these data. The investigator discusses the use of HLM to "control for the presence of multiple siblings in any given family." Without further discussion it is hard to know how the investigator plans to build such models. It is noted that the investigator has included consultants quite capable of guiding the analysis tasks, however.

The proposed project is expected to take four years with 6 months for measurement selection and piloting and 3 years for data collection. Although the PI plans to have data coded and entered throughout the course of data collection, the final analysis will need to occur after data collection is complete. It is not clear from the timeline that this would be possible. The PI does note that ideally data collection should continue into the fifth year and that such a plan would be possible should funding from another source occur.

Evaluator 3

Originality Importance
The significance of maternal characteristics, early childhood experiences, and adolescent achievements have previously been studied individually as important dimensions of optimal development. This project will extend the longitudinal work that the authors have undertaken with a group of low-income, predominantly African America families and children, who are now transitioning into their adult phases of life.

This proposal directly addresses the issues raised MCHB Goal 4.3.2, which focuses on conducting longitudinal studies on the normative development of children in minority and other at-risk populations. Building upon data from their Abecedarian and CARE samples, which were collected nearly 30 years ago, the investigators will collect age-21 data on the CARE sample and later adult data on participants in both studies. In this way, the investigators will have data that allows them to examine the developmental trajectories over a broad range of time.

In summary, this proposal provides a unique opportunity to develop an understanding of the developmental pathways of low-income African Americans. While the data may not be generalizable to all racial/ethnic and socioeconomic groups, it does represent an important opportunity to understand resilience and coping mechanisms.

Regional and National Significance
If this project is successful, researchers, practitioners, and policy makers should be able to understand some of the critical dimensions that support healthy developmental outcomes. In short, the proposed investigation has the potential of offering insight into the protective and risk factors of development across the life-span and in subsequent generations. In essence, the investigators assert that the prediction of adult outcomes in a longitudinal context where extensive prospective measures of the early 30 years exist.

Scientific and Technical Merit
This is a very well written, justified, and scientifically rigorous investigation. The investigators have attempted to address potential confounders in and biases and tried to control for them. More importantly, the evolution of their work illustrates the integration of new theoretical models and variables that have been found to be critical dimensions of growth and
development.

While a significant proportion of this work will involve secondary data analysis, the authors have proposed the collection of new data to complement existing data. The new data will involve not only new adult measures, but also include data for the third generation of subjects. Toward this end, the investigators have attempted to insure the richness and integrity of these data.

Hypotheses, specification of variables and concepts, and methods
Two main hypotheses undergird this proposed investigation. The concepts and variables are clearly specified, and the general model is clearly specified and presented. The theoretical paths linking early childhood experiences to adult adaptations and intergenerational outcomes is also presented, and based on the literature review, is conceptually strong. The primary variables for this study are, and measures used to assess them, are presented along with information related to the accompanying norms and validity. Several of these constructs were previously developed for this targeted population, and have been used in other scientific studies undertaken by other investigators.

The proposed investigation is described as a descriptive, co relational study to test theory-driven regression models to explain adult outcomes. Participants in the original studies were assigned to either a treatment or control group. Hence it is argued that the random assignment becomes one among many family and environmental predictors for developmental outcomes.

Specific hypotheses related to contextual, ecological, intra- as well as interpersonal, and intra-familial variables are presented. In addition, specific hypotheses related to child outcomes for the new wave of data to be collected are presented and tied conceptually and theoretically to their literature review.

Statement of the problem and literature review
A range of studies, including their own previous work, is used to present a clearly defined and well-conceptualized statement of the problem. The investigators argue that this theory-driven research will help promote an understanding of the impact of ecological circumstances that contribute to individual outcomes. Moreover, it is argued that a unique aspect of this investigation, and strength of it as well, is the ability to predict adult outcomes. Earlier findings from the Abecedarian and CARE studies are used to support the current investigation. The primary study variables are tabled and clearly described. Based on their previous work, there is little doubt in the mind of this reviewer that this research team will produce several scholarly publications should this study be funded.

Population and sampling
In their most recent wave of data collection, 104 of the original 111 Abecedarian parents agreed to participate, and sixty-five of the original CARE parents participated. A total of 170 families, then, are eligible to be recruited for this proposed investigation. Given the length of this study, and the relatively low attrition rate that they have encountered to date, it is highly likely that the investigators will be able to recruit a sufficient number of families needed to insure statistical power. Power estimates have been provided, and the investigators believe they will have little difficulty achieving the desired sample size.

Data Analysis
Three of the investigators will assume responsibility for data management and analysis. The proposal describes measures that will be undertaken to insure that the all data files are clean and prepared for analysis. Overall, the data analysis section is clearly written and detailed. The desired end results of the analyses for each specific hypothesis are presented and clearly described. Given the complex nature of each of the hypothesis, and the linking of multiple data sets, the investigators should be applauded for their innovation and scientific rigor.

Summary
In summary, this is an important topic and initiative. Conceptually, the ecological approach introduced by the PI provides a systemic approach to supporting the developmental outcomes of young children. More important, the proposed investigation provides a wealth of data that can increase the scientific communities understanding of the contextual and individual factors associated with the attainment of developmental outcomes. The proposed investigation is an important
topic and initiative. Conceptually, the ecological approach introduced by the PI provides a systemic approach to supporting the developmental outcomes of young children. More important, the proposed investigation provides a wealth of data that can increase the scientific communities understanding of the contextual and individual factors associated with the attainment of developmental outcomes. The investigators are prominent researchers who have, over the duration of their careers, published seminal pieces based on their previous work. There is no doubt that they will continue to do so if funding is approved for this study.
**Interparental Conflict and Adolescent Violence**

**Grantee**  
University of California-San Francisco

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**Project Number**  R40MC00118

**Project Period**  1/1/1997-12/31/2000

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**Summary**

**Statement of the Problem**

Although violence among adolescents is increasing, little is known about its causes. Parental marital conflict is a potentially important but understudied influence on adolescent violence. Results of this study will be useful in developing primary and secondary prevention programs for parents and for adolescents, aimed at decreasing violent behavior and victimization among adolescents. This research will also provide the basis for developing prevention programs tailored to the needs of Mexican-American families.

**Research Questions or Hypotheses**

The purpose of this research continuation is to determine the specific components of parental conflict that are related to violent behavior and victimization among adolescents and the processes by which parental conflict influences adolescent violence and victimization.

**Study Design and Methods**
The proposed longitudinal research will use a cognitive/emotional model to examine how parental conflict influences adolescent peer violence, dating violence, and sexual aggression. Both violent behavior and victimization among adolescents will be examined. Multiple dimensions of parental conflict will be measured to identify aspects of parental conflict that are beneficial or harmful to adolescents. The theoretical model will be tested separately in white and Mexican-American families.

Adolescents will be interviewed about parental conflict, their emotional distress, violence, and victimization. Parents will be interviewed regarding their marital conflict. The Marin acculturation scale will be administered. Six focus groups will be held for the purposes of instrument development and refinement, with particular emphasis on the assessment of violence. The research will use a strong multidimensional approach to assessing inter-parental conflict. Six dimensions of conflict are targeted: frequency, intensity, content of the conflict, conflictual processes, conflict resolution, and child involvement in conflict. This conceptually and methodologically sophisticated approach to studying parental conflict allows the researchers to address precisely associations between conflict and child outcomes.

Population and Sampling Plan

This study will use 303 adolescents and their parents who are participating in currently-funded research as study subjects. Adolescents, aged 15-18, and their parents will be interviewed individually by telephone three times at 6-month intervals. Families will be recruited from the membership of Kaiser Permanente, a large HMO serving Northern California.

Analysis Plan

The scales developed for this research, factor analyses will be conducted, followed by Cronbach’s alpha. Items for a scale will be equally weighted and combined. The hypothesized cognitive/emotional model will be tested using latent variable structural equation modeling (SEM). The model will be tested separately for white and Mexican American families. Following this, differences between Mexican American and whites will be assessed using multi-group SEM, which will test whether the same model applies to both groups and whether the coefficients for each parameter are the same across groups. The multi-group analysis will include only those scales common to both groups.

Pre-Award Evaluation

Evaluator 1

Originality and Importance
This application requests 3.7 additional years of support to extend a currently funded study. The current project is a prospective study of the relationship between aspects of marital conflict and adolescent health risk behaviors, including unprotected sex and use of alcohol, tobacco, and other substances. The proposed research would follow longitudinally the study sample, with a focus on the predictors of adolescent violence. The research is based on theories of emotion and cognitive models of stress and coping.

The purpose of the continuation study is to determine the specific components of parental conflict that are related to violent behavior and victimization among adolescents, and the processes by which parental conflict influences adolescent violence and victimization. Peer violence, dating violence, and sexual aggression, addressed in the proposed study, are all of significance and concern. The researchers make a convincing argument that parental conflict is a relatively unexplored but potentially powerful influence in the development of adolescent violence. In addition, the researchers' focus on studying culturally relevant aspects of family conflict and adolescent violence is an important strength of the proposed research.

Regional and National Significance
The involvement of adolescents in violence, both as perpetrators and as victims, is a major national public health issue. The study’s results should make an important contribution to our knowledge of risk behavior and violence among white and Mexican-American youth. The information obtained from the study could be useful in developing culturally relevant intervention and prevention programs. For example, programs could teach parents to develop those aspects of parental conflict that are helpful to adolescents and to reduce those conflict behaviors that are harmful.

The investigators discuss the possible development of such programs within the health maintenance organization (HMO)
system and describe how information could be used to develop educationally based interventions for adolescents, focusing on conflict management and coping with distress arising from parental conflict. Important information would be generated to better understand how to tailor such interventions to Mexican-American adolescents and their families. The topic of this project is of regional and national significance, given the importance of this issue.

Scientific and Technical Merit

The study uses a strong multidimensional approach to assessing interparental conflict. Six dimensions of conflict are targeted: Frequency, intensity, content of the conflict, conflictual processes, conflict resolution, and child involvement in conflict. This conceptually and methodologically sophisticated approach to studying parental conflict allows the researchers to precisely address associations between conflict and child outcomes.

The researchers have been very responsive to the review committee's requests for clarification and additional information. The first issue concerned the reliability and validity of data obtained through telephone interviews. The investigators provide a detailed response to this question, citing the advantages of data collection by phone rather than face-to-face interviews (namely, ease of scheduling and completion, and cost savings). Using certain sensitive questions as a basis, the investigators have analyzed their existing data collected from adolescents through phone interviews and through face-to-face interviews, and have found minimal discrepancies between the two data-collection formats. Inconsistencies averaged 1.8 percent for whites and 3.0 percent for Mexican-Americans. Extensive detail is provided on strategies to ensure the reliability and validity of telephone data, including using focus groups of parents and adolescents to develop the phrasing of questions, pretesting the interview, ensuring the adolescent's privacy during the phone interview, and building checks for internal consistency into the interview.

The most substantial questions arising from the current review concerned the conceptual framework for the study. These concerns centered on two areas: (1) The different associations between the adolescent risk behavior and the three types of violence to be studied; and (2) expectations for similar or different processes in whites compared with Mexican-Americans. The investigators address each of these areas in detail, supplying an expanded review of the literature and clarifying the data analyses to be performed.

The investigators argue that the factors determining intimate-directed versus peer-directed violence are yet to be determined. They suggest that it is not yet known to what degree peer aggression, dating violence, and sexual aggression are a function of the same factors. The planned research would investigate these associations. The researchers present a theoretical model that posits differing processes leading to peer aggression, dating violence, sexual aggression, and to victimization by each of these three different forms of violence. The model posits similar basic processes for Mexican-American and white adolescents. In addition to these basic predictions, the investigators suggest that the within-family processes of acculturation, as well as societal forces such as economic hardship and discrimination, may place Mexican-American youth at greater risk. The investigators predict that the model components of parental conflict, primary appraisal, and emotional distress will have stronger effects on adolescent violence and victimization among Mexican-American youth.

In sum, the investigators have provided a thoughtful and detailed response to the questions posed. The conceptual framework has been tightened and improved, and methodological concerns related to the phone interviews have been satisfactorily addressed. The proposed investigative staff seems well qualified and experienced in conducting studies such as the proposed project. The budget is a bit high and could be reduced by at least 15 percent. The recommendation is for approval, with reduction in budget.
**Life Around Newborn Discharge (LAND)**

**Grantee**
American Academy of Pediatrics

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**Project Number** R40MC00117

**Project Period** 10/1/1998-9/30/2001

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**Year 2010 Objectives**
16.1, 16.8, 16.19

**Study Design**
Observational

**Time Design**
Mixed

**Care Emphasis**
Noninterventional

**Population Focus**
Neonates, Parents/Families/Mothers/Fathers

**Race/Ethnic Focus**
No Stated Race, Ethnic Focus

**Priority Research Issues**

**Summary**

*Statement of the Problem*

The immediate postpartum period is one of biological and social transition, providing an important opportunity for the health care system to identify and respond to both acute and chronic medical and social problems that families face. Insurers, managed care companies, and hospitals operating under capitation have sought to reduce costs through initiatives to shorten hospital stays, including the length of postpartum hospitalizations for mothers and newborns. With a reduction in the lengths of hospital stays and the services, opportunities to screen for medical and social risks diminish. Therefore, practitioners and parents must shoulder substantial added responsibility for monitoring during the critical neonatal period. The safety and feasibility of discharge are dependent on the medical and psychosocial needs and risk status of the mother and infant pair, together with the health care infrastructure available to monitor them after discharge. Despite the breadth of these concerns, recent studies have found seemingly contradictory conclusions with respect to identifying substantial medical harm because of decreased postpartum hospital stays. Traditionally, practitioners have judged the degree of readiness and risk and have determined suitable timing for discharge. The components of this judgment about discharge timing are complex and probably include intuitive assessments of biological and social risk, barriers to access, adequacy of education and postpartum services, and, admittedly, tradition. Economically inspired, rule-based...
decision making may limit good judgment and result in unsuitable discharge timing and insufficient postpartum services for some mothers and infants. An optimal length of postpartum stay for healthy newborns and mothers is not well defined. Good judgment and available data do not tell us where services should ideally be performed, by whom, and with exactly what content or methods.

We feel the most revealing investigation will be one that examines the mothers', pediatricians', and obstetricians' judgments of readiness for discharge and that identifies the components of practitioner judgment or family readiness for discharge. We then will relate these judgments to health care utilization, health-related behaviors, and infant and maternal health status during the first month after postpartum discharge. A comparison will also be made between the supplemental services and family supports and adjustments perceived as necessary by mothers, pediatricians, and obstetricians with those that are actually delivered.

The eventual product of this and related work will be to provide the basis for recommendations for service delivery in the peripartum period; the recommendations will be based on this empirical study of the medical and psychosocial needs during the first month of life. Our project is well timed to examine scientifically the critical perinatal period and to help with the monitoring of the Newborns' and Mothers' Health Protection Act of 1996 (as required by law), which went into effect January 1, 1998.

**Research Questions or Hypotheses**

The study will focus on the following questions:

1. How often do mothers, pediatricians, and obstetricians agree on readiness for postpartum discharge?
2. What influences these perceptions of readiness?
3. How do these perceptions affect health care utilization, health outcomes, and health-related behaviors during the first 4 weeks after discharge?
4. How do these perceptions of readiness change over time?

**Study Design and Methods**

This will be a prospective, observational cohort study of 6,000 mother and infant pairs who will be followed for the first 4 weeks after postpartum discharge. These infants are healthy, term newborns who weigh more than 5 pounds and who will be followed in one of our national sample of pediatric practices. Exclusion criteria include maternal chronic illness; multiple births; mothers without a telephone; and newborns who have a major congenital anomaly, have been placed for adoption, or have been in the special care nursery for more than 8 hours for medical reasons. Each practice will enroll all eligible newborns seen consecutively for visits in the hospital nursery during a period of 8 weeks, including holidays and weekends.

Data will be collected by questionnaires completed by mothers, pediatricians, and obstetricians. Mothers, pediatricians, and obstetricians will answer self-administered questionnaires at the time of enrollment. A mother's enrollment questionnaire contains items about care received during pregnancy, labor and delivery, and time in the hospital, and about decision making during discharge planning. The discharging pediatrician's questionnaire documents prenatal problems, birth data, nursery problems, discharge data, and practitioner judgment regarding discharge and followup plans. The discharging obstetrician's questionnaire documents the obstetrical considerations about postpartum discharge, including the medical and psychosocial factors.

Beginning the first day after postpartum discharge, mothers will complete daily diaries during the infant's next 14 days of life. These diaries request information about health concerns, behaviors, and health care use for both mother and infant. Pediatric practitioners will also complete an encounter form at each pediatric office encounter during the first 4 weeks after discharge. This form records key information about the encounter, including the articulated reason for the visit, the initiator of the visit, the disposition, and the diagnosis, as well as sufficient other information to assess the clinical context.

Four weeks after discharge, mothers and pediatricians will each complete self-administered followup surveys. The mother's survey documents maternal confidence level in her newborn's care, maternal ratings of the quality of encounters with various health care practitioners, maternal health-related behaviors, and maternal health and mental status. The pediatrician's followup questionnaire documents health care utilization including office visits, hospitalizations, outpatient procedures and referrals, infant's weight gain, and whether (in the practitioner's opinion) the mother and/or infant would have benefited from an earlier or a longer hospital stay. Finally, each mother will complete a postcard at 7–8 weeks postpartum to document the date of her obstetrical checkup. All patient questionnaires will be available in English and Spanish; the mothers' reading level is approximately fifth-grade to sixth-grade level, and the questions have been modified to insure cultural sensitivity and
relevance.

Population and Sampling Plan

The intent of our sampling plan is to obtain a heterogeneous set of community-based practices serving diverse populations. This study will be conducted in a national sample of approximately 200 pediatric practices, each with an average newborn enrollment of 30; there will be oversampling of certain practice sites, as required, to ensure that there are adequate numbers of underserved and minority subjects. Subjects will not be excluded from this study based on their race, ethnicity, or the gender of the infant. Mothers and their newborns will primarily be drawn from a geographically diverse national sample of pediatric primary care practitioners in Pediatric Research in Office Settings (PROS), a national, practice-based research network of the American Academy of Pediatrics (AAP). All PROS practices will be asked to participate. This source will be supplemented with additional inner-city practices recruited through Health Watch, a not-for-profit organization located in Brooklyn, NY, and dedicated to "improving the health and longevity of minority populations.

Surveys on the structure of the practice, demographic characteristics of both the practice and each practitioner, and routines relevant to newborn discharge will be completed. A subset of these same items will also be answered by a random sample of AAP practitioners. National, practice-based research networks allow investigators to conduct studies requiring large, national primary care samples from a pool of volunteer practitioners. Although this is clearly not a random sample, repeated PROS analyses from other studies have demonstrated that PROS practitioners are similar (in a number of important ways) to random samples of AAP practitioners. Therefore, we feel our results will be appropriately generalizable.

This prospective, observational cohort design provides a substantial advantage in addressing our study aims. First, this study seeks to understand patterns of practice as they occur in real-life settings; we endeavor to generalize as broadly and appropriately as possible. The use of a highly specialized population, as typically occurs in randomized trials, and the intensity of follow-up involved in most such trials limit the ability to generalize from findings in randomized trials. This study provides low costs per patient and per clinician as compared with randomized, controlled, multisite trials with similar numbers. Second, we seek to minimize the impact of recall bias, that is, the bias that occurs when the outcomes of interest have already occurred and shade the recollection of possible exposures. Prospective data collection is the most desirable means of limiting such bias. Third, we seek information on a broad array of outcomes; such an approach precludes the use of a design, such as case control, based on the occurrence of one particular outcome.

Analysis Plan

Analyses of the data concerning the 6,000 newborns in this study will be complicated primarily by the fact that the medical care and advice will be limited to approximately 200 practices. Therefore, it is possible that outcomes for mothers and infants seen in the same practice will be more closely related to each other than to those in other practices. This correlation will be accounted for in all of the analyses that are carried out through use of the generalized estimating equation approach to cluster data. We will assume an exchangeable correlation structure within each practice and effectively increase the standard errors of the parameter estimates to reflect the reduced amount of "independent" information. These analyses, whether linear, logistic, or Poisson regressions, will all be carried out using a public domain Statistical Analysis System macro written to implement the generalized estimating equation approach. If we find that the sample of practitioners in our study is not representative of the national population, we will use weighted regression methods to estimate outcomes that are more representative of practitioners in general. The weights will be derived by comparing the study sample with the membership of the AAP.

Related to the issue of generalizability is the extent to which study results hold in specific subpopulations, such as minorities, primigravida, and those of lower socioeconomic status. In addition to analyses in which these variables will be included in multivariate models as explanatory factors, we will also provide descriptive statistics on the outcomes of interest for these separate subpopulations.

The choice of measures selected to be studied fits best with our conceptualization of discharge. Statistical analyses will include summary statistics (proportions and 95-percent confidence intervals or mean, standard deviation, median, interquartile range, minimum and maximum) for all study variables of interest and for calculated derived variables. We will analyze the readiness outcome, assessing the agreement among mother, pediatric, and obstetric decisions about maternal and infant readiness for discharge, using chance-adjusted kappa statistics.

To begin to elucidate the impact of certain explanatory variables on readiness, we will use two-sample *t*-tests or Wilcoxon tests for continuous data, and we will use the chi-square or Fisher's exact test for categorical data. As described above, we
will then build multivariate linear, logistic, or Poisson models, which reflect the clustered data structure, to explore factors influencing readiness. Similar methods will be used to assess the impact of readiness on health care utilization, health outcomes, and health-related behaviors during the first 4 weeks after hospital discharge.

We will also assess changes in decisions about readiness on the part of the mother and practitioner at 1 month postpartum; this will allow us to evaluate whether changes from the time of discharge to 1 month postpartum occur more frequently with judgments of infant or maternal readiness for discharge.

Pre-Award Evaluation

Evaluator 1

*Originality and Importance*
Pre-award evaluation outstanding from MCHB. Submitted second request 10/26/00, JMB.
Living With HIV/AIDS: Mother-Child Coping and Adjustment

Grantee
Wayne State University

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Project Number R40MC00190

Project Period 9/1/2000-8/31/2003

Costs

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Summary

Statement of the Problem

The primary purpose of the proposed study is to conduct a longitudinal follow-up of the HIV-positive mother – uninfected child dyads first interviewed one to three years ago, to test the stability of a theoretical model predicting child adjustment from a combination of maternal and child variables.

Research Questions or Hypotheses

Because the theoretical model informing this research is based on an inference of causality, the changes in constructs over time should parallel the relationships depicted in the model. For example, it would be expected that if maternal coping became more effective, then maternal psychosocial adjustment should improve. Likewise, improved child coping should improve child psychological adjustment. Additionally, the following research questions will be addressed:
1) To what extent do baseline measures (Phase 1) predict child adjustment at the end of Phase 2?
2) To what extent do the model constructs change over time?
3) How reliable are the changes in model constructs?


**Study Design and Methods**

This investigation has both quantitative and qualitative elements. The quantitative study involves a single group of mother/maternal guardian – child dyads that participate in three follow-up interviews over an 18 – 24 month period. These quantitative interviews follow the content of the baseline data obtained in the first study with refinement of additional measures. These data will allow us to examine the stability of the mother and child experiences, and provide the longitudinal data to better assess the validity of the dynamic theoretical model which, in turn, will allow us to identify critical intervention points for future research and practice. A qualitative component will be added to arrive at an understanding and thick description of the participant’s experience of being a mother who is HIV-positive and of being a child with an HIV-positive mother.

**Population Description and Sampling Plan**

Prior participants were contacted either directly by telephone or indirectly through contact with the personnel of collaborating community agencies. New participants were identified by agency personnel and provided with a letter describing the study and inviting her to speak with a project staff member. Mothers are encouraged to come with the study child to Wayne State University for all interviews. Transportation is provided at no cost to the mother. When necessary, interviews are conducted in the family’s home or in some other mutually agreeable location (e.g., a relative’s home, the agency).

Eligible women are those who (a) are HIV-positive and have primary parental responsibility (mother/maternal guardian) for an HIV-negative child between the ages of 10 – 17, (b) are physically and mentally able to participate, and (c) are willing to participate. In addition to the above criteria, eligible children are: (a) within normal limits for intelligence, (b) free of serious illness, (c) in contact with the biological mother at least twice a month, and (d) are willing to participate. Inclusion criteria (c) was designed to include children who may have temporary or alternative living arrangements, but who continue to maintain regular contact with their mothers. From the participating dyads, approximately 75 interviewees (50 women, 25 children) will be selected from the larger sample to participate in the qualitative portion. Eligible participants will be those who: (1) speak openly, willing to share verbally, speaks English clearly; and (2) quantitative data from the first follow-up interview reflect categories of qualitative interest (i.e., disclosure, religiosity). For children, the content of the interview will be limited to disclosure, and an additional inclusion criterion is that the mother has indicated that she has disclosed her illness to the child and is willing to let the child be interviewed about their experience.

**Analysis Plan**

Data analysis will include multi-level mixed design and structural equation modeling. Empirical Bayes estimates of individual true change will be utilized in these equations. Additionally, an accelerated longitudinal design will examine the extent to which key relations are moderated by the age of the study child.

**Pre-Award Evaluation**

**Evaluator 1**

*Originality and Importance*

Given the continued expansion of the HIV epidemic to minorities and women in the US, it is of utmost importance to postulate models of coping and predicting child and adolescent adjustment. Life with HIV is and will continue to evolve as a chronic illness with significant impact to those affected.

This group of investigators already have established a cohort of mother-child dyads, and are now proposing to expand and determine a causal model to explain children's psychosocial adjustments to a maternal HIV diagnosis.

The information gathered and the final model will provide sound guidance in the development of intervention and service programs.
The study of mothers living with HIV is of national significance since more and more the perinatal interventions will continue to be successful and the population of HIV positive mothers who care for MV negative children is expanding. This proposal is extremely well thought, planned and will be carried out successfully given the experience of the investigators.

The review of the literature is more than extensive and well organized by factors such as: maternal stress, social support, coping and psychosocial adjustment, maternal HIV infection and child behavior; Parent-child Relationships and Child Psychosocial adjustment; Environmental Risk and Child Psychosocial adjustment; Child Stress, Coping and Social Support.

The Conceptual Model and Hypotheses follow a previous model, which has been improved, by the preliminary data and the literature review.

For the quantitative aspect a long list of instruments was described for mothers and children. All instruments are pertinent for the proposed model. One missing component from the maternal HIV Associated stressors, which incorporates progression of disease but lacks pertinent information on treatments, adherence and difficulties related to care and disclosure, i.e. taking multiple medications in a situation of non-disclosure to children.

The issues of treatment and adherence are relatively new but extremely important to be considered and incorporated into this model. There are also side effects that affect body shape and image (fat redistribution) which may produce maternal self-image changes and difficulties.

The design does not include a control group and therefore all inferences are to be assumed to relate to the HIV diagnosis, which may be additional stressors in the life of a poor, urban, Midwestern African American women living with HIV, and not exclusively because of the HIV.

The investigators recognize a limitation in terms of sample size by acknowledging that it reflects the size of the local population available. The time schedule is adequate is not a concern to us.

The total direct costs for the proposal study are $752,258.

Evaluator 2

Originality and Importance
This proposal addresses a very important topic, that of familial responses to living with a mother with HIV/AIDS. The investigators have done an excellent job thinking through various conceptual issues in the coping and adjustment process to HIV, and in considering the impact that such would have on sero-negative children. The proposal follows on a previous study in which 150 mothers and their sero-negative children have already provided a wealth of cross-sectional data, and the PI now proposes to address the issues within a more longitudinal framework. This should provide a more detailed and important understanding of the psychosocial impact of HIV/AIDS in mothers on their non-affected offspring.

Although there is much to be admired in the proposed work, there are a number of issues that detract from the overall significance of the proposal. First, and perhaps of most significance, the study methodology is entirely self-report of the mothers and the children, and there are many, many questionnaires involved. And predominantly, the mothers are reporters. The absence of data from independent sources is a serious limitation, especially when the major measurements are psychological in nature and subject to the biases inherent in responses of individuals likely to be affected by their psychological status. For example, mothers who are depressed tend to report on other aspects of their own lives and the lives of others in ways that are congruent with feeling depressed, such as suggesting that their children's behavior is more problematic. Independent reports from others would add validity data to these reports, and strengthen this study tremendously. Teacher reports of children's adjustment would be an excellent addition. Also, observations of the mothers in some interactional context could be helpful in establishing the functional aspects of maternal behavior and the mother-child relationship that would provide a much more coherent and reliable index of functioning than maternal report alone. These observations would be coded by blinded, independent raters, thereby providing indices free of potential biases. Finally,
observations of interviewers, as independent raters of the mothers' behavior and well being, as well as the child's functioning, would strengthen the study methodology. Relying solely on the reports of the parents and children introduces source bias that could be obviated by the presence of these independent reports and observations. The current methods will result in substantial correlation between indices, but it will not be possible to know whether the relations found are true or represent source bias without some independent corroboration. Having other reporters and/or coded observations by blinded raters would do much to obviate this methodological limitation.

Beyond the issues described above, it is also the case that the investigator does not provide a compelling discussion of the longitudinal nature of this proposed work. The PI discusses the reliability of change that can be determined, but the longitudinal nature of these data really provide the opportunity to address issues in continuity more than reliability of constructs, and to address issues of lawfulness in the continuity of developmental processes across time. Within the measurement scheme, there was a curious disconnect. The vast majority of measures address issues of individual appraisal and perception of the significance of events or experiences. Yet, the SRRS is a life stress measure that arbitrarily assigns values to life stress events rather than seeking individual appraisal. This doesn't appear to be a good conceptual fit with the other stress indices.

The PI alludes to the continued availability of most of the subjects from the previous investigation, but it's not clear that the investigators have maintained contact with this group and it will be three years ago that some of these families were involved with this investigative group. Has there been any systematic attempt to re-contact and re-engage this group, and if so, what are the numbers that have been willing to re-enlist in the follow-up? Related to the sampling, the new group of 25-subjects will not have the full compliment of data that the previous retained subjects have, so not all analyses will be possible to address the longitudinal questions with all the subjects. Too, these new subjects are chosen for the presence of certain experiences or characteristics, and therefore they may not be entirely comparable to the previous group of subject families.

Investigators
This is a solid investigative team with some experience with this research area. Dr. Hough is a professor in the College of Nursing at Wayne State University, and has a record of scholarly publication and presentations. The co-investigators likewise have appointments in the College of Nursing, and bring research expertise to the project. Some, such as Dr. Brummitt, have specific experience with the previous cross-sectional project.

Budget
The budget seems somewhat high, and is particularly large in relation to investigator time. 125% FTE investigator time is requested, but its not well justified that so much FTE effort is actually needed.

Summary
There is much to admire in this proposal, not the least of which is the importance of the topic. Yet, the total reliance on self-report methodology detracts from the potential significance of the work, and greater clarity and coherence could be provided in relation to measurements chosen, sample acquisition and retention, the longitudinal function of the study.

Evaluator 3

Originality Importance
Minority women comprise one of the fastest growing populations of new HIV/AIDS cases. Many infected women are also mothers and research suggests that these children are at great risk for psychological and behavioral problems. Thus, intervention programs focused on the physical and mental health needs of these children are greatly needed.

The present project advances an excellent argument for exploring parent and child coping strategies as a vehicle for understanding how families adjust to HIV/AIDS. In her preliminary work, the PI was able to demonstrate that positive child adjustment in a family coping with a mother diagnosed with HIV/AIDS is best predicted by low environmental risk, good maternal emotional adjustment, good parent-child interactions and good child coping. Extending this data by conducting a longitudinal follow-up is an excellent idea. Coping for pre-teens versus teenager may be predicated upon a totally different
set of relationships than those found in the first study. Indeed, the fact that the older children in the first phase showed much stronger correlation than the younger children suggests that developmental issues may be operative in the model.

Another strength of the proposal is that it uses a constellation of instruments to measure the various constructs. Most of the constructs are measured in at least two ways allowing for the creation of a stronger variable to be entered into the analysis. It is more convinced that coping matters when two separate instruments show similar patterns of relationships.

The PI has already signed on 113 of the original 150 dyads so her ability to actually collect longitudinal data looks promising. Also her intent to complete a second sample of at least 125 suggests that beyond the longitudinal analysis she will be able to attempt to replicate the model found with phase one data.

One of the weakest aspect of the study is the qualitative investigation. While the intent is justified, it is very underdeveloped. The interview guide is simply a list of questions. Probes and follow-ups have not been standardized. To attempt to interview 75 of the participants with no real standardization of the protocol will lead to problems in the data. Without proper standardization there may be problem compiling like themes because there is a chance that individuals will respond to the questions in ways that may lead them in vastly different direction. If the follow-ups from any of the questions posed on the protocol are different then the substance of the interviews for each individual may also be different.

In general this is a well conceived and well presented proposal. The goals are clear and the methods have integrity. It poses some important questions for these mothers and their children.
**Maternal Health and Pregnancy Outcomes Among Hispanics**

**Grantee**
Regents of the University of Michigan

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**Project Number** R40MC00115

**Project Period** 10/1/1998-9/30/2001

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**Summary**

**Statement of the Problem**

Low birthweight is rare among Hispanic infants in the United States. Most research associated with birthweight in Hispanic communities has explored social, dietary, and behavioral aspects of traditional Hispanic culture, which is presumed to reduce the risk of low birthweight among Hispanic infants. Although sociocultural and behavioral lines of inquiry are important, the complex interplay of factors associated with birthweight must ultimately involve physiological processes. Obesity, insulin resistance, impaired glucose tolerance, and type 2 diabetes are prevalent among Hispanic women of childbearing age. The prevalence of diabetes during pregnancy is three times greater among Hispanic women than among non-Hispanic white women. Fetal exposure to maternal hyperinsulinemia is associated with fetal overgrowth and increased incidence of neonatal respiratory problems and metabolic abnormalities. Increased body mass index (BMI), upper body fatness, and blood pressure in infants, and increased risk of obesity, hypertension, abnormal glucose tolerance, and other metabolic abnormalities in adolescence and young adulthood have been documented in the children of diabetic mothers. Maternal obesity and an increasing level of screening glucose in nondiabetic mothers are also associated with higher birthweight and blood pressure, as well as other adverse neonatal outcomes. Mothers who are obese or have abnormal glucose tolerance...
during pregnancy are at increased risk for pregnancy, labor, and delivery complications and type 2 diabetes after pregnancy. Given the focus on low birthweight as a major public health indicator of maternal and neonatal health, the perception of good outcomes, according to this measure, has reduced health policy, program, and research attention to Mexican American mothers and infants. The influence of maternal obesity and metabolic characteristics on Hispanic infant birthweights and on the increasing risk of obesity and diabetes that is observed among Mexican American children, adolescents, and young adults remains to be systematically assessed, along with the preventive health care needs of women and children in this population. The rising prevalence of both obesity and diabetes among young people and women of childbearing age in this country suggests that the health of an increasing proportion of mothers and infants will be affected by the processes examined by this study, particularly in immigrant, minority, and other populations undergoing lifestyle changes. Study findings should have significance for design of both policies and programs for women and infants.

**Research Questions or Hypotheses**

This study will describe the following: The distribution, prevalence, and relationships among maternal body fat distribution, BMI, glucose tolerance, pregnancy weight gain, and sociodemographic characteristics, including level of acculturation; the relationships among maternal anthropometric, BMI, and metabolic measures; the patterns of pregnancy weight gain, maternal sociodemographic and family characteristics, cigarette smoking, other maternal health conditions, and prenatal care therapies; and the prevalence and distribution of several measures of birthweight, gestational age, and adverse maternal and newborn outcomes in this community-based Hispanic population.

This study will also test the following hypotheses:

1. Among nondiabetic mothers, increased central body fat distribution and an increasingly abnormal maternal metabolic profile (glucose, insulin, free fatty acids, triglycerides) will be associated with increasing birthweight (adjusted for gestational age), infant BMI, birthweight ratio, and incidence of large-for-gestational age (LGA) births. The impact of sociodemographic characteristics, prepregnancy BMI, pregnancy weight gain, other maternal health conditions, and prenatal care will attenuate but not account for all of this relationship.

2. As maternal central body fat distribution increases and metabolic profile becomes increasingly abnormal, the incidence of adverse maternal and neonatal outcomes will increase, after accounting for prepregnancy BMI, other maternal health conditions, and infant gestational age.

3. Adding central body fat distribution, metabolic characteristics, and prenatal treatment variables will result in a better fitting model by which to predict birthweight and gestational age outcomes than the traditional models, which are based on sociodemographic, medical risk, and prenatal-care-use characteristics.

**Study Design and Methods**

This is a 3-year prospective cohort study of 700 mother-infant pairs. Data sources include medical records, metabolic assays, maternal anthropometry, and interviews. Independent variables include the following: (1) Sociodemographic and family characteristics—family (mother, father, sister, brother) history of diabetes, maternal age, parity, marital status, ethnicity, level of acculturation, maternal and paternal educational level, income, and insurance type; (2) level of acculturation (measured by ethnic identity; duration and pattern of residence in the United States, in Detroit, MI, and in a Latino community; primary and preferred language and need for a Spanish translator); (3) metabolic measures (maternal glucose, insulin and triglyceride, free fatty acid, and glucagon); (4) anthropometry (waist, hip, and upper arm circumference; upper arm skinfold; prepregnancy weight; height; and BMI); and (5) pregnancy weight gain, cigarette and alcohol use, anemia, and hypertension during pregnancy. Dependent variables include the following: (1) Birthweight adjusted for gestational age (e.g., birthweight ratio, percentages of LGA), and (2) neonatal BMI. Adverse newborn outcomes will be classified in categories to include hypoxia and asphyxia, respiratory problems, need for resuscitation, birth injuries, metabolic abnormalities, congenital abnormalities, and infection. Adverse maternal outcomes will be classified as antepartum, intrapartum, and postpartum, including labor and delivery complications, cesarean section, preeclampsia, and infection.

**Population and Sampling Plan**

All self-identified Hispanic women entering prenatal care between January 1999 and December 2000 at the Community Health and Social Services Center (CHASS) in southwest Detroit will be asked to participate in the study. High-risk obstetric care and deliveries take place at Henry Ford Hospital in Detroit. The final study population (allowing for patient
refusal to participate, no parental consent for some women under 18 years old, pregnancy loss, multiple gestations, and loss to CHASS or Henry Ford care before delivery) is expected to include 700 mother-infant pairs. Ninety percent of these women are expected to be Mexican or Mexican-American and have incomes at or below the poverty line. With the exception of slightly lower proportions of women under age 18, the study population is expected to include the full range of age, health status, and other characteristics of the population of Hispanic women who use this community-based health center. The entire cohort should have delivered their infants at Henry Ford Hospital by July 2001.

Analysis Plan

We will calculate descriptive statistics (including frequencies, means, standard deviations, coefficients of variation, and confidence limits, where appropriate) for the independent and dependent variables. We will describe the distribution of maternal metabolic characteristics, BMI, and central body fat distribution by degrees of abnormality. For example, increasing glucose intolerance will be described by histogram, division of the population into quartiles, and the proportion of women in categories commonly used for glucose screening and diagnosis. Measures of central body fat distribution and prepregnancy BMI will be examined as continuous variables whenever possible. However, categorical variables will also be created when they conform to categories used for clinical care decisions. We will use correlation coefficients, phi coefficients, and plots (variously depending on whether the variable of interest is categorical or continuous) to assess the relationships between pairs of independent variables that may influence fetal growth and other maternal and infant outcomes. Independent, additive, and interacting effects of these variables will also be assessed.

The distribution and confidence limits for birthweight (in grams), gestational age (in weeks), birthweight at each gestational age, newborn BMI, percentages of LGA, and birthweight ratio will be described for the whole study population and by subgroup classified by measures of maternal body fat distribution, BMI, and maternal metabolic characteristics. The incidence of adverse maternal and newborn conditions will be calculated for the whole population and by glucose level, maternal BMI, and body fat distribution category. The proportion of mother-infant pairs affected by one or more adverse outcomes will also be calculated because it is expected that the incidence of many of the outcomes will be low. The relationships between the independent variables and each of the birthweight and maternal and newborn health outcome variables will be examined using correlation coefficients, phi coefficients, and plots. We will develop multiple variable regression models of the relationships among sociodemographic characteristics, glucose level, central body fat distribution, prepregnancy BMI, and pregnancy weight gain as independent variables and the various birthweights and maternal and infant health as dependent outcome variables. Linear, logistic, and polynomial models will be used, depending on the nature of the outcome variables.

Pre-Award Evaluation

Evaluator 1

Originality and Importance
No statement of originality and importance.

Regional and National Significance
No statement of regional and national significance.

Scientific and Technical Merit
This is an extremely well organized, well presented proposal. A very good literature review is given which supports the hypotheses to be tested, however additional information could have been provided on the incidence of adverse effects associated with high birth weight. Much preliminary work has been done and the investigators have an excellent relationship with the clinic where the patients are to be enrolled. Approximately 300 prenatal records have already been abstracted, along with partial abstraction of 125 labor and delivery obstetric and newborn records. The calculations are based on numbers from the population to be studied. The hypotheses and specific aims are clearly stated. The independent mediating and outcome variables are clearly summarized in a table. For the most part, measurement of the variables is clearly defined. Central body fat distribution, which is key, will be measured in three different ways, i.e., waist circumference, waist-to-hip ratio, and sum of trunk skinfold thicknesses to the sum of extremities skinfold thickness ratio (although whether measurements of waist...
circumference are useful at 28 weeks gestation is not certain). It is not clear how they will determine the pre-pregnancy weight for mothers whose first prenatal visit weight was obtained after 10 weeks of pregnancy. The specific list of adverse maternal and neonatal outcomes to be collected is given and seems to be appropriate, although not specifically justified. However, they are excluding stillbirths and pregnancy losses from analysis since this can be associated with gestational diabetes, they may want to reconsider whether they want to include these as an outcome.

The strength of this study is the investigator's experience with this population. Although they state that most Hispanic women enter prenatal care later, this population seems to enter relatively early. They may not be a completely representative population. The study is to be integrated into the normal routines of the clinic, and very few extra or disruptive studies will be performed. Additional blood tests will be drawn, but only at the time of routine testing. The data collection forms have already been developed and pre-tested. Inter- and intra-observer reliability will be 98%. This will be measured again on a 10% randomly selected sample every 8 weeks. No plan is given for if this high level of inter- and intra-observer reliability is not maintained. The sample size seems appropriate and based on realistic numbers. They have not considered how many women will decline participation in the study. Data analysis is clearly described for each specific aim and hypothesis. A time line is given and is primarily devoted to conduct of the study. This is clearly a strength, as much as the preliminary work has already been done and the study can begin in month 2.

Financing has not been requested from other places. The budget seems reasonable and well justified. There is $16,000 in other costs requested, which are primarily for subject incentive and laboratory tests. A strength of the study is the plan only to run a laboratory test on patients for whom outcomes are available.

**Evaluator 2**

**Originality and Importance**

This proposal is for three years of funding to investigate the impact of central body obesity and metabolic abnormalities among Hispanic women and their impact on maternal and newborn complications. The problems of obesity, impaired glucose tolerance and diabetes have not been systematically assessed, nor have the associated risks. Studies have confirmed links between increased acculturation and behavioral risk factors associated with poor fetal growth, but a direct effect of acculturation on birth weight has not been demonstrated. Studies of the impact of acculturation on birth weight have not accounted for the potential impact of maternal weight and metabolic status on birth weight. Also, despite increased risk for obesity, insulin resistance and diabetes among Hispanic women of childbearing age, very little is known about the impact of these conditions on fetal growth, birth weight, or adverse maternal and newborn outcomes. In addition studies of maternal body fat distribution have not assessed its importance on fetal growth or other outcomes. Recent studies have identified increased risk for neural tube defects among infants of obese women. The former controlled for diabetes status, but neither study measured maternal fuel metabolism. There are also gaps in research on prevalence and impact of obesity and diabetes on birth outcome.

**Regional and National Significance**

The results of this study can be applied to Hispanic women living in the United States, as well as other pregnant women who have central obesity and metabolic abnormalities. It is proposed that information from this study could lead to the design of appropriate treatment strategies that should result in improved care and improved perinatal outcomes.

**Scientific and Technical Merit**

An important strength of this proposal is that the principal investigator and her team have already collected preliminary data and are doing a pilot study on 300 Hispanic women. Also the majority of the procedures are already collected as part of their routine prenatal care.

The hypotheses are clearly stated and testable and the pertinent variables are identified. The independent, mediating/confounding, and outcome variables are clearly defined and the measures are clearly indicated. Pertinent terms and
concepts are also clearly defined. The data gathering procedures are clearly described and appear adequate and appropriate. The design is appropriate to the research problem. However, a weakness in study design is that the clinicians will not be blinded to the results of the maternal glucose tests because they need to be referred to the clinic for insulin and/or diet counseling. The sample size is adequate and allows for attrition or loss to follow-up. The subject population is well described and appropriate. The community being studied includes 60% of Detroit's Hispanic population and 80% of the prenatal patients at their clinic are Hispanic. Data analysis is presented in detail and the rationale for the sequence of steps to be taken. These plans are appropriate to the nature of the data, design and sample. The sample size is adequate for the proposed linear regression modeling.

The time schedule is set up for the three years of the study and a detailed time schedule is included. This proposal has not been submitted to any other Federal agency or private foundation for consideration. Preliminary studies of medical record data are being funded through October 1998 by the University of Michigan and the CDC Academic Prevention Research Center.

The principal investigator has been previously funded by the Hawaii State Department of Health, W.J. Kellogg Foundation, University of Michigan, and Blue Cross Shield Foundation of Michigan. She has published research on maternal diabetes on many different in ethnic groups in the United States.

The budget seems reasonable and realistic in terms of the aims and methods of the study. The consultant and staff's time will be used in a very economical and logical fashion.

The resources and facilities support the investigation. Much of the data is already being collected as part of the routine prenatal care given at the facility. The staff are from the performance sites (University of Michigan School of Public Health, University of Michigan School of Medicine/Diabetes Research and Training Center, Community Health and Social Services and Henry Ford Health System) and there appears to be appropriate coordination.

There are no concerns about the treatment of the human subjects since the majority of the materials and procedures are collected by staff as part of routine prenatal care. Investigators will remain alerted to signs of emotional, psychological or physical discomfort and attempt to identify and reduce its cause. Clinicians will not be blinded to glucose test results and will give treatment as appropriate. Patients will be given prenatal care with stringent protocols to identify maternal health problems associated with pregnancy. Follow-up care will be given, as well as education regarding obesity and glucose tolerance.

Evaluator 3

Originality Importance
This proposal addresses sections 3.1.4, 2.4.2,2.4.3 of the MCHB Research Priority Agenda.

Regional and National Significance
No statement of regional and national significance.

Scientific and Technical Merit
The statement of the problem is comprehensible and compelling. Aims are stated clearly. The literature review is thorough and well organized. The hypotheses are derived from the aims and testable. A conceptual model illustrates the potential role of central body fat distribution, maternal fuel metabolism and the role it may play among the other well-known factors associated with adverse infant and maternal outcomes. Variables for analysis are given with justification for their use, characteristics of measurement and their role in analysis (dependent, independent, mediating variable). The study design, a prospective cohort study, is carefully justified, and the circumstances under which data will be collected and clinicians blinded. The number of Hispanic women and their socioeconomic characteristics available for study is described and about 700 mother-infant pairs are expected over two years of recruitment. The data analysis for each aim and hypothesis is carefully outlined with sample size justification.
The major problems are in the loss to follow-up and the effect it will have on the sample size and power.

The principle investigator has a number of publications in perinatal epidemiology and maternal and child health. She has active research support (20%). There is demonstrated consultant support for (1) statistical design and analysis, (2) expertise on maternal weight, pregnancy weight gain and their impact on maternal and infant outcomes, (3) quality assurance with respect to measurement and recording of neonatal outcome variables, (4) diabetes and other metabolic abnormalities and their influence on pregnancy, (5) maternal body composition and nutritional status, and (5) data management.
Maternal PKU Resource Mothers Program: A Clinical Trial

Grantee
Childrens Hospital

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Project Number R40MC00162

Project Period 8/1/1999-7/31/2003

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Summary

Statement of the Problem

A randomized clinical trial of the Maternal PKU Resource Mothers program will assess the feasibility and efficacy of a home visitation program designed to improve outcome in maternal PKU. Women with PKU are at high risk for having babies with mental retardation, microcephaly, congenital heart disease and low birth weight. If the women are treated with a low phenylalanine diet and if they maintain metabolic control at the recommended level prior to and throughout pregnancy, their risks are greatly reduced. Nonetheless, over 70% of women with PKU achieve metabolic control after 10 weeks gestation, when damage to the fetus has already occurred. To reduce the number of late and inadequately treated pregnancies, mothers of children with PKU (who are familiar with the special diet) are trained to assist women with PKU who are preparing for pregnancy or who are already pregnant. While experiences with this program on a limited basis have been promising, it is not known whether the Resource Mothers home visitation program increases maternal metabolic control during pregnancy and hence improves offspring outcome.

Research Questions or Hypotheses

Year 2010 Objectives
No Stated Healthy People Objectives

Study Design
Experimental

Time Design
Longitudinal

Care Emphasis
Interventional

Population Focus
Infants, Pregnant women (not otherwise identified as adolescents)

Race/Ethnic Focus
No Stated Race, Ethnic Focus

Priority Research Issues
Women with PKU followed by an intervention that includes Resource Mothers compared to women with PKU followed by an identical intervention without Resource Mothers will 1) attain metabolic control sooner in their pregnancies, 2) have babies with better outcome at birth and 3) better outcome at one year of age.

**Study Design and Methods**

Women who contact a metabolic center for maternal PKU treatment will be randomly assigned to a group that receives Resource Mothers or a group that is treated according to the identical Maternal PKU Treatment Plan except that no Resource Mothers are involved. Resource Mothers are mothers of children with PKU who go to the homes of pregnant women with PKU and provide them with information, practical assistance and emotional support. The primary outcome variables to assess the effectiveness of the program will be the number of weeks from treatment initiation to maternal metabolic control, offspring birth head circumference, and offspring development (DQ) at one year. Secondary analyses will be performed to assess the cost of the intervention and the ways in which the Resource Mothers program affects the course of treatment. Information about pregnancy blood phenylalanine levels, weight gain, and dietary intake will be obtained. Questionnaires measuring social support and other psychosocial factors will be administered soon after enrollment and at the 7th month of pregnancy. After the baby is born, information on birth head circumference, weight, and length will be retrieved from medical records. At one year of age, the baby will receive developmental testing and the mother will be interviewed about her baby's health history.

**Population and Sampling Plan**

The sample of 80 completed pregnancies will be obtained from all maternal PKU pregnancies treated in the selected metabolic clinics: Children's Hospital, Boston, MA; St. Christopher's Hospital, Philadelphia, PA; Children's Memorial Hospital, Chicago, IL; University of Illinois Medical Center, Chicago, IL; Emory University School of Medicine, Atlanta, GA; Johns Hopkins Hospital, Baltimore, MD; Waisman Center, Madison, WI; Children's Hospital of Los Angeles, CA. All women with PKU at the selected study sites who are planning a pregnancy or who are pregnant will be recruited for the study. Informed consent will be requested during a clinic visit from those who require treatment, are less than 20 weeks pregnant and plan to continue their pregnancies. PKU is rare among Ashkenazi Jewish, Asian and Black populations. Based on data from previous studies, it is expected that 1% will be Black, 1% Native American, and 10% Hispanic. The study will include pregnant women and male and female offspring. The study does not address issues of gender, race or ethnic health. Secondary descriptive analyses may be possible to address issues related to ethnic background in terms of acceptability of the Resource Mothers Program.

**Analysis Plan**

Data analysis will proceed according to our primary model, which postulates that the independent variable (Resource Mother support) affects maternal metabolic control, the home environment and offspring outcome by way of altering the mediating factor of adherence to treatment protocol. The first step will be to test for potential biases between the randomly selected study groups in terms of the "intervening variables". Due to the random selection process, it is hoped that the groups will be comparable. If not, separate analyses may have to be performed for the subgroups. Although we expect the Resource Mothers treatment group to attain metabolic control sooner and hence have better outcomes, we will conservatively use two-tailed tests and confidence intervals in order to be able to comment on results that may occur in the opposite direction to our hypotheses. Analyses to test the specific hypotheses are as follows:

- **Hypothesis 1:** The Resource Mothers treatment group will attain metabolic control sooner. The nonparametric Wilcoxon Mann Whitney test will be performed on the number of weeks from treatment initiation to metabolic control, since all women who achieve metabolic control prior to pregnancy receive a score of 0 weeks.
- **Hypothesis 2:** The Resource Mothers treatment group will have babies with better outcome at birth. A T-test based on z-scores of birth head circumference, birth weight and birth length will be used. The relative occurrence of congenital heart disease and other anomalies will be analyzed by the Fisher's Exact Test.
- **Hypothesis 3:** The Resource Mothers treatment group will have babies with better outcome at one year of age. A T-test will be used to compare the DQ, motor development, and language quotients of offspring in each group.
- **Hypotheses 4, 5, 6, 7:** The Resource Mothers treatment group will have greater adherence to the Maternal PKU Treatment...
Plan, a higher percentage of recommended weight gain, a higher percentage of recommended nutrient intakes and provide a more stimulating environment for their child at one year. These hypotheses will be tested using the Wilcoxon Mann Whitney test. We selected this statistical test over parametric tests because of concerns about distribution, especially in the measurement of the home environment. Our experience has been that a bimodal distribution often occurs. For similar reasons, nonparametric correlations will be used to determine if percent of recommended nutrition intake is related to birth outcome and development at one year.

Pre-Award Evaluation

Evaluator 1

Originality and Importance
This is an important project that has national significance. The number of infants born to women with PKU will only continue to increase as newborn screening remains in place.

Regional and National Significance
See above statement.

Scientific and Technical Merit
Strengths of the proposal continue to be qualifications of the investigators and their experience in working with mothers with PKU. Regional centers, such as those involving the six centers in the study, generally have very good follow-up of PKU patients, and in particular mothers with PKU.

The investigators have been very responsive to the criticisms raised in the previous review. Of primary concern was the number of patients who were expected to be available. It was felt that recruiting 72 patients was over-optimistic. They have now expanded the number of recruiting centers to six, extended the study to five years and now expect to have 115 pregnancies occur. This now allows 30% attrition, which is increased from their previous estimate of 25%, to reach the 36 subjects needed in each group. Power calculations were also redone using more conservative techniques and were based on two-tailed tests so that results obtained which were not in the expected direction could also be discussed. They also include an additional 10% adjustment to account for the use of the non-parametric Wilcoxon test. There was also concern previously about women entering prenatal care early enough to be included. They have now defined their recruiting gestational age cut-off as less than 20 weeks. They give evidence that the vast majority of their maternal PKU patients present for prenatal care before this time.

It is still likely that most women will present after they become pregnant. This will be taken into account by stratifying the groups prior to randomization on whether they present prior to or after conception.

Another previously raised concern was that some important information would be obtained by report from the PKU mothers, whose mean IQ as a group was given at 85. It was questioned whether the standard measures to be used were valid in women with lower IQ's. Seven of the psychosocial instruments to be administered are said to be valid in this group. The Social Support Questionnaire was "one of the best predictors of adherence to medical recommendations" in a previous maternal PKU study. Knowledge of maternal PKU has been validated on a population of women with a man IQ of 84 and had a validity coefficient of 0.63. The Self Esteem Questionnaire, a "standard measure", had been found to correlate .95 with longer measure of self esteem, but may not have been specifically studied in individuals with lower IQ. Locus of Control, another "standard measure", is stated to have "excellent reported reliability and validity and can be administered to those with a fifth grade reading level". List of Threatening Experiences has been found to be "reliable and valid in extensive piloting", but again the group in which it was tested is not clear. The home organization scale was developed for the resource mothers program and in preliminary studies was found to be associated with economic status but not with IQ. No reliability or validity is given. The attitudes about treatment questionnaire is a revision of one used in evaluative study of the Maternal PKU Camp. It has also not been validated but uses a variable that is highly predictive in the psychosocial study and its results were not related to IQ. Investigators give a detailed plan for training the resource mothers in administration of these questionnaires. They will be trained to assist the women who may not understand the questionnaires or interview questions.
Those interviews previously have shown no differences in scores related to IQ.

Similarly, there was concern about obtaining detailed food intake information from the PKU mothers, particularly attempting to have them record their food intake for three days. This three-day record is a standard part of the Maternal PKU Treatment protocol; however, acknowledging that this may be of questionable validity in the study, for those women who are not able to do this, a nutritionist will do a detailed one-day food intake history. A check-off list will be used for those women who have difficulty maintaining food records. It is felt that this will be helpful as only a limited number of foods are allowed in the PKU diet. However, I am concerned that women will be eating foods that are not allowed on the diet and that these will not be recorded. Amount of formula consumed will be verified by comparing to the amount ordered and/or amount remaining on the woman's shelves.

A previous concern was that some information would be obtained from clinic records which might not be accurate, would not be obtained during metabolic clinic visits at the time of delivery, and would be verified by obstetrical and delivery records. Newborn data collection forms are to be sent to the birth hospitals prior to delivery and a study coordinator will ensure that these forms are filled out when delivery occurs. This system resulted in 100% success in the Maternal PKU Collaborative Study. The local coordinator will be responsible for updating each form after each assessment metabolic clinic visit, obstetric appointment, or provision of services in the community. Head circumference is still included, as it is the measurement most highly correlated with maternal blood phenylalanine levels during pregnancy and is an indicator of brain growth in-utero.

Other issues have also been addressed. There was concern that no women would maintain the target phenylalanine level below 6. This indeed may be the case, but this is the recommended level below which women should maintain their phenylalanine level. If this does not occur, the investigators will also analyze their data using a target level of 10 mg/dl. The use of paper food models has been dropped. Measures of adherence to the treatment plan by the metabolic clinic and obstetrician, including community services used, cost of medical treatment, and time spent by the metabolic center, have all been dropped. There is no plan now to do any sort of economic analysis. However, the cost of the resource mothers program will be calculated and reported, but not analyzed for this study.

More detailed plans are given for data analysis, and more conservative estimates of power have been proposed.

The budget has been completely revised. Emergency supplies of low-protein food will be available for any patients. Those with resource mothers will also use these foods for demonstration of food preparation. This remains a problem unless the availability of low protein food is a part of the standard treatment protocol. If not, it introduces an additional intervention into the model. Costs regarding the principle investigator’s travel to each center one a year to monitor the progress of the study and provide supervision have been dropped, as all of the information is being made available through the Internet. The justification for including a social worker is now given and her time decreased to .15 FTE. This seems reasonable as these resource mothers may need continued support throughout the project. It is stated that she will provide a liaison between the resource mothers and patients with multiple different community agencies as needed. It does seem that the local centers should also have a person who would routinely do this. It appears that her main role should be to support the resource mothers who may be overwhelmed with the social problems of the PKU mother. The time commitment for Diane Sullivan, the trainer, has been reduced, but still seems high. She is budgeted for 40% in the first year, 35% in years 2, 3, and 4, and 25% in year 5. However, most of the training will take place in the first year or two, and why so much time is needed in the remaining years is not clear.

There are no particular human subjects concerns. IRB approval is pending from four sites. The proposal has not been submitted to any other agency for review. The group of investigators is well qualified to carry out this resource. They have extensive experience in the management of individuals with PKU, particularly maternal PKU. Dr. Waisbren is currently funded about 55% time, and there is no overlap with any of her current grants.

Evaluator 2

Originality and Importance
This application is the second revision of an application to conduct a clinical trial examining the efficacy of a resource mother intervention for mothers with PKU. The original application, which proposed a small pilot study, was deferred. The revision submitted in response to this deferral proposed a full clinical trial; that application was disapproved, primarily because of concerns related to sample size. The current application is a revision of that proposed clinical trial, specifically addressing reviewer's concerns about the sample. The reviewers expressed concern that the proposed sample was very small (36 intervention mothers; 36 controls) and stretched the capability of the participating sites to provide subjects. In the revision, the number of participating metabolic centers has been expanded (the Waisman Center and Hopkins have been added) and the study timeline has been extended to include a fifth year. The application states that in 1996, 23 PKU pregnancies occurred in the 6 participating centers. At least 115 pregnancies are expected across the period of the study. The authors anticipate that 80 of these will be completed and 72 of the women will remain in the study.

Many of the PKU mothers would be expected to have IQ's or 85 or less, which led to some concern about their ability to complete study instruments. The authors respond that all study instruments have been used previously with PKU mothers without difficulties relating to lower IQ. The authors argue that no differences in instrument scores have been detected related to maternal IQ. Mean differences in scores do not really indicate that the instruments are equally valid/reliable across groups.

The study hypothesizes that intervention mothers will attain metabolic control sooner and have babies that have better outcomes at birth and at one year of age. Pilot data, based on a doctoral dissertation, support the potential impact of the program. Secondary hypotheses focus on adherence to diet, maternal environment, and the stimulating nature of the home environment, while additional hypotheses focus on psychosocial benefits of the intervention for the mother.

The application now clarifies that key measures on the infants will be obtained by researchers, rather than from medical records. A defense of head circumference as a key outcome measure is presented, based on this measure being reported in the literature as most highly correlated with dietary control.

For the psychosocial measures, the application states that a checklist will be used to determine the percent of data collected for each variable. It is not clear what this means.

The Bayley, REEL, and the HOME will be obtained by contracting with local psychologists in the mother's home community. It seems unlikely that these practicing psychologists will be familiar with the HOME and its administration.

A nutritionist or social worker has been designated as the Study Coordinator at each metabolic center that will be enrolling patients. This person will assume responsibility for coordination, data collection, data entry and adherence to the Study Protocol. This person will participate in an initial training workshop in Boston to learn the study protocol and to learn the role of resource mothers. All nutritional assessments are to be conducted by Registered Dietitians at each clinic site, yet, these individuals do not seem to appear in the budget. It is still not clear that the researchers will be able to maintain consistent quality control of both the intervention and the data collection at the distant sites.

In the previous review, there was some confusion about the role of the project social worker. The revised application describes the social worker's role as: assisting in identifying and procuring local services for the pregnant women with PKU, including making arrangements with the pharmacy to assure that correct formula is ordered and that billing is done properly; getting approvals from insurance/Medicaid/WIC (often involving advocacy and follow-up, assistance with budgeting and obtaining low cost foods); getting prior approvals so women can be seen at metabolic centers; getting referrals for prenatal care; and developing back-up plans in case the women have difficulties attending medical appointments, submitting specimens, etc. It would almost seem that the activities of the social worker constitute an additional study intervention over and above the intervention implemented by the Resource Mothers. Do both intervention and comparison women receive all these services? If they are available primarily to women in the intervention women, they would seriously confound the test of the intervention. Are the services only available for women living in the Boston area, where the social worker is based? Do women in other clinic sites lack these services, thus lessening their intervention experience when compared with the women in Boston? These issues are of concern.

The application also states that without the guidance of the social worker. The Resource Mothers are at-risk for being overwhelmed by the needs of the young women with PKU. Does this mean that Resource Mothers working in isolation, at
sites other than Boston, are at risk of being overwhelmed and quitting their positions? How are these interventionists supported. Long distance phone calls would not seem to meet the intense need for support described in the application. Also, how does this affect the generalizability of the intervention? What support system do clinics have to have in place in order to adopt the Resource Mother intervention. Is it shown to be effective?

The description of human subjects states that mothers younger than 18 will be accepted into the study if their parents agree to the participation. How will the role of the mother’s parents in her dietary intake, adherence, etc. be addressed? It would seem that young women living with their parents would have their diets heavily influenced by the cooking decisions of their parents, primarily their mothers.

The application states that if there are biases between the randomly selected groups, analyses may have to be performed for the subgroups. It is doubtful that sufficient power will exist to conduct subgroup analyses. The plan to switch order of entry in hierarchical regression analyses for independent and adherence variable, for example, is based on the ability of this procedure to rule out other causative factors if the variance contributed by the independent variable disappears when it is entered second. This is not really true. Other factors may still be responsible for the effect. It mainly indicates that the independent and adherence variables are substantially correlated.

The number of participating clinics has increased by 2, and agreements are in place with these clinics.

The research team is well qualified to conduct the proposed research.

The application has received IRB approval from the main study site. Approval is pending in the other sites.

The budget appears appropriate.
Grantee
American Academy of Pediatrics

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Project Number  R40MC00107

Project Period  9/1/1990-8/31/2004

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Summary

Statement of the Problem

Standards for medical care of children are typically based on research in academic settings. Yet, the vast majority of children seen by a physician are seen not in academic settings but in a variety of ambulatory facilities that principally offer primary care. It is not clear what approaches to care and treatment are actually being used in children’s care in most of these settings, nor how effective the approaches are. Where approaches may be less than optimal—either because they are based on the "wrong population" (children seen in academic settings, who may be more ill than those usually seen in primary care practices) or because the best methods of practice are simply unknown—it is important to gather information that primary care physicians can use to improve their treatment of children.

Research Questions or Hypotheses

This project, carried out by the American Academy of Pediatrics (AAP), plans to work toward the identification of more effective approaches to children’s health care in ambulatory settings by meeting four objectives:
1. Gather information about pediatricians’ care and treatment practices in primary care settings;
2. Provide a structure for learning more about the effectiveness of care and treatment practices in primary care settings;
3. Provide feedback to pediatricians, other physicians and primary care practitioners, and public health groups so that they
may act on this information; and
4. Provide experience to a large group of primary care pediatricians concerning how to research these issues.

**Study Design and Methods**

The major activity of this project is to maintain a national network of pediatricians in primary care practice who cooperate in studies of their own choice to enhance the knowledge base addressing important child health issues.

To develop this network, called Pediatric Research in Office Settings (PROS), interested chapters of the AAP joined as chapter-level networks. Each identified a chapter coordinator to be in charge. A steering committee, named by the AAP, oversees this project, and a research management group (RMG), located in the Department of Research at the AAP, provides research expertise.

The PROS program calls for (1) annually developing ideas of topics for study, (2) annually testing a protocol chosen by the network in a pilot study, and (3) carrying out a full study annually on a previously piloted project. The RMG manages the data collection effort and analysis of the data. This project provides for the dissemination of the information developed by the PROS network.

A study on vision screening of preschoolers has been concluded, and a manuscript describing the study results has been published. During the third year of this grant we anticipate that a study on the development of secondary sexual characteristics of young females will be completed, and, pending funding, three other studies will begin: (1) The management of febrile infants less than 2 months of age; (2) management of gastroenteritis in children under 6 years of age; and (3) management of acute asthma in children over 3 years of age. The project has applied for funding for an additional study on the management of psychosocial problems in children ages 4–15 years, to begin at the end of the project period. In order to develop future study topics for PROS, a Delphi study of PROS practitioners is also being conducted to identify critical areas requiring research. Finally, PROS will create an age/gender registry of its patients to better describe its patient population.

In addition to the PROS network, a series of periodic surveys of fellows of the AAP are planned under this grant. These surveys gather information from randomly selected AAP members on a variety of practice-related treatment and management issues. Results of the periodic surveys are disseminated through AAP publications.
Neighborhood and Family Effects on Adolescent Health Behaviors

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Johns Hopkins University School of Hygiene and Public Health

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Project Number  R40MC00111

Project Period  10/1/1998-9/30/2001

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Summary

Statement of the Problem

Although health status measures for infants and young children have shown improvement over the past several years, markers of adolescent health suggest a decline in the well-being of U.S. adolescents. Low-income and minority adolescents, many of whom reside in the Nation's largest central cities, have borne a disproportionate share of these health-related problems.

Recent research suggests that some of the increases in problem health behaviors among urban adolescents can be attributed to the social environments in which they live. Neighborhoods, particularly those that are low income and socially isolated, have been linked to increasing rates of early adolescent pregnancy and criminal and violent behaviors. Yet not all adolescents who are growing up in impoverished neighborhoods become adolescent mothers or delinquents or engage in violent behavior. There is limited information about how neighborhood and family social contexts influence the onset of adolescent health-related behaviors.

This study attempts to fill the gap in research on neighborhood and family effects on adolescent problem behaviors by combining the following elements: (1) A longitudinal study of the onset of adolescent sexual activity and increased...
Research Questions or Hypotheses

The following questions will be addressed by this study:

A. Using national data, we propose to address the following three questions:
1. To what extent are neighborhood conditions directly related to adolescent sexual activity and delinquent behaviors after adjustment for neighborhood selection effects?
2. What are the ways in which neighborhood effects are mediated by family characteristics and parenting practices?
3. What are the ways in which neighborhoods interact with family characteristics and parenting practices to explain the onset of early sexual intercourse and changes in delinquent behaviors?

B. In Baltimore City, we propose to study family characteristics and parenting practices that are associated with adolescent involvement in sexual and delinquent behavior. Specifically, we will carry out the following: (1) An exploration of definitions of neighborhood boundaries by residents (i.e., adolescent and family members) and compare these definitions with the geographic definitions of neighborhoods derived from census data; (2) A description of variations in the social and institutional resources in the neighborhoods that differ in their levels of adolescent births and juvenile arrests; (3) Within each neighborhood, an investigation of the mechanisms that families use to obtain social and institutional resources; (4) Within each neighborhood, an assessment of the extent to which families who have and families who do not have adolescents involved in problem health behaviors differ in their responses to their neighborhoods, their use of social resources, and their parenting practices; and (5) An exploration of the role of cultural practices in forming both parenting practices and adolescent involvement in sexual intercourse and delinquency.

Study Design and Methods

The study uses a longitudinal design drawn from the National Longitudinal Study of Adolescent Health (AddHealth) to investigate neighborhood influences on the sexual activity and delinquent behaviors of 700 U.S. adolescents in the seventh or eighth grade. Outcomes will be the report of having ever engaged in sexual intercourse and scores on a 14-item measure of delinquency and aggression. Predictor variables include structural characteristics of neighborhoods (e.g., neighborhood sociodemographic status, racial and ethnic composition, residential stability, family structure), perceptions of neighborhoods, neighborhood social resources, family sociodemographic characteristics, family involvement in organizations, parenting practices, and adolescent involvement with deviant peers.

Using adolescent birthrates and juvenile arrest rates for Baltimore City, we will identify three categories of neighborhoods—those census tracts having high, medium, and low rates as defined as being one standard deviation about or below the mean rate for Baltimore. We will select three relatively contiguous neighborhoods that represent high, medium, and low rates of adolescent problem behavior. We plan to survey 300 adolescent-parent pairs, 100 pairs from each of the 3 neighborhoods, using a face-to-face interview and a self-administered questionnaire for items on sexual activity and delinquent behaviors. In addition to the measures listed above, we will ask questions about racial/ethnic identity and the racial/ethnic socialization practices of parents.

Population and Sampling Plan

Subjects for the longitudinal analyses of AddHealth data will be eligible for study inclusion if they are currently enrolled in the seventh or eighth grade in an urban-public or general-curriculums magnet school within close proximity to their residence; if they have completed two in-home interviews, a parental interview, and an in-school screening survey; and if they have school-level data provided by the school administrator.

Subjects for the Baltimore City study will be obtained through the rosters of students from the seventh or eighth grade from the Baltimore City–zone schools for the neighborhoods. Subjects will be eligible for study inclusion if they live in one of the study neighborhoods, are in the seventh or eighth grade, and have parental permission. An oversampling of 30 percent will be necessary to achieve the desired sample size of 300 adolescent-parent pairs.
**Analysis Plan**

Similar preliminary analyses will be conducted on both the AddHealth and the Baltimore City data. For both data sets, distributional properties of variables will be examined to make cut-point or transformation decisions, to assess the psychometric properties of study-constructed and existing scales, and to reduce the number of independent and intervening variables for the multivariate analyses.

To examine the first research question, a series of hierarchical, multivariate logistic regression analyses will be conducted to assess neighborhood and family influences on the likelihood of an adolescent having had sexual intercourse. We will repeat the analyses for delinquency and aggression using multiple linear regression models.

In order to assess the indirect neighborhood effects, we will regress the likelihood of an adolescent having had sexual intercourse on a restricted set of neighborhood characteristics, on family-level and adolescent-level characteristics, and on measures of family parenting and organizational involvement. In subsequent equations, we will regress parenting practices and organizational involvement on neighborhood-level, family-level, and individual-level characteristics. The indirect or mediated effects of neighborhoods on adolescent sexual behavior can be estimated from the product of the effects of neighborhood characteristics on measures of parenting and family organizational involvement. Analyses will be repeated for delinquency/aggression outcome.

To assess the extent to which neighborhood characteristics interact with family-level and individual-level factors to produce variations in sexual activity and delinquency outcomes, we will use multivariate regressions that include interaction terms reflecting the product of differing levels of neighborhood characteristics and levels of family processes.

For the Baltimore City data, we will assess the influence of family processes on adolescent sexual activity using an ordinal logistic regression model with an outcome of never having had sex, having had sex with one or two partners, and having had sex with three or more partners. In a second set of analyses, we will treat delinquency and aggressive behavior as a continuous variable and regress this outcome on the set of family-level, parenting, and neighborhood perceptions.

**Pre-Award Evaluation**

**Evaluator 1**

**Originality and Importance**

How the context in which one develops relates to behavioral outcomes has been a major concern of psychologists for many years. The decline of our inner cities and the preponderance of health risk behaviors observed in such environments has revitalized the urgency with which such a question needs to be addressed.

**Regional and National Significance**

If the study is successful at identifying those family characteristics most likely to serve as protective mechanisms against increasingly risky environments then preventive measures for those most at risk would more probably be forthcoming.

**Scientific and Technical Merit**

The major strength of the proposal is its use of both a national data set and local data set to assess the types of neighborhood characteristics related to the onset of problem health behaviors. The two data sets are complimentary in that the national data allows for conclusions about very diverse populations, while the local data sets helps us to understand problems effecting specific types of neighborhoods. In addition, the interview process to be used with the local data set will allow for more in-depth probes, which are lost within the national data set.

Another strength is that the study proposes to go beyond the basic neighborhood description (education, employment, etc.) by taking a closer look at what types of resources are actually available in these high risk areas and to also assess how availability and use of these resources relate to adolescent outcomes. In addition, the proposed project's intent to look more closely at the reasons why individuals reside in a given neighborhood will help to further define the process by which neighborhoods come to take on certain characteristics and patterns of interactions.
Finally, looking at the interaction between parenting practices and neighborhood characteristics will help us to understand the adaptive nature of how people rear children. There is much criticism of parenting styles characterized by "excessive control." However, if loose control of your child puts her/him at risk for early sexual activity, drug abuse and violent behavior, then control seems a good way to go.

One problem seen with the proposal is the dependent variable of sexual activity defined as # of partners. Why not a ratio of partners to times multiplied by number of partners (# of partners/# of times* # of partners) such that the researchers can account for both in one variable. The child who is having a lot of sex with a lot of partners should produce a much higher ratio than one who has a lot of sex with just one partner who would also look different than one who is having a little sex but with many partners.

The personnel and budget are well suited to conduct the study, and there are no human subjects concerns.

Evaluator 2

Originality and Importance
No statement of originality and importance.

Regional and National Significance
No statement of regional and national significance.

Scientific and Technical Merit
Using the ADDHealth data to set a national context is a great idea and should be used more often in the field of emergent adolescent behavior.

Using both ADDHealth and local definitions of neighborhood provides an excellent opportunity to evaluate the effects of methodological differences in operationalizing the concept of neighborhood.

The tests proposed for evaluating the kinds of roles (direct, mediating, and moderating) that neighborhood context plays in the development of emergent adolescent sexual activity is a welcome addition.

One issue that has not been addressed is the issue of retrospective reports of parental involvement being assessed over the last 4 weeks prior to the assessment period. This appears to be too time-limited; perhaps supplementing this with a longer retrospective period obtaining the adolescents judgment would give the principle investigator multiple methods for assessing this very important construct.

The other issue is the form of the data analysis. The principle investigator suggests that power is dependent on the extent of the intra-neighborhood correlation, which is accurate. Yet the statistical models as reported do not seem to take into account this hierarchical structure that exists, which would lead to inaccurate estimates of standard errors. The principle investigator should be clear that because of the structure of the data, methods for handling non-independent error structures must be used.
Post-Traumatic Stress Disorder After Pediatric Traffic-Related Injury

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Project Number R40MC00138


Costs

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Summary

Statement of the Problem

Traffic-related injury is the leading cause of death and acquired disability in children in the United States. Psychosocial consequences of these injuries for the child and his/her family are common but may receive insufficient attention. Descriptive studies suggest that children and their parents may suffer post-traumatic stress symptoms after injuries, but prevalence and risk factors are not well understood. Because Post-traumatic Stress Disorder (PTSD) cannot be diagnosed until long after most injured children have completed acute medical care, early screening for PTSD risk would be a useful tool to guide secondary prevention.

Research Questions or Hypotheses

The central hypotheses of the proposed project are: 1) that the prevalence of psychological distress in children (including PTSD) after crashes is significant and warrants clinical attention; and 2) that those at risk for developing PTSD can be
identified during the acute phase of care. In order to test these hypotheses, this research addresses the following specific aims:

- Determine the prevalence of PTSD in children which develops within 4 months after pediatric traffic-related injuries;
- Determine the contribution of several specific risk factors (including parent PTSD) to the development of child PTSD within 4 months after traffic-related injuries; and
- Develop and validate a PTSD risk assessment screening tool for use in the acute care setting.

**Study Design and Methods**

A prospective cohort of 360 children admitted to a Level 1 pediatric trauma center for treatment of traffic-related injury is currently being enrolled. After obtaining parent and child consent, children and their parents are interviewed in the hospital or in their home within 4 weeks post-injury, and again in 4 months. Children (and parents who directly witnessed the crash) are asked to describe the injury circumstances. In the initial assessment, parents report on the child’s pre-existing behavioral and emotional functioning (CBCL), previous exposure to traumatic events (TESI-P), prior family life event stressors (LES), as well as their child’s Acute Stress Disorder (ASD) symptoms (CSRC) and their own ASD symptoms (SASRQ) and social support (DSSS). Children report on their previous exposure to traumatic events (TESI-C), their ASD symptoms (CASQ), and their pre-existing anxiety or depression symptoms (MASC-10 and CDI-S). In the follow-up assessment, parents report on their own and their child’s PTSD symptoms (PCL and PCL-C/PR), and other aspects of their child’s emotional/behavioral functioning (DICA-R-P). Parents also report on their child’s physical health status (CHQ), the impact on the family from the child’s injury (IFS), any new interim traumatic events for their child, and their own social support and coping (DSSS and CHIP). Children report on their own PTSD symptoms (CAPS-CA), anxiety and depression symptoms (MASC-10 and CDI-S), as well as coping methods (KidCope) and social support (SSSCA). At each assessment point, parents and children also rate the child’s experience of physical pain associated with the injury.

**Population and Sampling Plan**

All children (between age 5 and 17) admitted to The Children’s Hospital of Philadelphia (a Level 1 Pediatric Trauma Center) for treatment of traffic-related injuries (injured as a pedestrian, bicyclist, or motor vehicle passenger) will be invited to participate in the proposed study during their acute hospitalization. Children or parents who cannot complete a verbal interview because of limited spoken English proficiency or severe cognitive impairment will be excluded from the study. Families will not be contacted if a child has died. The population of children admitted to the Hospital for traffic injuries is approximately two-thirds male, and is approximately 50% African-American, 40% White, 2% Hispanic, and 8% Other.

**Analysis Plan**

The analyses involve determining prevalence of PTSD, development of a PTSD risk assessment screening tool, and the analysis of a proposed theoretical model for the development of traffic injury-related PTSD in children. The main outcome for all analyses is PTSD in children measured as both the presence/absence of diagnosis and a continuous score of symptom severity. Secondarily, we will explore parental PTSD in response to pediatric traffic injury.

**Pre-Award Evaluation**

**Evaluator 1**

**Originality and Importance**

No statement of originality and importance.

**Regional and National Significance**

No statement of regional and national significance.

**Scientific and Technical Merit**

The theoretical model seemed to indicate that PTSD might happen without ASD, thus limiting the predictive value of the
tool. However, the literature review includes a section on PTSD in children and adolescents and the developmental implications of trauma in children. The investigators note that such occurrences are rare and that ASD is a primary predictor of PTSD.

The investigators have developed a working assessment tool. The tool will be tested on the first 100 subjects enrolled and, informed by analysis of that data, the tool will be revised and re-tested on the final 160 subjects. The description of the analyses related to this process are specific.

The plans for training interviewers is described. Using both didactic and practical components, the interviewers will be jointly trained by the research team and the Response Analysis Coordination Unit. Topics to be covered will include pediatric injury, ASD and PTSD, and approaching the family. The training will also include demonstrations of interviewing by the staff and role playing practice for the interviewers. Initial interviews with study subjects will also be observed. The quality of the interviews will be reassessed over the course of the study. One of the investigators will monitor interviews and re-interview a small number of families.

The timing of the interview will be aimed to be between 2-4 days to allow for a consistent relation to the traumatic event. Variations in timing will be analyzed.

The variables to be examined as potential risk factors for and predictors of PTSD include a range of factors related to acute treatment (such as length of stay) and post-discharge treatment (such as psychological counseling). In addition, the investigators have added measures of family stress both preceding and following the injury. Coping resources for parents will be evaluated. Finally, children will be asked about their attempts to cope with the challenges of this traumatic experience.

One issue is raised in the prediction tool assessment. The investigators note that they will consider promising a PPV and NPV of >70%. As the PPV and NPV are dependent on the prevalence of the outcome, these will differ from population to population. Concentrating the evaluation of the tool on sensitivity and specificity will provide better information for generalizing results to different settings.

No other financing is being sought.

This is a highly qualified team.

The budget generally seems reasonable. It is not clear why Dr. Kassam-Adams is at 40% for all 3 years since her responsibilities relate to overseeing training of interviewers and selection of instruments to measure PTSD.

Resources and facilities are adequate.

There are no concerns with Human Subjects. The investigators have carefully considered these issues.

Evaluator 2

Originality and Importance
The current effort builds upon some of the findings that this project team has noted in their Injury Circumstances Evaluation (ICE) study, which has resulted in the creation of a pediatric injury circumstances scoring system for use in triage, care, and research for pediatric traffic-related injuries. An extension of the ICE study to estimate rates of PTSD in children and parents illustrates their ability to discuss stressful topics with parents of injured children. Moreover, the preliminary results of the aforementioned investigation support the hypothesis of the proposed study.

Regional and National Significance
Traffic related injuries among children frequently results in subsequent psychological issues. Early identification and early
intervention efforts may bring about cost-saving perspectives in the future.

**Scientific and Technical Merit**

The proposal is well written and clearly builds upon the collective and individual expertise of co-investigators. While the ICE study enrolled 710 children, telephone interviews with 103 parents were conducted 7 to 12 months after their child's injury to obtain parent-report measures of PTSD in children and a related self-report measure of the parent's own PTSD symptoms. Of the 103 participants, 29% of the children met full diagnostic criteria for PTSD based on their parents' responses. Another 29% of the children were evaluated as having partial PTSD. Thus a total of 58% of the children experienced at least partial PTSD. Of the 102 parents who responded, 20% met full diagnostic criteria for PTSD, while another 29% reported symptoms corresponding to partial PTSD. Perhaps not surprising was that parent and child PTSD severity scores were highly correlated.

According to the investigators, the proposed study requires a survey contractor to conduct acute and follow-up interviews with families of children who are injured in traffic-related incidents. The purpose of the survey is to collect data that will help researchers at Children's Hospital of Philadelphia (CHOP) identify children most at risk for developing PTSD in the period following an injury. Response Analysis Corporation has been recommended for the subcontract. This corporation has an extensive record of collaborative working relationships with state and federal agencies, conducting the type of work that is outlined in the current proposal.

But, herein lies one of the more puzzling dimensions of the proposed investigation. Based on their pilot work, the investigators state: "As with other studies of pediatric trauma conducted by the Research Team, most parents were eager to talk. A number of parents recounted their stressful experiences and stated that parents of children sustaining traffic-injuries needed more resources than are currently available. " Why then is it imperative that a contractor be charged with conducting the acute setting and follow-up investigations?

The Child Behavior Checklist will be administered during interviews conducted in the acute setting and follow-up to establish a base line for behavioral and social-emotional functioning prior to injury. No psychometric properties are presented for this instrument. However, some of the questions on this instrument are deemed to be inappropriate for some of the older subjects that will participate in this investigation (e.g., bowel movements outside toilet). These data will be collected only from parents or guardians, yet many of the questions clearly focus on socialization outside the home environment.

The Family Inventory of Life Events and Changes (FILE) is a checklist of stressors and strains that may occur in the life of a family. Because stress has been defined as a contextual variable, it will only be considered as a pre-injury variable. It is not clear why this tool will not be repeated over time given that contextual dimensions of stress may contribute to a parent's ability to cope with the current situations.

It should be noted, however, that family stress and coping, as a post-hospitalization variable, is operationalized as the impact of the child's injury and course of recovery on the family. The Impact on Family Scale (IFS) will be used to assess several facets of parents' experience in the post-injury period. In addition to the IFS, parents' will be asked to respond to the Coping Health Inventory for Parents (CHIP), which yields a measure of coping strategies for parents of medically ill children. Children will be asked, using an open-ended question, about their attempts to cope with the challenges of this traumatic experience.

The remaining variables and tools that will be used to measure these variables appear to be in order.

A very impressive team of collaborators has been assembled for the proposed project. Evidence is provided demonstrating their past relationships on numerous projects. More importantly, this multidisciplinary team also reflects individual accomplishments.

All of the investigators have noted that they would "re-evaluate the effort needed to perform each project to ensure commitment is not more than 100%." However, one cannot assume that the reduction in their efforts will not come from the proposed project, which reflects an ambitious undertaking and commitment of time from several of the co-investigators.
Among the tasks assumed by the subcontractor is instrument finalization and pre-testing. According to the investigators, personnel at Response Analysis Corporation will: "(1) address issues related to the overall structure and format of the parent checklists, and (2) the overall structure and flow of the parent and child interviews." Herein lies one of the concerns that I have with this procedure. It appears from this brief it is possible that RAC will, in collaboration with CHOP research team, alter some of the questions on standardized scales without considering possible violations to the validity of these scales. Perhaps such an assumption is erroneous, but nonetheless, it appears that RAC will assume the responsibility for recommending the elimination or reordering of questions based on their perceptions of question flow.

This preliminary stage of work also includes the development of a contact information form (which will seek to obtain information of extended family who, with their permission, may be contacted to follow-up with hard-to-find families, and an advance letter to be used for contacting respondents prior to the four-month-follow-up interview. It is unclear why the latter is being subcontracted when essentially, this might be a task that the principle investigator can assume with relatively little or no additional cost.

A pretest will be conducted by Response Analysis to pilot the testing procedure, and to evaluate the format and overall structure of each survey instrument. Children in three different age groups (5-8, 9-12, and 13-18) will be recruited with the assistance of CHOP to participate in the pilot. The acute pretest interviews will be conducted in the hospital and follow-up interviews at 4 months will also be conducted at the respondents’ homes. The number of children and families participating in this pilot, however, remains unclear. Moreover, it is not clear how these protocols will be evaluated.

Quality control insurances related to the data that will be collected have been implemented throughout the study. These control mechanisms appear to be adequate for checklists and other quantitative data that will be collected. However, other than the initial two interviews that are directly observed and monitored by the research staff, it does not appear that any other precautions of data collection will be introduced. Given that Response Analysis will be employed and entails the collection of over 300 interviews, only the initial interviews will be part of a systematic review to insure that the protocol operates in the planned manner.
Predicting African American Children’s School Compliance

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University of North Carolina at Chapel Hill

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Project Number R40MC00145

Project Period 3/1/1999-7/31/2003

Indirect Costs
Awarded
86,744
76,668
72,250
7532

Statement of the Problem

African American children are much more likely to be poor than are white children (40% versus 16%), are more likely to experience gaps in achievement in school, and are over-represented among students enrolled in special education classes compared to other students. Determining whether risk and buffering/protective factors during early childhood affect African American children’s school functioning, and which different factors become important as children enter middle childhood, is critical for understanding children’s functioning in the later elementary school grades and is only possible with longitudinal study designs. Further, the lack of literature on African American children’s development leads to the dire need for research that will increase our understanding of the factors that promote and inhibit the development of African American children. Consistent with an ecological model of development, we are studying the child, family, school, and neighborhood factors that influence children’s competence in school in the later elementary school years. We are studying the role of peer adjustment (e.g., friendships, acceptance) and children’s coping skills in school success, and how constructs relevant to populations of color, and specifically to African American children, (e.g., ethnic identity and socialization, children’s use of African American Vernacular English) affect children's school competence, and how environments (home, school, and neighborhood) inhibit or promote these constructs. This project builds on earlier work which examined children’s health,
development, family environment, and child care experiences during infancy and the preschool years and the roles of early
and concurrent measures of the child, family, and school on children’s development during the first three years of elementary
school.

Research Questions or Hypotheses

This project examines the role of child, family, school, and neighborhood factors in predicting African American children’s
school competence during the later elementary school years. The aims of the study are to: 1) describe the developmental
trajectories of African American children’s language skills, social skills, and school competence from infancy through middle
childhood; 2) determine the multiple predictors of school competence including academic achievement and school
adjustment of African American children in middle childhood within an ecological model of child development; and 3)
identify the extent to which children’s social knowledge and behavior, language, peer adjustment, and the match between
Afrocultural beliefs and practices at home and school mediate the relationships between child, family, school, and
neighborhood background factors and school competence.

Study Design and Methods

Measures of child, family, school, and community are being examined for 75 African American children when children are in
third, fourth, and fifth grades. Child measures are assessing children’s language (e.g., African American Vernacular
English), coping skills (e.g., race specific coping strategies), Afrocultural beliefs and practices (e.g., movement expression),
social behavior (e.g., cooperation), peer adjustment (e.g., friendship), and school competence (e.g., achievement in reading).
Family measures examine family characteristics (e.g., maternal education), Afrocultural beliefs and practices (e.g.,
communalism), and parenting beliefs (e.g., parental perceptions of discrimination). School measures assess factors such as
classroom quality, Afrocultural beliefs and practices, teachers’ perceptions of relationships with students, and classroom
demographics. Neighborhood measures include factors such as parents’ perceptions of the neighborhood and demographic
characteristics of the neighborhood.

Population and Sampling Plan

Seventy-five African American children and their families who have been followed since early infancy are included in the
study. Children in the study were recruited from 9 center-based child care programs before the age of 1 year. All were
apparently normally developing when entering the study. The sample consists of 41 girls and 34 boys. At entry to
kindergarten, 60.3% of children lived below the federal poverty level (185% of poverty), 40% of caregivers were unmarried,
and 17.8% had less than a high school education.

Analysis Plan

Two types of longitudinal analyses will be used. First, using hierarchial linear models, we will examine the longitudinal
patterns of change in the child’s academic competence and social adjustment and relate those patterns to the types and
changes in social risk factors, parenting beliefs, and neighborhood characteristics. These analyses involve testing whether
characteristics, such as the child’s language skills, social skills school adjustment, coping strategies, racial identity, and peer
adjustment, serve to mediate associations between child outcomes and social risk and protective factors. Second, we will
identify various developmental pathways or prototypic patterns of development and determine which child, family, and
neighborhood characteristics distinguish children displaying different patterns of growth. Emphasis will be placed on
identifying factors that mediate or moderate observed relations between child, family, school, and neighborhood factors and
child competence in school. Study findings should have important implications for the sociocultural factors that affect the
school success of African American children.
Pregnancy Weight Gain-Birthweight Relationship by Race

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**Project Number** R40MC00204

**Project Period** 9/1/2000-8/31/2002

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**Year 2010 Objectives**
16.6, 16.12

**Study Design**
Observational

**Time Design**
Longitudinal

**Care Emphasis**
Noninterventional

**Population Focus**
Neonates, Pregnant women (not otherwise identified as adolescents)

**Race/Ethnic Focus**
Hispanic (Hispanic overall), African American, White (non-Hispanic)

**Priority Research Issues**

**Summary**

*Statement of the Problem*

The research problem addressed relates to the lack of knowledge about the relationship between rate of pregnancy weight gain and newborn weight. Less than optimal rates of weight gain during pregnancy may be related to decreased fetal growth and increased short- and long-term health problems in offspring. Excessive rate of weight gain during pregnancy may benefit fetal growth little while increase maternal risk of subsequent obesity. This project intends to identify rates of weight gain during pregnancy associated with term, newborn weights that represent a low risk of short- and long-term health problems.

A primary objective of this project is to produce information related to weight gain-birthweight relationships that can be used to guide women’s weight gain during pregnancy. Specifically, rates of weight gain associated with healthy birthweights in term infants will be identified for Hispanic, African American, and Caucasian women. Because prepregnancy weight status effects weight gain-birthweight relationships, women will be subdivided by pregnancy weight status.

**Research Questions or Hypotheses**
This project seeks to answer the following question: What is the relationship between rate of weight gain during pregnancy and birthweight in Hispanic, African American, and Caucasian women?

**Study Design and Methods**

Data on singleton pregnancies resulting in liveborn, term infants gathered from medical and public health records from California, Minnesota, Alabama, New York City, and North Carolina are being used for this project. These datasets were selected primarily due sample size, quality control measures used in data measurements and recording, and population characteristics. Records from these locations were eligible for the study given they provided data on: prepregnancy weight and height, ethnicity or race, maternal age, parity, WIC/MA participation, (Special Supplemental Food Program for Women, Infants, and Children/Medical Assistance) weight during each trimester of pregnancy, the presence of smoking, diabetes, and hypertension during pregnancy; and infant birthweight and gestational age. Sites cooperating in the study provided data tapes that were evaluated for quality in a variety of ways (eg. reasonableness of values, more than one pregnancy per women, completeness of data on each pregnancy). Cases with incomplete data were omitted from the study.

**Population Description and Sampling Plan**

Data were obtained from existing databases. Original datasets provided data on approximately 20,274 pregnant women and newborns. Sample size was reduced to 11,856 after deleting cases with incomplete data, unrealistic data, and cases representing ethnic groups other than Hispanic, African Americans, and Caucasians. Of the 11,856 cases, 4,614 represent Hispanic Americans, 6,904 African Americans, and 3,338 Caucasian Americans. The average age of women in the sample is 25 (range 13-45) years; 3.2% experienced diabetes and 4.6% hypertension, and 19% of women reported smoking during pregnancy. Newborn gestational age averages 39.6 weeks, and birthweight 3344 grams in the sample. Subpopulations of Asians, Native Americans, and other ethnic groups are excluded from the study due to low sample sizes.

**Analysis Plan**

Dataset development began with verification of data (outlier and distribution checks, coding problems, unrealistic data) and description of the overall sample. Data for each ethnic group from the various sources were then merged. Samples of ethnic groups that did not meet the sample size requirement of at least 173 cases of underweight women, 317 normal weight women, 415 overweight women, and 835 obese women were omitted from the master dataset. Only Hispanic, African American, and Caucasian women were represented in adequate numbers in the prepregnancy weight status groups. The statistical approach to identifying rate of weight gain-birthweight relationships is proceeding in the following way: for each of the three ethnic groups and for women within each prepregnancy weight status category, regressions models are being developed to identify the effect of weight gain by time in pregnancy on birthweight. PROX MIXED statistics are being used to explore various models and covariance structures. Various model diagnostic methods are being used to check the adequacy of the models. Once the coefficient estimates are determined, means values of weight change with respect to different time points during pregnancy will be identified. The effect of gestational age, maternal age and parity; and other potential confounders on weight gain-birthweight relationships will be controlled for in these analyses. Given a specific time point, mean values for predicted weight change related to the delivery of infants within various categories of birthweight would be generated. If predicted values do not differ by ethnic group, then one, overall set of rate of weight gain-birthweight relationship graphs will be generated. Separate graphs will be generated if the relationship varies by ethnic group.

Analyses will then proceed to the evaluation of potential confounders to rate of weight gain-birthweight relationships by determining whether the variables significantly influence the relationships. Potential confounders will include smoking, diabetes, hypertension, source of data, and WIC/MA participation.

**Pre-Award Evaluation**

**Evaluator 1**

*Regional and National Significance*

The proposal remains consonant with MCHB research priorities.
Scientific and Technical Merit

The strengths of the study are in two major areas: 1) the sample data sets spanning over several sites in order to analyze weight gain and allied precursor risk factors, and 2) the acquisition of fundamental knowledge relevant to various ethnic and racial subgroups and to add neonatal birth weight categories.

The study is exploratory in design with intent to produce further research questions. The sample accommodates this. The study spans two years with adequate staff, sites and budget to accomplish goals.

The study is restricted to exploratory analysis of potential pre-pregnancy weight gain relationships, and that it is premature to propose weight gain graphs for use by practitioners.

As an exploratory study there are no hypotheses proposed. The convenience samples serve their purpose of adding the requisite subpopulations although the proposal states that certain subsample groups subdivided by mother's weights, race, and outcomes may be unacceptably small. That latter caveat notwithstanding the analysis will proceed in two general stages: (1) development of the BMI and race-specific weight gain curves using several alternative formulations of weight gain and birth weight, and (2) evaluation of effects of potential confounders within each BMI and race group using polynomial regressions. This is a specific set of regressions exploring various models, covariance and autoregressive structures. This rather general set of various techniques will be used to evaluate models as well as potential confounders.

This aspect of the data analyses and multiple model building cannot be further described as it is more of a data dredging. An effect average or mean values will be employed, this should undoubtedly smooth the data. The example given in the proposal for a cubic regression fit illustrates the time dependent shape using the factors identified and the potential confounding variables.

There will be extensive development of empirical models based on the general exploratory regression analyses. Several aspects of the regression are alluded to both group regression and subgroup regression. These may have no comparability and may well produce inconsistent results. Furthermore, interindividual differences within group will be predictably great but averaging will smooth these differences and hence possibly different patterns of individual dynamics. This in turn would remove the study farther away from understanding individual patterns.

Although possible site differences do exist and will be examined there is limited ability to control for confounding variables. It is not possible to appraise the effect of the reliance on self reporting variables such as: determining length of gestations, self reporting, etc..

Significant questions arise about the homogeneity and consistency of the enlarged data sets. It is difficult to access the comparability and uniformity of data sets from disparate sites. In part, the PI recognizes this fact, for example reliance on self reported recall pregnancy weights, race, and height are noted as often unreliable. Several remedies are proposed. There will be quality control and training procedures in place for data abstracted in collaborating sites. A site variable will be included in the analysis, though it is problematic that this would detect individual errors, rather they would reflect in some added imprecision in the analytic results.

In general, for this large descriptive study, grouping will undoubtedly produce patterns, but identification of intervention factors and individual pattern would remain problematic. The study presupposes that more research will be needed and would follow from research questions to be developed from the study results.

Evaluator 2

Originality and Importance

Information generated by this study may be used in the future for development of recommended rates of pregnancy weight gain by BMI, race and Birth weight groups. It may also provide information needed for planning and implementing randomized, controlled trials related to weight gain - birth weight outcomes in various race groups.
Scientific and Technical Merit

While it is acknowledged that the applicants have contributed extensively to the literature on maternal weight gain, the literature review is limited and may impact on study design. For example, Dr. Carol Hickey, a consultant on this study, concludes in a 1997 paper in Obstetrics and Gynecology (vol 90; No 4 p489) titled, "Prenatal Weight Gain Within Upper and Lower Recommended Ranges: Effects on Birth Weight of Black and White Infants" that these preliminary observations do not provide support for the presence of ethnic group-specific recommendations within guidelines for prenatal weight gain. There would be some value in a robust discussion regarding the above conclusion and the current attention to race, weight gain and birth weight.

Moreover, in an earlier paper by Hickey et al, published in Obstetrics and Gynecology (Vol 86 No 2. Aug 1995) titled "Relationship of Psychosocial Status to Low Prenatal Weight Gain Among Non Obese Black and White Women Delivering at Term" they conclude, "an important role for psychosocial factors in the etiology of low prenatal weight gain among white women but show no such role for black women. Along with reports of wide inter-individual variability in energy costs of pregnancy, the data also suggest that attempts to manipulate pregnancy weight gain through dietary means will meet with variable success until psychosocial and other factors affecting prenatal energy intake and/or utilization are further delineated." A discussion of the multiple factors influencing weight gain and outcome and its impact on weight graph interpolation would be illuminating.

By examining only term births and estimating weight gain the investigators are drawing inferences from a truncated population. Do maternal weight gain patterns differ for preterm birth? Can the pattern of weight gain be similar for both groups differing only in gestational date of birth? If this were the case, could one support the clinical interpretation that a given recommended weight gain is associated with a term birth and birth weight category? Is there a need to examine all birth and birth weights before considering the relationship and formulating recommendations?

It is not clear why weight gain has been trifurcated into <3000g, 3000g - 4000g and >4000g. While the previous review criticized the definition of optimal birth weight through >4500g it is not clear why pre-determined birth weight categories need be established before the fact. Moreover, gestation age, week, month or trimester specific weight gains may be as important as pre-pregnancy weight status, total weight gain and categorical birth weight.

Attention to gestational age and weight gain and gestational age specific weight gain might provide a more comprehensive understanding of preferred weight pattern at different points along the fetal viable pregnancy spectrum. Accordingly, there may be specific racial weight difference by gestational age that may reflect differential fetal growth patterns.

It is not clear how smoking, alcohol and other behavioral factors will be defined, quantified, reconciled and analyzed among population groups.

Weight gain birth weight relationships are central to the study. Yet, prenatal weight gain in overweight African-American women may increase to the point where the proportion of low birth weight infants declines but the risk of maternal and postpartum obesity increases (Caulfield et al. AJPH. 1998). How will this trade off be examined and what are the clinical implications for inferences and recommendations?.

While the investigators note a major strength of the design is "that it includes a large number of women ... from which standard weight gain - birth weight relationships can be described". Yet, the data sets vary considerably in origin and representativeness. Medical Center data collected in an Obstetric unit may vary considerably from WIC clinic data that may be collected by WIC certifiers under hectic conditions. Moreover, WIC certifications take place every six months. Since a more frequent number of visits is needed to qualify for inclusion into the study will there be differential factors that would have women return more often to a WIC clinic? If they are drawn from an obstetric clinic; will WIC have updated records available, given the infrequent contacts? Of interest is the fact that approximately 20% of the 4,600 WIC women, as outlined in the Summary of Characteristics of Data Sets included in the appendix are underweight compared to 10% in the Hickey/Cliver Alabama data on 11,000 women and 13% of all women to be included in the analysis. Can poverty specific considerations be as important as race/ethnic specific factors?

The WIC maternal weights may come from health records that must be linked to WIC records. While WIC public funded
prenatal records and birth fetal death records are computer matched, the clinic record is not. It is quite optimistic to believe that North Carolina staff will be able to match 4,600 records reliably from 1993 to 1999. This is acknowledged in the Roholt letter of collaboration stating, "It is possible but ... as noted in the latter statement, will be difficult."

The data for analysis derive from existing data at six sites across the country. All of the data contain weight information for a minimum of one visit in the first trimester; 2 to 13 times in the second trimester; and 3 to 10 times in the third trimester. While frequent contact is desirable, is the multiple visit population of women whose number of visits exceed ACOG recommendation, representative of the general population? Women with 10 visits in the second trimester, when I visit per 4 weeks is recommended, may have required closer scrutiny for clinical problems. Three visits in the third trimester can reflect inappropriately low level use of clinical services and may therefore may reflect a different population of women.

Establishing SGA criteria may be an important if not difficult challenge for each ethnic and racial group. How will this be accomplished? Will the distribution of birth weights for the entire population be computed? Will they be computed for each subgroup? If so, will the numbers be sufficiently robust? How will obvious errors in dating be resolved? How will outlying values be evaluated? How will edits be established and decisions made? Will a Z score be established on the basis of the deviations in birth weight on the normalized distribution curves stratified by race and ethnicity and duration of pregnancy at delivery?

Normal birth weight, SGA and LGA will be linked to prepregnancy weight and pregnancy weight gain. There may be value in further categorizing the SGA birth weight by Ponderal index or other indices to identify short term, long term fetal growth restriction and normal birth weight in the "SGA grouping". If the investigators use the 10' and 90' percentile as cut offs, clearly 20% of the population would be expected. A more refined analysis may provide more detailed information regarding the relationship of maternal weight patterns and low percentile birth weight for gestational age.

Is there a need to consider outcomes? If there is a higher mortality in the SGA subgroup, will the live birth group of infants represent a truncated population thereby skewing weight gain - birth weight inferences? Similarly, is there a need to understand maternal weight gain patterns and preterm birth weight.

The investigators are internationally recognized for their scholarly contributions to the field. Nevertheless, many questions require consideration. On a conceptual level, one study consultant in an earlier paper (1997) appears to challenge the applicants' study by noting a lack of support for the presence of ethnic group-specific weight gain recommendations. Further in an earlier publication challenges the notion that weight gain considerations, absent of attention to psychosocial factors, that differ by race, rather than dietary recommendations influence prenatal weight gain. Additional questions are raised as to why the investigators will only examine term births. The truncated population may mask the fact that the same gestational age specific weight gain and rate of weight gain result in preterm births, thereby limiting the value of subsequent inferences that a particular weight gain pattern or rate of weight gain is consistent with term births when only term births have been studied. The issue of balancing appropriate recommendations for increasing birth weight above SGA levels by increased maternal weight gain resulting in short and long term maternal obesity is not discussed. In addition, the data sets vary considerably by proportion of underweight women that raises the question of comparability and generalizability. Further, the WIC population data (4,600 women) must be retrospectively matched to clinic records over a six year period. This may be very difficult to accomplish. "Me use of SGA and LGA cutoffs is valuable. At the same time it must be realized that if conventional cutoffs are established, 20% of the population is expected to fall in one or other categories. There may be value in trying to categorize this group further by Ponderal Index or other measure as to fetal growth restriction, early or late. Further, will a higher mortality in the SGA category skew the maternal weight pattern for the live born SGA’s?

Evaluator 3

Originality Importance

The proposal is original and will fill the gap in knowledge about pregnancy weight gain among the underweight, normal, weight over weight and obese women of various racial and/or ethnic groups. This information might be used to generate recommendations for rates of weight gain during pregnancy and perhaps to plans and implement intervention programs. It is of national significance since a diversity of minority group information will be gathered.
Regional and National Significance
This proposal is of national significance since a diversity of minority group information will be gathered. The project addresses MCHB’s priorities as it relates to pregnancy low birth weight and nutrition and it might address health outcome disparities as they relate to race/ethnicity.

Scientific and Technical Merit
The relationship between maternal pregnancy weight gain and infant birth weight and outcome is well known. The scope of this proposal reflects a need to have this information and relationships before attempting to devise interventions. Although knowing absent how a woman deviates from the "expected" rate of weight gain might not influence that rate, it might prompt providers to interventions amenable for that particular population.

The review of the literature described well-known associations between maternal weight gain and infant outcomes and the gaps in knowledge between those factors, maternal pre-pregnancy weight and race/ethnicity.

The concept of "net rate of weight gain" is appropriate to the scope of the project.

As this is a descriptive study, no hypotheses are needed. The study variables are Birth weight, maternal pre-pregnancy BMI (Body-Mass Index as wt ht2) wt gain by week, race/ethnicity some sociodemographic variables (marital status, age, education, income) and lifestyle/medical information.

It is a descriptive study from a large database of 26,620 pregnancy and births charts from 7 studies. Protocols will be developed for the transfer of computerized and hard copy record data from the difference sources. A data abstraction and entry quality control system will be in place.

A sample of 665 women from the investigators site was described on detail for this proposal and used for power calculations per BMI category. The sample size is adequate to determine differences of 2 pounds in maternal wt gain between birth weight group and BMI categories.

Two steps are involved in the data analysis: 1) development of BMI and race wt gain regression models using several expressions of weight gain (rate, net rate) and birth weight (continuous and categorically); and 2) evaluation of the effect of potential confounders within each BMI and race group.

This timeline and budget are adequate.

The principal investigator, Dr. Judith Brown, is well-recognized for her work in this field and has assembled a reputable team of co-investigators and consultants.
Prehospital Arrest Survival Evaluation: Pediatric Phase

**Grantee**
New York University School of Medicine

**Investigator**
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**Project Number** R40MC00262

**Project Period** 1/1/2001-12/31/2003

**Year 2010 Objectives**
16.1, 16.2, 16.3

**Study Design**
Observational

**Time Design**
Longitudinal

**Care Emphasis**
Noninterventional

**Population Focus**
Neonates, Adolescents

**Race/Ethnic Focus**
No Stated Race, Ethnic Focus

**Priority Research Issues**

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**Summary**

**Statement of the Problem**

The literature on pediatric resuscitation and outcomes is predominantly retrospective, small non-population based studies. Prospective, population-based studies are needed to accurately determine incidence, epidemiology, interventions, and outcome of pediatric resuscitation that include patients with respiratory as well as cardiac arrest. Pediatric resuscitation utilizes a large amount of resources and the outcome is devastating to family and society the majority of the time. This information will better define the causes, process and outcome of pediatric resuscitation and allowing for planing of interventions and new research to improve the outcome of pediatric resuscitation.

**Research Questions or Hypotheses**

Hypotheses being considered:
1) Ventricular fibrillation in children in cardiopulmonary arrest is a more frequent occurrence than previously has been thought;
2) After adjustment for initial rhythm, the outcome of cardiac arrest in children is different than that of adults;
3) Patients in respiratory arrest who are "adequately treated" demonstrate no difference in outcome if they are treated with bag-valve-mask vs. endotracheal intubation; and
4) What are the epidemiologic elements, causes, locations, interventions by bystanders or family, timing, interventions by EMS, initial cardiac rhythm, and outcomes (survival or not survival and if survival neurologic function) of all children less than 18 years of age in NYC who suffer cardiac or respiratory arrest.

**Study Design and Methods**

The Center for Pediatric Emergency Medicine (CPEM) proposes to perform a population-based, prospective observational study of all children under 18 years of age requiring resuscitation from respiratory or cardiovascular etiologies over a 12 month period in New York City (NYC) cared for by the 911 NYC Emergency Medical Services (EMS) system. For this study, resuscitation is defined to be when a patient requires assisted ventilation.

CPEM’s PHASE Project will utilize the standardized uniform data reporting elements from the "Pediatric Utstein Style." CPEM will collaborate with the Fire Department of NY (FDNY) PHENYCS (Prehospital Evaluation of New York Cardiac Survival) study, using a prospective data collection methodology that previously captured 100% of the population. Specially-trained FDNY paramedics, will provide 24 hours a day/7 days a week coverage, to track all out-of-hospital cardiac and respiratory arrests in adults and children. The PHASE medics will conduct a structured interview with ambulance personnel using a closed-question format, to complete a standard data entry form. The data elements will include: presumed etiology; order of arrival of medical services; patient age, ethnicity, gender, arrest location; presence of a witness; presence of bystander CPR, effectiveness of bystander ventilation and/or compressions; cardiac rhythm (all children transported by paramedics); defibrillator shocks, intubation; vascular access in children; drugs used in the resuscitation; return of spontaneous circulation (ROSC) and duration; return of spontaneous ventilation (ROSV) in children and duration; transportation to the Emergency Department (ED); admission to the hospital, and ultimate outcome. Time points will be recorded by the PHASE medics: collapse-recognition, first CPR/bystanders, call receipt, vehicle mobile, vehicle stops, time at patient; begin EMS-CPR, first defibrillator shock, time CPR abandoned, time of ROSV, ROSC and duration.

Information will be collected on all patients <18 years of age who require assisted ventilation or CPR cared for by FDNY paramedics; track all pediatric patients into the hospital ED, hospital ward, through final disposition; and analyze pediatric data collected.

Outcome tracking: The primary end point of the study will be discharge from the hospital or death (including prehospital death). The PHASE medics will obtain the outcome of unsuccessful resuscitations from the ambulance crew. Short-term survivors will be tracked with telephone calls by the FDNY and CPEM administrative staff to the sixty-one 911 receiving hospital EDs. Neurological status will be assessed for survivors to discharge using the Pediatric Cerebral Performance Category Scale. We will work with the NYC Medical Examiner’s Office to track all pediatric cases seen by or reported to the Coroner's office to confirm that no cases of pediatric patients who died and received assisted ventilation by EMS were missed.

**Population Description and Sampling Plan**

NYC has approximately 7.3 million population with 20% being children less than 18 years old. Approximately 58% are white, 25% are African American, 12% are Latino and 2.5% are Asian. The population for the study will be all children under 18 years of age in NYC and who require assisted ventilation due to respiratory or cardiac arrest cared for by the NYC 911 EMS system over a 12-month period. Sampling Plan: We expect to obtain all cases of children under 18 years of age who live in NYC and who require assisted ventilation during the study period. We will collect an estimated 300 cases of pediatric cardiac and 100 cases of pediatric respiratory arrest. Data will be collected on ethnicity/race to determine if there is a higher risk of arrest in minorities as compared to the general population.

**Analysis Plan**

1) A comparison of the crude rate of ventricular dysrhythmia (VF or VT) in other pediatric cardiopulmonary arrest studies will be made to the rate in our study. A point estimate and a 95% confidence interval will be reported for all children. We will define several age groups, and determine point estimates and 95% CIs for each age group. We will develop a multiple logistic regression model to determine which children are most likely to have VF/VT. Predictor variables for a basic model would include: age, prior heart disease, discovery interval, medical vs. trauma. Outcome variable: VF/VT.

2) We will compare survival rates across all different rhythm groups and collapse them into VF/VT vs. all other rhythms. A logistic regression model with survival as the outcome will be constructed. Independent variables include: Bystander CPR;
Interval from collapse to initiation of CPR; Interval from CPR to initiation of ACLS; Age; Presenting rhythm (VF/VT or not). The coefficient of an interaction term between rhythm (VF/VT or not) and age would demonstrate whether outcome is independent of age, given the same initial presenting rhythm.

3) We will define "adequately treated" as: A child who has good chest rise with assisted ventilation and a pulse oximetry saturation of greater than or equal to 90% as measured upon arrival in the ED. BVM ventilation will be defined as patients who have assisted ventilation performed using a bag valve mask device without endotracheal intubation. ETI will be defined as patients who have an endotracheal tube placed in the pre-hospital setting, fulfill the criteria for adequate treatment, and have confirmation of correct endotracheal tube placement in the ED (via direct visualization or end-tidal CO2 measurement and chest x-ray). This analysis will be stratified by the etiology of respiratory arrest.

Pre-Award Evaluation

Evaluator 1

Originality and Importance
One of the strengths of the previous iteration was the potential for a broader look at the issue of cardiovascular arrest in children, for which there is only one population based study. In developing more specific hypotheses, this broader scope seems to have been lost, and no analyses are planned to address this. Thus, the importance of the current iteration rests on the importance of the hypotheses presented. Further, the authors have not argued persuasively what this study might contribute or replicate from the one population-based study with the exception of the comparison of BVM vs. ETI.

The significance of the hypotheses was less clear to this reviewer. The investigators argue that establishing the prevalence of VF in children would have implications for the treatment strategies, namely calling in a defibrillation team. However, they go on to say that, despite attention to this in adults, the results have not been impressive. In view of the fact that the current estimates of VF are low (<20% of children in arrest), it would seem unlikely that a reliable predictive model could be developed unless the investigators already have a pretty good idea of what variables are likely to be important. Even if it were possible, what would be the policy conclusion—de-emphasizing defibrillation for adults (unlikely) or emphasizing it for children (with the adult results in mind)? The third hypothesis will not be adequately addressed by this data collection, and may not even be the appropriate research design.

Regional and National Significance
Clearly, the study would be of regional significance for New York. As noted above, the national significance is not readily deciphered.

Scientific and Technical Merit
The study continues to incorporate some significant methodologic strengths. Among these are a population-based approach, the use of a well-defined data-gathering approach which has been demonstrated to work in previous studies, the use of carefully defined variables, and careful monitoring for missed events. The existence of an adult study is also a major strength. The proposal also provides a detailed description of the EMS system in NYC which clearly identifies both the sources of information and sources of missed events. It has been strengthened by the addition of more specific analytic plans and methods to gain more precision for some of the variables.

The study is still weakened by several factors. First, the authors still are unable to provide data on prevalence of the problem of pediatric cardiopulmonary arrest events in NYC, and rely on estimates derived from published studies for estimates of sample size.

Second, while the hypotheses have been made more specific, it is not clear that they are the most important issues in pediatric cardiovascular arrest, and that they can be addressed in this study. As noted above, it is not clear what the results from the first hypothesis would be in terms of resuscitation hypotheses in view of the adult experience. No power calculations for the second hypothesis are provided, but it is likely to be very low for comparing outcomes in events in 10-20% of the population with survival rates of 2-4%. The data collection planned under this proposal is demonstrated to elicit sufficient relevant cases, and more data will be collected. While the commitment of the fire department to this effort is commendable, it is not clear that an observational study is the appropriate study design to compare two treatment strategies.
This reviewer continues to believe that they would have done better to generate a set of more thoughtful research questions to be addressed by an admittedly descriptive and hypothesis-generating study.

While the data-collection methods and instruments are carefully described, and the description is strengthened by provision of a pediatric instrument and clarification of the role of the large study in the data collection. They have been further strengthened by the additional data collection to address the specific hypotheses (rhythm strips) and improve precision of measurements.

The data analysis section has been dramatically improved. However, in doing so, the investigators have narrowed their scope, and indicated that they may not be able to address all the hypotheses with the current data collection.

Evaluator 2

Originality and Importance
A main concern of the original submission was difficulty in assessing how this project would contribute to the literature. The investigators have now provided the most recent and key articles and review of the literature justifying the need for this project.

The existing literature of pre-hospital pediatric resuscitation is limited by small numbers, retrospective studies, and non population based methodology. Of the two population based studies, one does not use standardized definitions (Pediatric Utstein Style) and one does not address respiratory arrest in children. The investigators now state several aims that are based on questions raised by the existing studies in the literature, including the prevalence of ventricular arrhythmias and need for defibrillation as a first step in resuscitation for children.

Regional and National Significance
Although the study is based in one urban area (New York City), the results will add greatly to the national literature. The existing population based studies are from Seattle and Houston. The quality of the data from this prospective population based study will add to the knowledge of pediatric arrest nationally, regardless of region. There may still be a need to examine differences in response time, outcome, and etiology in non-urban areas.

Scientific and Technical Merit
A major concern of the original proposal was that the hypotheses were not well thought out or justified and the data analysis section was underdeveloped. The investigators have changed their hypotheses or objectives in this revised proposal. In addition, they have justified their objectives with documentation from the medical literature. The current key hypotheses are:

1. Ventricular fibrillation in children is cardiopulmonary arrest is a more frequent occurrence than previously has been thought. The literature ranges from 3% to 20% collection and may vary by age. If VF is prevalent in children, the initial approach to resuscitation in children would need to be changed.

2. After adjustment for initial rhythm, the outcome of cardiac arrest in children is different as compared to adults. Data will simultaneously be collected on adults which will allow comparison from the same system and time.

3. Patients in respiratory arrest who are "adequately teated" demonstrate no difference in outcome if they are treated with BVM vs ETI. A recent population based randomized clinical trial in California found no difference in outcome of pediatric respiratory arrest patients who received bag-valve-mask ventilation versus intubation and ventilation. If paramedic training for intubation of pediatric patients is to change, this data should be validated in a separate sample.

Unfortunately, the sample size calculations and data analysis remains weak in this proposal. For hypothesis #1, they estimate that there are 200 cardiac arrest patients and that 10 – 17% will have Ventricular Fibrillation (or 20 to 34 patients). With these small numbers, they propose to stratify results by three age groups and develop a multiple logistic regression model to determine which children will likely have VF/VF. With only 20 to 30 outcomes, this model could have no more than 2 to 4 variables. The 95% confidence intervals of the prevalence of VT/VF for the whole sample if the prevalence is
14% would be 9% to 19%. Similarly for hypothesis #2, the outcomes of pediatric vs adult patients with VT/VF will be compared by age group. Numbers will be small and 95% CI’s will be large.

Finally, hypothesis #3 compares the outcome of BVM vs ETI for respiratory arrest patients. There are to be less than 100 patients in this category and choice of method will not be randomized (unlike the recently quoted study) making comparisons and validation difficult. The authors state that the city intends to collect data after this study ends, but no details or assurances are given. In order to adjust for the non-randomized nature of this observational study, "adjustments based on risk factors for survival will be included in the analysis to determine if any difference between outcome of BVM vs ETI remain.” What does this mean?

The investigators need to acknowledge the hypothesis generating nature of this study and its contribution in gathering reliable prospective information about prevalence and outcome in the pediatric population. Hypothesis testing, in most cases, will not be possible for subsets of patients.

In summary, this is a major opportunity to study pediatric out of hospital arrest using a validated methodology. The authors have successfully justified the need for such a study. Flaws in statistical analysis should be corrected and the project funded.

Evaluator 3

Scientific and Technical Merit

This proposal has a number of interesting strengths that has existed since the first submission and these strengths have only increased with the re-submission. In the interest of saving everyone time, let me just say that the PI’s have been extremely responsive to the suggestions of the committee. That being said, there is still one major issue that remains for this reviewer.

The committee was very concerned over the ultimate value and practicality of this project. Specifically, the utility of the project depends crucially upon changing the current futility of outcomes on children with arrest. That is, the outcome is currently so poor that it is not clear to this reviewer that anything is necessarily to be gained by the kind of precise analysis of EMS services that the PI intends to provide. Again, it would seem that bystander intervention, applied quickly and appropriately, would seem the best strategy to take in terms of increasing the survival rate. Yet little in this study actually addresses this issue. Even the PI admits that it is unlikely that EMS personnel can make a valid judgment of the CPR as administered.

Yet this is a technically sound study. Whether the information to be gained is worth the expense is a judgment that is difficult to make. Clearly, the study is sound yet it may simply not be a high-priority study.
PRWORA & Low Income Women's Insurance & Prenatal Care Use

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Project Number  R40MC00209

Project Period  8/1/2001-7/31/2003

Year 2010 Objectives
1.1, 16.6

Study Design
Quasi Experimental

Time Design
Longitudinal

Care Emphasis
Noninterventional

Population Focus
Pregnant women (not otherwise identified as adolescents)

Race/Ethnic Focus
No Stated Race, Ethnic Focus

Priority Research Issues

Summary

Statement of the Problem

The implementation on August 22, 1996 of the Personal Responsibility and Work Opportunity Reconciliation Act of 1996 (PRWORA) was one of the most far-reaching policy changes in the past decade. This Act replaced Aid to Families with Dependent Children (AFDC) with the Temporary Assistance for Needy Families (TANF) program, thereby restricting welfare tenure, imposing new work requirements, and de-coupling welfare and Medicaid eligibility. The primary effects of PRWORA are visible in terms of reduced caseloads nationwide. However, it is also likely that additional effects have occurred with respect to the financing of prenatal care and prenatal care utilization. Projects to monitor the impact of welfare reform have focused primarily on the social and economic well being of children and families. After several decades of policy efforts to improve access to and utilization of prenatal care, it is essential that changes in welfare eligibility and health insurance coverage be monitored and that policies be developed to counteract any negative impacts of these changes on women’s initiation and use of prenatal care.

Research Questions or Hypotheses
Among women who report public assistance as a source of income during the 12 months prior to the PRAMS interview and among their very low income counterparts:

1) The percent who report health insurance coverage for prenatal care will be lower in the years following welfare reform (1998-2000) than in the years prior to the full implementation of welfare reform (1994-1996).

1a) The percent who report health insurance coverage prior to pregnancy will be lower in the years following welfare reform (1998-2000) than in the year prior to the full implementation of welfare reform (1996).

2) The percent who report financial barriers to prenatal care will be higher in the years following welfare reform (1998-2000) than in the years prior to the full implementation of welfare reform (1994-1996).

3) The percent who have inadequate prenatal care will be higher in the years following welfare reform (1998-2000) than in the years prior to the full implementation of welfare reform (1994-1996).

3a) The percent who are both uninsured during pregnancy and have inadequate prenatal care will be higher in the years following welfare reform (1998-2000) than in the years prior to the full implementation of welfare reform (1994-1996).

Study Design and Methods

This pre-post comparison of sampled birth cohorts uses Pregnancy Risk Assessment Monitoring System (PRAMS) data from 9 states (Alaska, Florida, Georgia, Maine, New York State, Oklahoma, S. Carolina, Washington and West Virginia) for the years 1994-96 and 1998-2000 to examine the effect of the PRWORA on the insurance coverage, prenatal care utilization and barriers to care of women on public aid and their low income counterparts adjusting for demographic changes and changes in the economic and health care environment over time. Because the PRAMS survey uses complex sample survey methodology, weighted percentages are presented.

Population Description and Sampling Plan

The PRAMS dataset for the nine states for 1994-1999 (2000 not yet available) includes 88,442 women. In this population, seventy-one percent of the women identify as white non-Hispanic, 17% identify as black non-Hispanic, and 8% identify as Hispanic. The mean age of the study population is 27 with 78% of the women between the ages of 20-35. Twenty percent of the women are recipients of any public assistance. Forty percent of the women had unintended pregnancies, with 11% receiving no or inadequate prenatal care. While the study’s hypotheses are not focused on racial and ethnic differences, the analyses can be stratified by race/ethnicity to determine if the effect of welfare reform on women’s health insurance status and prenatal care utilization differs by race/ethnicity.

Analysis Plan

Data from the nine states have been pooled into one dataset. The sociodemographic characteristics of women who are public aid recipients and their very low-income counterparts in both the pre and post welfare reform periods will be examined. If the characteristics of the women within these two groups differ over time and are also related to the key dependent variables, these characteristic variables (e.g., age, education, intendedness of pregnancy, medical risk status) will be included in the multivariable analyses.

Each hypothesis will be tested in a univariate and multivariable fashion with time period as the independent variable and Medicaid or private insurance coverage, barriers to care, and prenatal care utilization as the dependent variables. Multivariable analyses will be conducted using logistic regression (all outcomes will be dichotomous); individual level and state-level potential confounders or effect modifiers will be included as appropriate. These multivariable models will include state dummy variables to represent other unmeasured factors in each state that might affect the dependent variables. These models will also include state/time interaction terms as a way to determine if the impact of welfare reform is different between states. Analysis is being conducted using SUDAAN (Software for the Statistical Analysis of Correlated Data), software that calculates estimates and their standard errors accounting for the complex sampling scheme.

Pre-Award Evaluation

Evaluator 1

Scientific and Technical Merit
The revised proposal is substantially the same as the original submission. The investigators did address concerns about varying economic and health care conditions in the nine states across time. They specifically included measures to address the safety net that might be available to the women seeking prenatal care and they also included measures of economic well-being in each state. They also will use pregnancy complications as recorded on the birth certificate as a measure of severity for each woman.

These measures are incorporated into their conceptual framework, which is based on Anderson and Aday's access to care model. They also discuss issues related to potential multicollinearity among the economic and health care delivery system variables and propose an appropriate strategy to address those concerns.

Another concern raised with the initial proposal involved sample size considerations. The investigators had originally provided power estimates and indicated that the sample sizes were large enough to detect differences that would be relevant for policy recommendations.

The investigators still have the issue of differences in questions from the different administrations of the PRAMS. Some of the questions are worded only somewhat differently. One of the main questions is not included in all versions of the PRAMS. The investigators propose to address this issue by coding questions that are similar and they believe they can do this, despite wording differences. They also propose to address the issue of non-equivalent questions by using only certain years of the data that contain the question of interest.

The investigators have submitted this proposal to the Agency for Health Care Research and Quality.

Evaluator 2

Originality and Importance
This revised application proposes to use data from the CDC Pregnancy Risk Assessment Monitoring System (PRAMS) from 9 states for 1994-2000 to test several hypotheses concerning the changes in Medicaid insurance coverage, prenatal care utilization and financial barriers to health care. The overall aim of this proposal is to assess the impact of recent changes in welfare law on women's health insurance coverage during pregnancy and on prenatal care utilization. As noted in the previous review, little is known about the impact of welfare reform on women's health, particularly reproductive health. From this standpoint, the proposed study Bif it is successful in addressing the stated specific aims B stands to fill an important information gap.

Regional and National Significance
The topic of research is of high regional and national public health significance. Assessment of the impact of public health reform on women's insurance coverage during pregnancy on utilization of prenatal health care and the occurrence of adverse pregnancy outcomes are important public health aims.

Scientific and Technical Merit
The investigators have done an excellent job in summarizing the available literature and in promoting the relevance of their proposed research. The investigators provide a compelling justification for testing their proposed scientific aims. The conceptual model, study hypotheses and variable specification are overall, well presented. The investigators' thoughtful and thorough discussion of the strengths and limitations of the PRAMS database reflects the care they have taken in assessing their overall ability to successfully address the scientific goals stated in this proposal.

Although PRAMS appears to be a reasonable database for this study, it is evident that the investigators will have significant methodological hurdles to clear, particularly when it comes to creating analytical variables that are key to their two set of specific aims.

Specifically, the investigators have considered the difficulties they are likely to have with defining some variables, as different data collection instruments were used during the different phases of the PRAMS project. Although the
investigators= plan is reasonable, the fact remains that some degree of misclassification is likely to be introduced in the study (non-differential misclassification), and as a result interpretation of a null finding will likely be problematic.

Another considerable concern pertaining to the limitation of the PRAMS data relates to the fact that the investigators will not have sufficient information to identify very low income families not receiving, but who would have qualified for AFDC before its termination. In response to this previously noted limitation, the investigators have amended their research plan to now include 5 additional covariates which will be helpful in tracking changes in the health care and overall all economic environment over time. The analytical plan is strategically designed to optimally manage this important limitation. Specifically, the investigators will restrict their analysis (for the 2nd set of aims) to the 4 states in which data are available to more accurately characterize very low income families. This is reasonable approach, and the power and sample size section of the proposal suggest that they will likely have adequate statistical power to address the relevant aims.

The investigators, in response to previous concerns about the likelihood of type I errors, note that their power estimations were completed using a 0.05 and 0.01 statistical significance cut-point. Though a step in the right direction, the response is inadequate. Given the relatively large number of statistical comparisons to be made, the investigators should include cautionary remarks regarding the impact of multiple comparisons reporting results.

As noted previously, the investigative team is excellent.

Available computing facilities appear to be adequate for support a study of this scope.

The budget is reasonable for a project of this scope but could stand some trimming.

This proposal has also been submitted to the Agency for Health Research and Quality (AHRQ). Dr. Handler notes that if MCHB funds the proposal, she will notify AHRQ and follow the appropriate procedures.

The protection of human subjects appears to be adequate.

Evaluator 3

Originality Importance
Whether proportionately fewer women are receiving prenatal care associated with the uncoupling of welfare and Medicaid in the switch from AFDC to TANF is an important question.

Regional and National Significance
The study could be of substantial significance if it documents that fewer low income mothers are now receiving timely prenatal care. If so, it would be important to ask whether birth outcomes or maternal health were also affected.

Scientific and Technical Merit
As in the original proposal, the research issue was clearly stated and the literature review provided clear support for examining this issue. The advantage of secondary data analysis of the PRAMS data was clearly presented. The rationale for why prenatal care may be less prevalent among low income families under the revised system was also clearly argued. The literatures linking medical insurance coverage to prenatal care, and prenatal care to healthier birth outcomes were also succinctly, but clearly presented. The preliminary studies also demonstrated that the investigators have experience using analyzing complicated survey data like PRAMS and addressing issues related to prenatal care among low income and minority families.

The overall model, hypotheses, and variables were all presented in some detail. The investigators provided extensive information on decisions that would need to be made to address their research issues in this secondary data analysis. This section provided insight into the extent that a priori decisions were needed because the data collected did not always match the research question exactly. They were forthcoming that because income was collected in categories only 4 of the 9 states collected data that allowed very low income mothers (at or below poverty threshold) to be separated from low income
mothers. The hypotheses are clearly stated and linked to the specification of variables. The conceptual model describes access and use of medical care as a function of five interrelated components to test their hypotheses that health/welfare policy impacts the characteristics of the low income population such as access to insurance/Medicaid which in term affect utilization of prenatal care services. Terms are defined and variables are well specified.

The revision involved addressing concerns about whether income categories used in the PRAMS allowed one to distinguish among low-income mothers who did and did not qualify for AFDC/TANF and about the economic conditions in the state. As before, the investigators propose to use the four states in which the lowest income category only included families that would be eligible for AFDC or TANF. They propose to include only single mothers with at least one other child so welfare criteria for a family of three is relevant. A question not raised in the first review involves whether one of the four states, Alaska, may have other income categories that could be included (as of now mothers with incomes of 41% or less of the poverty threshold are in the lowest category).

The nagging concern that remains is the ability to use this database to correct for time-dependent changes in the Medicaid coverage or other aspects of medical care.

The design is a secondary data analysis of survey of sampled birth cohorts. The distinction between the use of data from four states to address some questions and from 9 states to address other questions was described again. Strengths and weaknesses of the design are described.

The investigators describe how the PRAMS sample was collected and how they will partition the database to address their research questions. They provide a power analysis based on preliminary analyses of the PRAMS 1996 data from these 9 states. While the power analysis was well described, it was not clear whether the anticipated relative risks were what should be expected given their hypotheses. One would expect they are, but would have appreciated a little more guidance. It appears that the PIs should have reasonable power for all analyses that include all selected states. Finally, the sample should be ethnically diverse based on preliminary analyses of the 1996 data.

The data analysis section is reasonably detailed and seem appropriate in most cases. The investigators are to be commended for recognizing the need for specialized software for analyzing these complex stratified sampled data and for the need to adjust for potential confounders. Logistic regressions are proposed to examine these binary outcomes (e.g., adequate prenatal care or not) as a function of the hypothesized variables and potential confounders of moderators. The list of potential confounders is includes many demographic variables such as education, parity, and medical risk status that clearly need to be considered.

The investigators addressed some of the analytic concerns. First, all analyses are now proposed using across-state pooled data, dramatically reducing the number of analyses proposed. Some consideration of potential inflated Type 1 error rates is needed. This reviewer is still concerned about the idea of conducting all analyses related to use of welfare twice B once using any welfare (family who did or did not report receiving welfare as any part of their family income) as the primary predictor and once using welfare only (family who did or did not report receiving all family income from welfare). A multinomial logistic analysis would allow them to look at three groups (only welfare, welfare + other, no welfare) simultaneously. Contrasts could test whether the first two groups differed from the third group.

Proposed time table seemed adequate, although there is not much time reserved for manuscript preparation. One hopes that manuscript preparation can begin while final analyses are being conducted during the second year.

IRB approval was obtained on April 18, 2000.
Psychosocial Sequelae of Bronchopulmonary Dysplasia and Very Low Birthweight-Phase Two

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Project Number R40MC00127

Project Period 1/1/1997-12/31/2000

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Summary

Statement of the Problem

Bronchopulmonary dysplasia (BPD), a chronic lung disease of prematurity, currently occurs in 25 to 40 percent of very-low-birthweight (VLBW) infants and has been found to be significantly related to poorer developmental outcome in VLBW cohorts. The first waves of postsurfactant survivors are now approaching school age, with little known about their long-term pulmonary outcomes, growth, or functional abilities. Further, there is little available data on the behavioral, psychosocial, and family outcomes of VLBW cohorts in general, and no data in which prospectively recruited cohorts of VLBW and term comparison groups have been longitudinally assessed to identify the processes by which outcomes might be affected.

Delineating the specific relationships between early medical conditions (such as BPD) and (1) other complications of preterm birth and (2) child outcomes may lead to early identification of those VLBW children at highest risk for learning and behavior problems; it may also elucidate biological and psychological mechanisms related to the negative sequelae of VLBW birth.

Research Questions or Hypotheses

Year 2010 Objectives
No Stated Healthy People Objectives

Study Design
Quasi Experimental

Time Design
Longitudinal

Care Emphasis
Noninterventional

Population Focus
School-age children, Adolescents, Parents/Families/Mothers/Fathers

Race/Ethnic Focus
African Americans

Priority Research Issues
Four study hypotheses are posed:

1. At 7 1/2 years of age, children with a history of BPD and VLBW are expected to continue to exhibit impaired functioning, compared with VLBW children without BPD and term children of similar age, race, sex, and socioeconomic status (SES), when assessed on measures of physical health and growth, lung function, cognition, school achievement, language, behavior, and specific neuropsychological abilities.

2. Parents of children age 7 1/2 who had BPD are expected to experience more symptoms of psychological distress and more stress, and to have less optimal interactions than parents of children without BPD and parents of term children.

3. After other neurological, medical, and SES risk factors have been taken into consideration, BPD is expected to account for independent variance in overall cognitive, motor, and neuropsychological outcomes in children.

4. BPD and VLBW are expected to have direct effects on children's school achievement, and indirect effects through their impact on both earlier and concurrent maternal distress and mother-child interactions.

The proposed research will investigate school-age functional abilities, with a particular focus on the influence of BPD (relative to other risk factors) on pulmonary, cognitive, language, neuropsychological, and behavioral/emotional outcomes.

**Study Design and Methods**

Standardized measures of child outcomes will be administered, teacher and parental report of child behaviors will be obtained, and parental self-report of psychological and parenting distress, coping mechanisms, and social supports will be provided. Videotaped observations of maternal-child interactions will also be made. Study measures to be collected include a medical history focusing on lung, cardiac, kidney, and neurological problems; vision examination; physical assessment; hearing screening; conversational language sample; and measurements of weight, height, and lung function. The Wechsler Intelligence Scale for Children (WISC III), Woodcock-Johnson Tests of Achievement, Continuous Performance Test of Attentional Processes, Bruininks-Oseretsky Test of Motor Proficiency, Clinical Evaluation of Language Fundamentals, and the Children’s Pictorial Depression Scale will be used. Teachers of study children will be asked to complete the Adaptive Language Inventory and the Connors Teacher Rating Scale. Parents will be asked to complete the Child Behavior Checklist, the Parenting Stress Index, COPE, the Brief Symptom Inventory, the Multidimensional Scale of Perceived Social Support, and the Family Inventory of Life Events and Changes.

**Population and Sampling Plan**

The study sample will comprise 302 white and African-American children ages 7 1/2 who were followed prospectively from birth to age 3 in two separately funded longitudinal studies of the medical and psychosocial correlates of BPD and VLBW. Of the 302 children, 110 were VLBW at birth with subsequent BPD, 80 were VLBW at birth without BPD, and 112 were healthy term infants. The groups do not differ in age, race, sex, SES, or parental education/marital status. Ninety children will be assessed each year for the first 3 years of the study, and 32 children will be assessed during year 4.

**Analysis Plan**

Descriptive statistics, multiple analysis of variance (MANOVA) and multiple analysis of covariance (MANCOVA), and hierarchical multiple regression will be used to assess group differences and the relative effects of BPD, VLBW, and other risk factors on outcome. To assess change over time and predictive models of infant risk, data sets from the two prior longitudinal studies will be merged with the outcome data from this study, and hierarchical linear or structural equation models will be applied.

**Pre-Award Evaluation**

**Evaluator 1**

**Originality and Importance**

This is the second phase of a continuation study of bronchopulmonary dysplasia (BPD), a chronic lung disease affecting an estimated 7,000 infants each year. Very low birthweight (VLBW) infants with BPD constitute approximately 25 to 40
percent of VLBW survivors, so this is an important group to study longitudinally. The continuation phase of this study provides the opportunity to follow a group of BPD and VLBW infants into the early years of school. Following VLBW infants through the early elementary school years should provide information that will increase our understanding of the developmental outcomes of VLBW children, including those with BPD.

**Regional and National Significance**
This important study has both regional and national significance. The research to date has been competently executed and has resulted in numerous quality publications.

**Scientific and Technical Merit**
This application is a revision of a proposal initially reviewed in June 1996. Although the previous review panel pointed out the application's numerous strengths, several important weaknesses were also noted. The researchers have revised the proposal to address each concern raised by the review panel. In general, the investigators have been very responsive to comments in the initial review. Concern was expressed that the small number of cocaine-exposed infants in the sample would preclude meaningful analyses. This group was dropped from the revised application. The investigators argue that long-term developmental outcomes for this group are largely unknown. They hypothesize that children who had BPD in infancy will exhibit, by the time they reach school age, a lag in cognitive and behavioral competence relative to their VLBW and term peers. Understanding the long-term outcomes of infants with BPD may partially explain the heterogeneous outcomes of VLBW infants.

All parents whose children were enrolled in the prior studies in 1989–91 (except for the small group of cocaine-exposed infants) would be recontacted and asked to make a followup visit to the researchers' laboratory. To date, study data have been collected on the infants at 1, 8, 12, 24, and 36 months of age. The infants who participated in the first phase of the study became eligible for the 7.5 year followup beginning in January 1997.

The review panel noted that clear information on past and anticipated attrition was not presented in the original application. The revision contains more detailed information on attrition. Power analyses including attrition estimates were provided, creating confidence that a sufficient sample of children will remain for the 7.5 year followup to support the desired data analyses. As requested, the researchers also provided a definition for the classification of children as having mental retardation. In addition, issues relating to subject replacement have been clarified (i.e., no subjects are to be replaced).

One of the review panel's more substantial concerns relates to whether the amount of variance in BPD-related child outcomes is sufficient to warrant continuation of the longitudinal data collection. Reviewers also noted that many of the differences between BPD and VLBW infants in the initial study disappeared after socioeconomic status, parenting, and neonatal risk factors were controlled. To address these concerns, the investigators argued that their results to date are clinically significant and thus important, regardless of the amount of variance accounted for by BPD. After other factors are accounted for, BPD was found to be responsible for a 10-point decrement in the third year's Psychomotor Development Index on the Bayley Motor Development Scale. This is a .5 standard deviation on this measure, and the investigators argue that this is clinically significant. By 3 years of age, the effects of BPD on cognitive development had disappeared, but the investigators have indicated their interest in looking for "sleeper" effects in cognitive development, which may emerge as the children progress in school.

The review panel requested additional information on the meaning of study findings concerning lower performance by BPD infants at 3 years on receptive, but not on expressive, language skills. In the revised application, the investigators speculated that the receptive language deficit may be due to undetected hearing impairments in the BPD infants. A hearing screening was not included in the initial data collection protocol. Other possible explanations presented by the investigators include poor attending to the receptive test and the possible presence of actual receptive-expressive language differences resulting from neuropsychological problems.

As requested by the review panel, the investigators provided additional information in the revised application concerning factors they believe will mediate and moderate the effects of BPD on children. They provide examples of how these processes may operate, along with preliminary STM analyses. The researchers also cite recent papers that have addressed these issues.

The former review team noted that the data protocol was extremely extensive; the approach seemed to be one of trying to measure as many things as possible, to "cast a wide net" in order to detect possible group differences. This approach lacked focus and made the research extremely expensive. The panel suggested streamlining the data collection protocol substantially, focusing on those outcomes considered critical in the researchers' previous work. The researchers have been only partially successful in this regard. Several measures have been dropped, including the Tactual Performance Test, the
Marching Test, the Category Test, the Narrative Skills Task Skillbook, the Goldman-Fristoe Test of Articulation, and the Oral and Speech Motor Control Protocol. Even so, the data to be collected are still very extensive, without a compelling rationale for including or excluding measures. Although the budget has been reduced, the data collection remains an extremely expensive effort, in part because of the large number of measures to be collected.

The study includes two primary racial/ethnic groups, Euro-Americans and African-Americans. Concern was expressed during the past review that study measures were not selected based on their appropriateness for these groups of families. In the revision, each measure has been justified (to the extent possible), based on its use with African-American children and families. In addition, preliminary data analyses have been conducted, examining racial/ethnic differences in the processes underlying study outcomes.

In summary, the investigators and supporting staff are well qualified and have sufficient experience to conduct the proposed study. The proposal has been approved by the Institutional Review Board. Human subjects protections appear to be adequate. Continuation of the research is recommended, with a reduction in the budget.
Puerto Rican Young Fathers' Involvement with Their Children

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Project Number R40MC00161

Project Period 8/1/1999-7/31/2002

Costs

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Summary

Statement of the Problem

The specific aim of the research is to answer what predisposes Puerto Rican young men to become the kind of fathers that they are by testing a random sample of Puerto Rican young men living in two Northeastern states. Our theoretical model posits relationships between social stratification derivatives (family of origin, social and economic context, and the young father’s demographic characteristics) and father involvement outcomes moderated by individual risk and protective factors and mediated by normative definitions of fatherhood and life priorities. Additionally, father involvement is influenced by proximal factors, which are social support, perceived competence as a father, the quality of the relationship with the mother, and the child’s characteristics.

Father involvement has direct and indirect implications for child health, and encompasses (1) the promotion of healthy development, (2) prevention of unhealthy development, and (3) intervention in cases of failure to attain developmental milestones and of illnesses through seeking appropriate health care.

Research Questions or Hypotheses
Hypothesis 1: Social stratification derivatives that are associated with the family of origin, social and economic context of the residential community, and the young father’s demographic characteristics will predict normative definitions of fatherhood timing and life priorities.

Hypothesis 2: A set of variables that can operate as risk or protective factors (perception of racism, alienation, machismo, risky behaviors, and acculturation) will moderate the relationship between social stratification derivatives and normative definitions of fatherhood and life priorities.

Hypothesis 3: Normative definitions of fatherhood timing and sequence and life priorities will predict father involvement outcomes. Here, following the logic of the integrative model of minority youth development, we examine culturally based cognitive beliefs regarding what is fatherhood, when is it best to become a father, and a young man’s life priorities.

Hypothesis 4: Men who receive social support for fathering from their extended family, peers and, social institutions with which they are involved (such as the work-place) and who see themselves as competent fathers are likely to be involved with their children if they have a positive relationship with the child’s mother and have a first-born, easy, male child.

Hypothesis 5: The nature of the normative definition of fatherhood will covary with acculturation.

Study Design and Methods

The proposed research is a theory-driven, multi-method, cross-sectional study of 300 Puerto Rican young fathers’ involvement with their children. While the young men will be the unit of analysis, their self-reports of father involvement, child characteristics, and relationship with the mother will be augmented by independent interviews with the mother/s of their child/ren; quantitative and qualitative information will be collected from both father and mother through face-to-face interviews. Data on social and economic characteristics of the municipalities in which the father resides will be obtained from on-line data sources.

Population and Sampling Plan

The population being studied is Puerto Rican young fathers aged 18–26, living in the greater Boston and greater Providence areas who have experienced the birth of a child in the past year. The sampling plan includes two subsamples. One will be 150 married Puerto Rican young fathers recruited from the birth records of babies born in the greater Boston area, the other will be 150 married and unmarried Puerto Rican young fathers from Rhode Island.

Analysis Plan

Piloting of survey instruments - We will field test all measurement instruments in order to establish their psychometric properties with this population. In order to establish each instruments’ reliability, we will conduct item-by-item analyses of all scaled measures (test-retest where appropriate), and estimate an internal consistency coefficient (Cronbach's alpha) for each scale. We will examine each instrument's validity by estimating inter-correlations among the constructs to ascertain whether they are mutually distinct and correlated in appropriate directions.

We will code the data regarding educational and occupational aspirations and expectations to form a rating list of life priorities. We will code the definitions of fatherhood and its perceived ideal timing to form closed-ended questions to be scaled. The final forms of the interview instruments will be determined from the results of these analyses.

Data Analysis - The first step will be data reduction through the construction of the proposed scaled indices among our predictor variables. A scale will be constructed using confirmatory factor analysis to arrive at a unidimensional scale. If the item analysis suggests the presence of more than one underlying factor, the scale will have more than one subscale. If necessary, we will correct the nonnormality or excessive kurtosis by either power transformations of the observed variables or dichotomizing prior to fitting the linear models to test our hypotheses. We will assess the internal consistency of each scale (Cronbach’s alpha) and will estimate inter-correlations among the various scales to ascertain whether they are mutually distinct (divergent validity). This is especially important as not all of the proposed measures have undergone psychometric analyses for use with minority populations (e.g., the scales for family and peer support for fathering).

The second step will be the construction of our outcome variable: Puerto Rican father involvement. We propose four inter-related dimensions: disciplinarian, provider, nurturer and maternal support to measure father involvement. We will fit a
covariance structure model (CSM) using LISREL in order to determine whether 1) the items in each of the four scales are reliable; 2) each scale is internally consistent; 3) the four scales represent four mutually distinct constructs and 4) these four factors might be related to a single construct of Father Involvement. The advantages of fitting a CSM for our outcome variable lie in the explicit acknowledgment of measurement error and the definition of latent constructs by covariances among multiple indicators of a construct. These analyses will determine whether we will be able to use a single continuous variable for Father Involvement in our hypothesis testing or whether each model will be fit separately for each the disciplinarian, provider, nurturer and maternal support dimensions of father involvement.

The third step will be to complete descriptive analyses of the data collected from the subjects concatenated with the municipal level statistics because systematic descriptions of the multiple contexts of Puerto Rican young men's lives is lacking in the literature.

The fourth step will be to fit the appropriate models to test each of our hypotheses. The relationships among all of our variables will be examined using linear modeling techniques (e.g., correlational analyses, multiple regression, logistic regression and ordinary least square-moderated multiple regression) as determined by the level of measurement of each outcome.

Pre-Award Evaluation

Evaluator 1

*Originality and Importance*

The investigators use their reading of earlier research (including their own work) to make a strong argument for the need to address the central concerns of the study. They point out that some common assumptions about teen fathers (depression, limited earning capacity etc.) hold true when one looks at the profile of Euro-Americans but not at other minorities. Since common assumptions do not necessarily hold, they can make a good case for research to look at some fundamental questions regarding fathering outcomes of mainland Puerto Rican young men.

*Regional and National Significance*

No statement of regional and national significance.

*Scientific and Technical Merit*

For the most part, the investigators spell out very clearly the tasks they will be conducting and why. The research team is very sophisticated and productive. Several members of the team have worked together for quite some time. Their extensive research and scholarly work, both individually and collectively, is evident in the writing of the proposal, as well as being documented in their biographical sketches.

They are concerned to draw from and develop a theory-driven study. A great deal of their theoretical foundation derives from the work of one of the investigators, Garcia Col., who has proposed an "integrative model of development."

Major constructs are clearly stated in operational terms. The hypotheses are equally clear. The central hypothesis is that the four variables they call "stratification derivatives" (education, employment, income and family of origin) have a causal influence on fatherhood outcomes as moderated or mediated by a set of other variables they define as "personal characteristics," (sex-role ideology, acculturation, alienation and risky behavior syndrome).

The team proposes collecting multiple sources of data on the same construct in order to determine "convergent validity." This is a real strength of this proposal since self-reports alone can be notoriously unreliable and the researchers carefully note that it is important in cases where the relationship between mother and father of the child is not intact.

The team is multilingual and interviewers will be multilingual and bicultural. The investigative team has extensive experience within the Puerto Rican community in this area.

While in the redesign of their earlier study the investigators attempt to address many of the sampling questions raised by the
last MCHB review and members of the site team. They have opted to modify their earlier proposal by recruiting an entirely new sample (and increasing the upper age range to more easily meet their sampling needs). While this addresses sampling concerns, it raises some new difficulties.

The investigators are concerned to probe in a culturally sensitive and culturally reliable way a number of quite sensitive issues. They make a compelling case for the need to be keenly aware that even within a Latino community, sub-cultures are significantly distinct and may have very different responses to fathering. Since the great majority of Latinos in the U.S. are Mexican, it is essential, they argue, to devise instruments that are specifically targeted to the Puerto Rican mainland community. If this level of attention should be paid to the development of culturally appropriate instruments (as I can well believe it should), what about the whole process of conducting interviews and administering tests? In many cultural communities, a stranger asking questions of the sort these tests and questionnaires are designed to elicit, would not be welcome.

This research intends to elicit data that is potentially highly sensitive. Informants may not be inclined to be forthcoming about their attitudes and behaviors regarding fathering and their own sexual behavior.

While the investigators plan to try to address this problem through independent interviews with mothers, it is not clear that this will be enough in assuring that reliable data is gathered. What if the women give information about the behavior of the fathers that is very different from that which emerges in interviews with the young men? Does this mean that the women are to be believed?

What if the father and mother are both present at the time the interviewer comes to visit. Will the interviewer try to reschedule with one and interview the other?

While an interview about this topic in the home might seem like the most comfortable place for the interviewee, the opposite may be the case. Even if teenage pregnancy does not carry the stigma that is often associated with such a situation in white middle class families (as the researchers suggest) the question of stigma and shame will surely vary by family. Presumably, many of these young mothers will be living at home with their own parents and siblings. How will the interview handle the potential discomfort of discussing the child in the home?

In some families and in some cultures, other members of the family will often try to "speak for" the person who is identified to be interviewed. This results in a kind of "group interview" or an interview in which a dominant spokesperson for the family, perhaps a grandmother, offers answers to questions. (This is so common in many cultural situations that anthropologists often speak of co-narration as a standard part of the interviewing process. See, for example, Byron and Mary-Jo Good, on interview attempts to elicit illness narratives in Turkey, or Catherine Reissman on eliciting data on child infertility among South Indian women).

The research design now depends upon data collected from a single interview (with earlier phone or letter contact). Can the investigators really count on the forthrightness and honesty of their informants based on such brief contact? While they intend to ask for the most sensitive material through written answers, will the mothers feel they can answer such questions confidentially if other family members are present in the interview situation? What about the literacy issues for the written material?

Although these are smaller issues (because presumably they will not be difficult for the researchers to address), some new concerns arise regarding the recruitment of potential subjects given the new study design. This may not be a problem, but two worries come to mind. One is that names of potential subjects must be gained through access to confidential vital records for the underage single mothers. These will be available after IRB review by the state's Bureau of Health Statistics. The investigators have begun the application process. How difficult is it to obtain permission for this access?

One of the advantages of the proposal is that it proposes to build upon a longitudinal study, following the male half of the cohort into late adolescence and young adulthood to study transitions into the world of fatherhood. The researchers were already well placed, so that subject recruitment would not be a major issue. And they already had a great deal of information about these subjects.
Finally, regarding the hypotheses. Many of these do not seem very startling. From an anthropological perspective, at least, they represent mainstream common sense. That is, we would expect, for example, that social, economic and cultural factors would shape beliefs about such important matters such as fathering. We also expect that these factors will be mediated by the kinds of risk and protective factors that the investigators point toward.

It might also be expected that normative beliefs would significantly influence behavior—though this latter connection is always interesting to explore and it is interesting to discover when and under what circumstances there is a gap between espoused beliefs and behavior.

Given the common sense nature of many of these hypotheses, will this study yield new culturally specific insights that the researchers have so skillfully maintained are necessary regarding the issue of young fathering in the Puerto Rican mainland community?

Evaluator 2

Originality and Importance
The proposed investigation addresses MCHB's Research Agenda. In particular, this proposal relates to the study of social context as a source of variation. Secondarily, it addresses investigations of the community context, and studies of the influence of the timing of fatherhood in men's lives and in the context of their own roles.

Regional and National Significance
The proposed study is grounded in an integrative model of minority youth development anchored on social stratification theory. This theory is significant to the proposed investigation in two ways. First, the authors argue that Puerto Rican young men may be significantly affected by their minority position in the social hierarchy of their communities. Moreover, the impact of this social position is mediated by alienation resulting from racism and prejudice. They argue that adaptation to these inhibiting environment exigencies is moderated by resources available to these young persons, their level of acculturation, and current contextual demands and opportunities. Thus they argue that father involvement will be a product of many influences inclusive of those internal to the individual, relationship with partner, extended family, peer group, neighborhood/community and institutional forces. This is a very comprehensive and compelling argument that is worthy of exploration.

Scientific and Technical Merit
There is one curious oversight that is not addressed, and, that is: Are there cross cultural differences in perceptions of fathering and paternal responsibilities? That is a very good possibility. The investigators point to the work of Garcia Col, one of the co-investigators, who has found that adolescent childbearing among Puerto Ricans on the mainland is a normative life event. They also cite earlier work published by Garcia Coll and Vasquez Garcia reinforcing that "in spite of the possibility that adolescent parenting may be viewed as normative among Puerto Ricans on the mainland, external stresses created by migration and becoming a minority in the majority Anglo society may render young parents (both men and women) susceptible to negative consequences of early parenthood." Hence, it seems critical that the investigators might want to focus some attention on the cross-cultural conflicts and their consequences.

Several research questions will be examined within this investigation. A central question that is proposed explores two theories of contextual developmental perspectives with the four-factor model of father involvement. Unlike previous investigations, the integration of these theories permit the investigators to examine father involvement from the perspective of potential positive involvement. Four factors that will be examined within this investigation are the perception of the father’s sense of self-competence as a father, the nature of the paternal and maternal relationship as well as the paternal and child relationship, the child’s characteristics, and the support received for fathering from extended family. This model
represents a departure from previous research and by the same token a culturally relevant approach in that the extended family is viewed as potentially impacting the contribution of young fathers. Unfortunately, it is not clear if the investigators believe that circular migration, and the involvement with the extended family in proximity versus at a distance, will make a significant impact.

A second research question is proposed to examine the impact of social stratification derivatives (e.g., family of origin, social and economic context, demographic characteristics) and the affect that these have on father involvement through their influence on young fathers' definitions of fatherhood and its timing and his life priorities. A concern with this question, albeit minor, is related to the stress that may occur from the complex interaction of individual self-perceptions and desires with familial, cultural, and/or contextual issues. In other words, the question is important, but does it really provide us with the insight that the investigators claim can be addressed through the use of the integrated model of development?

A third question that will be examined is whether a set of individual characteristics, defined either as risk or protective factors, can moderate the relationship between social stratification derivatives and normal definitions of fathers and life priorities. While this focus on both risk and protective factors is critical, one would recommend that the investigators focus more effort on the protective factors for two reasons. First, as the authors note, this investigation is an effort to examine the unique dimensions of normative development among young Puerto Rican males. I fear that the focus on risk factors will simply parallel previous research which provides insight into what is wrong as opposed to what can be done to enhance and/or minimize the negative consequences of circumstances that surround young fatherhood.

An exhaustive set of measures has been proposed. Psychometric properties for these are reported. Substantial effort will focus upon the translation of instruments if not available. Using the dual-focus approach that has been developed by the investigators, careful attention will be devoted to the cultural sensitivity of questions and their related psychometric properties. This effort in and of itself is a worthy contribution, and as such, the investigators should be commended for their careful attention to culturally relevant scientific procedures.

The target population is young Puerto Rican fathers (up to age 26) living in the greater Boston and greater Providence areas who have experienced the birth of a child within a one-year period. A multi-method, cross-sectional study will allow the investigators to interview mothers in the language of their choice. Approximately one year will be allocated to the interviews and collection of data.

Of minor concern is the sampling methodology that will be utilized. Although the investigators recognize that the recruitment of fathers from birth records will not permit immediate access to father after the birth of their child, they argue that it will provide them with a more accurate sampling frame of births than from other methods. It can only be assumed that careful attention will be devoted to recruiting Puerto Rican fathers and Puerto Rican mothers. If this is not the intent, then the meaning of the aforementioned statement is unclear. In other words, it is assumed that inter-ethnic relationships may violate the model that has been presented for this investigation. Specific dimensions of the sampling frame should be clarified with related justification.

One final comment on the sampling frame. These collaborators are highly skilled and have previously effectively engaged in, and are currently involved in other research projects. The projects that they have engaged in have resulted in a high level of public trust and participation in their investigations. Given their previous successes, it is somewhat unclear why the choice has been made to use a more restrictive sampling frame.

Adequate statistical power can be derived from the target sample.

The time frame for this study seems more than adequate. Ample time for the analysis of the psychometric properties and need to translate any additional instruments, using the methodology that they have developed in previous projects, will be employed. Data collection is anticipated to take approximately 12 months, which may be somewhat optimistic. The third and final year will be devoted to data reduction, analysis, and generating manuscripts

Based on their previous track records, this is a highly compatible group that appears to work well together. The research team includes expertise in several pedagogical areas, with a mixture of junior and senior researchers. More important, their
previous efforts have provided them with community recognition and support for their research.

Evaluator 3

Originality Importance
No statement of originality and importance.

Regional and National Significance
No statement of regional and national significance.

Scientific and Technical Merit
The study focuses on predicting fathering with emphasis on an appropriate new and different sampling plan. Variables to be measured are based on validated measures or previous surveys. Recruitment of young Puerto Rican fathers will be accomplished by searching vital records for father's ethnic status. The investigators must deal with the fact that records of underage mothers are not public record and that they must obtain access through an IRB review. They have already begun this process. One problem with this form of recruitment is the accuracy of the vital records with respect to Puerto Rican ethnicity. The other issue is that the mother may not be of Puerto Rican descent but father may be and father may not be acknowledged on the birth certificate. The investigators have provided information on the extent to which this might affect the sampling. They estimate that only about 10% of fathers remain unidentified in birth records. On the whole the investigators did a good job of getting this component of the proposal together.

Sample size estimates seem to be appropriate. Methods for data collection appear appropriate. Methods of analysis are carefully laid out with the hypotheses to be tested, the variables to be used and the method of analysis. Missing data issues will be addressed through the IvfIX program. Dr Ronald Seifer will be the consultant senior statistician.

This team of researchers did an excellent job of getting this proposal organized. It clearly demonstrates their ability to work as a team and dedication to their subject matter. They are quite capable of conducting this research.

The direct cost per interview is $743,362/300 = $1,445 per interview. This is quite pricey for an interview study. Some of this is appropriate because the individuals have to be tracked down. However, there is no doubt that the investigators have been generous with their time on the budget. It is rather heavy on principle investigator/Co-principle investigator FTEs.
Reducing Preterm Birth by Bacterial Vaginosis Screening

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Project Number R40MC00001

Project Period 10/1/1997-9/30/2001

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Summary

Statement of the Problem

Despite the dramatic decrease in the infant mortality rate over the past several years, preterm and low weight births remain an intractable problem within the MCH community and contribute to high rates of neonatal morbidity and mortality. The problem is most acute among African-American women who have almost double the number of preterm live births and more than double the percentage of low birthweight newborns than do white women. Despite advances in the science of obstetrics, understanding the basic causes of preterm labor, low birthweight, and intrauterine growth retardation is limited. It is known that the determinants of low birthweight, including genetic, social, environmental, and behavioral factors, as well as underlying medical or biological conditions. In many cases of premature birth, however, no association with a pathologic factor can be identified. Newly published experimental data suggests infections of the genital tract double the number of preterm births, contributing up to 40% of preterm births. Bacterial vaginosis (BV), the term applied to an overgrowth of bacteria resulting in vaginal infection, is the most prevalent cause of vaginitis found in childbearing women today. BV doubles the risk of spontaneous preterm delivery and has been experimentally associated with a number of other adverse birth outcomes. Pregnant African-American women have nearly three times the level of BV as pregnant white women. Half the population of pregnant African-American women with BV are asymptomatic. Current prenatal care in the
community has not integrated BV screening as part of overall prenatal care. In the absence of a screening and treatment program for asymptomatic BV, these pregnant high-risk women are unidentified and untreated during their pregnancy. The integration of a community-based program to identify and treat BV asymptomatic women can contribute to a significant reduction in the high rates of preterm birth and low birthweight among pregnant African-American women.

Research Questions or Hypotheses

This community-based intervention study is designed to determine the effect of a screening/treatment program for bacterial vaginosis (BV) which will be integrated into existing prenatal services. The program will identify and treat asymptomatic and symptomatic pregnant African-American women with BV in order to reduce preterm and low birthweight births.

Study Design and Methods

This study applies a previously experimental model to a new population and will generate knowledge as to the efficacy of the model and the ability to integrate it into existing systems of community based prenatal care, while sustaining the nature and effectiveness of the prototype. This study will screen all participants presenting at the clinics for BV on initial prenatal examination. Patients confirmed to have BV will be treated with 250 mg of metronidazole three times a day for seven days or .75% metronidazole vaginal cream twice a day for five days. These patients will have a test of cure when they return following their therapy, and if they have not been cured, will be retreated.

The design of the study is a five-period cross-over design of over 30 months in which each clinic will alternate six-month periods in which they enroll patients in either the treatment or control arms of the study. Outcome variables include the incidence of preterm births, number of low birthweight babies born to mothers in the study, and the incidence of newborns who exhibit intrauterine growth retardation. Potential confounding variables to be assessed and statistically controlled for include: cigarette, alcohol, and drug abuse; gestational weight gain; infant sex; maternal age; parity; prior incidence of low birthweight or prematurity; and socioeconomic status.

Population and Sampling Plan

The sample is expected to consist of 2500 pregnant African-American women from 4 east Baltimore community clinics. About 750 of these women are expected to be symptomatic and will be treated as usual. Of the remaining 1750 asymptomatic women, half will be screened for BV in the treatment arm at some point prior to 33 weeks. Those who test positive in the treatment arm will receive immediate treatment as well as follow-up treatment as needed. Partners of asymptomatic women in the treatment arm will also be assessed and treated whenever possible.

Analysis Plan

Data analysis consist primarily of exploratory data analysis and logistic regression.

Pre-Award Evaluation

Evaluator 1

Originality and Importance

The purpose of this study is to implement a screening program for bacterial vaginosis (BV) within a community based system of prenatal care that serves high risk women. The aim of the study is to demonstrate that a reduction in preterm birth among African-American can women can be achieved as a result of the detection and treatment of asymptomatic BV.

Regional and National Significance

A reduction in preterm births is a topic of regional and national significance and is relevant to the mission of the Maternal
and Child Health Bureau.

**Scientific and Technical Merit**

Initially, one of the concerns raised at the review was that the application did not fit the guidelines for a CISS research award. In the current revision, this criticism has been rectified. The investigators have now included a very good summary of how the application meets each of the 13 special requirements. These are clearly spelled out and adequately addressed.

In the last submission, as a research project, several questions were raised at the review. Each of the criticism raised in the review have been individually addressed as specific revisions made to the application. The investigators argue well that their proposed study will be a complement to the ongoing Maternal Fetal Medicine Network (MFM) study of bacterial vaginosis (BV), which is whether treatment of bacterial vaginosis Will reduce risk of preterm delivery in low risk women with asymptomatic BV. This proposal win look at an overall high risk group and treat both symptomatic and asymptomatic women diagnosed with BV. The proposed study population is different from that studied in the MFM network. This study is community-based rather than selecting women from specific centers and provide data on the feasibility of applying findings to community-based medical centers.

In the earlier review there was concern about using two different treatment regimens, that of oral versus vaginal metronidazole. Although both of these are acceptable treatment, disagreement it is still argued that they should be viewed as equivalent. The investigators, however, argue well that a very low number of women will be likely to need treatment with vaginal metronidazole. However, it is recommended that they consider this group separately in their analyses, at least preliminarily.

Information will be collected on other sexually transmitted diseases in the patient and in her partner. This information is routinely available in the antepartum record on the patient and they Will collect more detailed partner information for the study. This information will include partner treatment.

Some issues still require clarification, however; there was concern that the BV status enrolled during the non-treatment blocks would not be known. Women enrolled at this time will be screened for BV at the time of delivery. However, this will not give information on the BV status of these women in the second trimester at the time of enrollment. This is better than not collecting any information at all, but the two groups are still not going to be comparable, as BV may be acquired much later in pregnancy when it might not be a cause of preterm labor and delivery.

The investigators do not clearly state whether they will perform recruitment in the same way during the intervention and nonintervention periods. If formal recruitment is not performed during the nonintervention periods, it would have important implications for many other aspects of conduct and analysis of the study. (Even with formal consent in the two periods, because of the crossover design, it would be important to monitor the percent refusal in each time period and be cautious about the comparability of the populations being studied.) The investigator also state, that the study will "as a practical matter, enroll all women who meet the criteria outlined above." It is not clear what his means. Will women who refuse to enroll have their medical records abstracted and be included in the analysis?

The application does not specifically describes how the group of symptomatic women will be identified. Will there be a specific set of questions asked of every woman during both the intervention and nonintervention periods? Given the fact that the investigator focus on the asymptomatic group and use only that group to determine the number of subjects required, it is also important that the "symptomatic" women be identified in a consistent and systematic way in both the intervention and nonintervention periods.

There also remain questions related to the role of the community workers. The application states that each clinic Will have its own community worker for 20 hours per week. First, this is not reflected in the budget which has the same personnel for the same number of hours as the previous submission (two workers for 30 hours each). Second, is the community worker only present at the clinic for 20 hours per week or are the individuals employed full time by the clinic but will have half of their salary paid by the study? The number of hours the community worker is physically present at the clinic has important implications for recruitment.
The monitoring of patients under treatment was raised in the last review and addressed by the investigators by stating that there would be no additional monitoring as this might introduce confounding (as the intervention was no longer just treatment of BV.) The proposal now notes the following forms of monitoring follow-up for compliance and side effects: (1) Medication calendar; (2) follow-up appointment within 2-4 weeks; (3) counseling if compliance is less than 80%; (4) ability to receive care when presenting at unscheduled times; (5) daily review of missed appointments and follow-up class from community worker and written follow-up from project personnel; and (6) provider/nurse contact of women receiving medical to check for side effects. Is this the same follow-up currently used for other patients receiving treatment for BV?

The investigators have increased the study population from 2000 to 2500 and present new power calculations. Their power calculations are based on changes in outcome for asymptomatic women only (875 screened and non-screened subgroups). It is not clear why the investigators have chosen to base their power calculations on an add-ratio with an estimated standard error. They report an overall study power of 84% to detect a difference in rate of preterm birth. However, if one performs a power calculations the more direct way of looking at the comparison of the expected rate of preterm birth in the two asymptomatic groups (25.7% unscreened, 20.6% screened), the power to detect a difference is only 72%. Overall, the study seems to lack adequate power.

In addition, the investigators propose screening women in the unscreened group at delivery and comparing the rate of preterm birth in the asymptomatic, BV positive women from the screened and unscreened groups. The investigators suggest that this approach will improve the power of their comparisons. There are substantial number of problems with this approach. First, the investigators estimate that they Will only be able to perform delivery screening on 80% of women (though the basis of that estimate is not given). For delivery screening to be valid, data needs to be presented indicating that the ability to obtain a screen is not related to the presence of BV and prematurity. Also, for some women, BV status at delivery may not reflect BV status earlier in pregnancy. In addition, there are logistic problems, as collection of the specimens at delivery will need to rely on non-study personnel and may be inconsistent. Finally, if these specimens are not clinically indicated, who will pay for them? The addition of this element does not seem to add substantially to the protocol.

It is unclear as to the extent of community integration that is involved in this study. As far as one can tell, the community involvement consists of the study being conducted in community clinics, with 4 community liaisons being involved. One could not even find where the community liaisons were funded as part of the grant.

Finally, some aspects of the study still seem unrealistic, although it might be the case that community involvement might help here. For example, the women are supposed to keep detailed diaries as to their medication regimen. It seems unlikely that this will entirely successful, yet not provisions or discussions are made which address this issue, which goes at the heart of treatment compliance.

Another issue that is not clear relates to the community workers. The budget continues to have funding for 2 workers for 30 hours each while the grant proposals indicate that each of the four clinic sites will have a 20 hour worker. The reason for the discrepancy should be explained.

Overall, this revised application is an improvement. Concerns, however, remain about adequate power and various aspects of the conduct of the study. The recommendation, nevertheless, is for approval with the conditions that: (1) The plan to screen women in the unscreened group at delivery be eliminated; and (2) that the PI addresses in writing the issues described in this summary statement.
Responsiveness of CHIP to Children With Special Health Care Needs

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Project Number  R40MC00165

Project Period  8/1/1999-7/31/2002

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Summary

Statement of the Problem

Statement of the Problem is not available for this project.

Research Questions or Hypotheses

The purpose of this project is to examine in detail the structure of freestanding state CHIP programs and their implications for access to comprehensive services for children with special health care needs. The overall focus of the study is the 25 states that as of April 1999, were approved by HCFA for the establishment of freestanding programs for some or all targeted children. In the first phase, the study will gather detailed descriptive data and carry out a series of qualitative site studies regarding implementation of freestanding programs. This phase is necessary to determine whether and the extent to which freestanding programs depart from Medicaid principles and in which dimensions (e.g., eligibility, entitlement, benefits, coverage, conditions or participation for managed care plans, protections against erroneous denials and benefit termination). In the second phase, the study will use initial findings to model coverage for purposes of using MEPS to simulate the design features of freestanding programs in order to study their effects on key classes of children with special physical and...
mental health needs, using variable definitions of children with special health care needs.
Hypothesis 1: States with freestanding programs will depart from Medicaid structure in certain basic ways that have implications for coverage for children in general and children with special needs in particular. These points of departure include entitlement status of coverage, eligibility criteria, depth and extent of coverage and contract elements in the case of MCE agreements.
Hypothesis 2: Freestanding programs will offer less coverage for children with special health care needs.

**Study Design and Methods**

1. In depth descriptive studies of characteristics of freestanding programs and comparative analysis of coverage in Medicaid and freestanding states. Data sources include state plans, state enabling legislation and implementing regulations, managed care service agreements.
2. Qualitative study of CHIP implementation in freestanding and Medicaid expansion states to identify issues affecting access to care for children with special needs; semi-structured interviews with key informants in 6 states. Data sources include site studies and telephone interviews.
3. Analysis and modeling of coverage in freestanding states, using MEPS data and related databases. Data sources include MEPS, NHIS, ARF

**Pre-Award Evaluation**

**Evaluator 1**

*Originality and Importance*

No statement of originality and importance.

*Regional and National Significance*

No statement of regional and national significance.

*Scientific and Technical Merit*

This well-written proposal has several major strengths. First, it focuses on the fundamental choice of states to use CHIP to extend the Medicaid program, or to develop an alternative, non-entitlement, freestanding program that may use different eligibility criteria and whose benefits and insurance structures may more closely resemble those found in traditional commercial insurance plans.

Second, the investigators provide an excellent discussion of the key differences between the requirements of Medicaid and the options available to states for freestanding CHIP programs. These differences are important to document because of the constraints that Medicaid places on the design of programs and the preferences of families for non-Medicaid coverage.

A third major strength of the proposed study is the ability to piggyback the current annual ongoing point in time study of Medicaid managed care contracts that is conducted by the Center for Health Services Research and Policy (CHSRP) with data collected about the features of freestanding CHIP programs. This ongoing study has not only given CHSRP researchers experience in abstracting contract documents, but it also insight regarding the departures of the typical Medicaid managed care contracts from the requirements of Medicaid. It also points to the approach that many states use in dealing with MCOs to supplement their plans with additional services and benefits, particularly wraparound services traditionally available from health departments. The investigators use their experience from this study to indicate the types of information they plan to abstract about eligibility from the legal documents of states.

Despite these major strengths, there are also some important weaknesses of the proposed study. The first is the lack of details about some aspects of Part I of the proposed project, particularly with regard to the actual states that will be surveyed, the specific data collection instruments, issues related to confidentiality of human subjects, and the plan of analysis for the descriptive studies. While, in general, it is likely that the investigators will do an excellent job with filling in details as the
project is developed, their omission is important, particularly with regard to the analysis of data.

The major weaknesses of the proposed study involve Part 2 of the proposed project. These weaknesses relate to the many implicit assumptions inherent in this part of the study. The most important is the investigators' inability to directly assess the impact of CHIP in states with freestanding programs and the presumption that data will be obtained in Part 1 which will actually inform the analysis of the national databases. It is not evident that there will, in fact, be enough distinct features of either the eligibility criteria or the benefits structure of freestanding CHIP programs to relate them to the information in the national databases and, in turn, to look at their effects on access and utilization of care. In addition, the investigators provide a laundry list of measures of access and utilization available from MEPs and indicate that they plan to look at all measures without prioritizing any of them. Surely, issues related to the content of services available are more important as measures of access than waiting time at the site. The investigators do the same for various measures that may define the population of children with special health needs.

Part 1 of the study is descriptive, involving three components, each of which draws on the results of the previous one. The investigators specify the eligibility criteria that will be abstracted from legal and other publicly available documents. They will develop, review, pre-test the instrument to be used to abstract these documents and will collect data using the instrument in the first project year. This timeline seems somewhat ambitious given that there is no discussion of how the documents will be accessed from the states, nor whether or not states have agreed to provide the needed documents.

A major concern related to this component is that the plan for data analysis only involves detailed tables being prepared. There is no discussion of the specific aspects of eligibility that will be targeted in the analysis, nor what specific methods will be used to prepare the detailed tables. Since some of the results from this component will be used to inform the analysis of the MEPS, this information is important in evaluating the potential usefulness of data from this first component. The investigators also note that, with the appropriate data on the value of Medicaid deductions and disregards, it would be possible "to simulate the additional reach of a state's CHIP program were its gross income standard to be increased in order to offset the loss of a disregard." There is no evidence in the proposal that the data that will be obtained in component one, as it is currently described, will yield this type of information, particularly because there is no mention of the population data needed for such a simulation.

Component two addresses an important aspect of the freestanding CHIP programs, their benefits structure, and the investigators do a good job of pointing out the potentially important effects of variations in benefits coverage. This component is an extension of the data collection in component one, but deals with the benefit structure of the CHIP program rather than eligibility criteria, and draws upon data from their ongoing annual survey of Medicaid managed care. This ongoing study will be expanded in 1999 to include contracts between state CHIP agencies and MCOs from states with freestanding, non-Medicaid CHIP programs. Although not explicitly stated and, accordingly somewhat confusing to the reader, it appears that this data collection effort will provide data for both components one and two. The investigators indicate that they will supplement the contract database with data from state statutes, regulations and program guidelines for both Medicaid and freestanding CHIP programs. They will also determine the extent of available wraparound services for families of children in CHIP and Medicaid. While this is very important information to obtain, the investigators do not discuss their strategy for obtaining it.

There is no data abstraction instrument included in the proposal for component two, despite the fact that the investigators are already conducting an ongoing study for which some instrument must be used to collect data. To the investigators credit, however, they do provide a list of specific items they plan to obtain under the categories of managed care and residual state plan coverage under freestanding CHIP programs and the conditions of participation of MCOs in freestanding programs. Within each of these categories, a number of features of CHIP freestanding programs are to be addressed.

Like component one, a major missing piece of the methods in this component is the analysis plan. This is particularly disturbing because this second component is the only one in Part 1 for which hypothesis testing can actually be conducted. The proposal mentions only that reports will be prepared that compare benefits and conditions of participation across freestanding CHIP programs and between CHIP and Medicaid programs. Will statistics actually be used to evaluate these comparisons. Is hypothesis testing really the focus here, or is this component, like one and three, primarily descriptive?
Component three of Part 1 of the proposed project involves case studies in up to six states with freestanding CHIP programs and in which the CHIP programs use Medicaid extension as its approach. While the investigators indicate that they are studying the 25 states with HCFA approval for freestanding CHIP programs, component three appears to broaden the number of states for which sampling will be performed to ones which use Medicaid extension in their CHIP program. If this is the case, are data being collected in the ongoing Medicaid study for these latter CHIP programs?

There are a number of other concerns about this component. First, the investigators do not provide a justification of how the information from this component adds to that obtained in the first two; their list of questions to be addressed can be asked of all states. Secondly, while only up to six states will be studied, there are 15 criteria to be used to select these states. Some priority needs to be placed on the most important criteria. Thirdly, using only six states does not seem adequate to cover the variability across states that is likely to be seen in the freestanding CHIP programs, their current Medicaid programs, and other issues that may affect their decisions to choose various options. Consideration should be given to increasing the number of states to yield more meaningful results. This can be accomplished by reducing the number of stakeholders that will be the focus of key informant interviews. This component is likely to yield little valid information about the effects of CHIP variations. The focus of the key informant interviews would best be placed on informants with decision making power politically and who administer the programs and with providers that may be responsible for extended services for children, such as safety net providers or providers of wraparound services. Information collected from CHIP enrollees with special needs and, to a lesser extent, from consumer or advocacy groups may be unreliable, given the need to obtain a large and representative sample of enrollees to obtain meaningful data for this group.

Again, the analysis plan is a problem for this component because there is none provided. Given the number of stakeholder groups represented in the case studies and the use of semi-structured interviews, a carefully conceived analysis strategy is important here. This strategy needs to address the key domains that will be summarized across key informants as well as the use of appropriate techniques to analyze qualitative data.

As noted above, a major weakness of the proposed project is Part 2, which uses national databases to simulate the effects of the eligibility criteria and benefits structure of freestanding CHIP programs. There are also problems with inferring that the impact of CHIP features on individuals who now have insurance through CHIP would yield the same effects of the insurance features for families with children who had insurance before CHIP. Because actual data about children enrolled in CHIP will not be available, the investigators will not have information about the differences in characteristics of CHIP enrollees versus insurance recipients in MEPS to understand how they might influence the effects of eligibility or coverage. It is difficult to envision with these constraints and those noted above that there would be meaningful results from Part 2. Moreover, these analyses could lead to erroneous conclusions about the potential impact of freestanding CHIP programs.

The investigators, themselves, point out limitations of Part 2 related to the fact that the MEPS data were not fully released at the time of proposal writing and related to the need to preserve the confidentiality of human subjects with linking data from the NHIS, MEPS and ARF.

In the discussion of issues related to human subjects, the investigators do not address the procedures to be undertaken to protect the rights of the respondents in the case study. Even with semi-structured interviews which primarily address issues related to public programs, procedures still need to be used including disclosures or informed consent forms and assurance of anonymity of respondents.

The investigators appear to be highly capable of undertaking the proposed research, particularly for Part 1, based on their previous experience with similar studies and their track record of disseminating the results of their studies. The one area of deficiency is related to the lack of individuals with experience in data analysis, especially with regard to qualitative data. This expertise needs to be added to the study team.

The budget for the proposed study does not adequately cover the scope of personnel needed to complete project tasks. It includes a number of investigators with large salaries on the project for small amounts of time, but a limited number of individuals who will actually conduct the daily work, and be involved in data abstraction, data entry or data analysis. An example is the project director who will spend 35 percent of his effort on the project, but who appears to be highly overqualified to be a project director. Sara Rosenbaum, the Principal Investigator, is included in the budget for 10 percent
effort in year one and 5 percent in years two and three. Is this adequate time to fulfill her role as PI? Also, who and what is the role of the person listed as TBN for $20,000 on the personnel line in the budget?

Recommendation:

Approval with the following conditions:

1) The investigators eliminate Part 2 of the proposed study. The number of assumptions required in this study, and the lack of a focused strategy for data analysis, make the potential results of this part not very meaningful.

2) The study methods for Part I be more clearly specified including the following:

- The 25 states who were approved by HCFA for freestanding CHIP programs;
- The methods that will be used to gain participation of states;
- The details related to the acquisition of contracts and other documents from states and the extent to which this is done only as a part of the ongoing study or is an additional contact and data collection effort with states;
- The data abstraction instrument that is currently used in the ongoing study and recommended modifications of or additions to it for the proposed study
- An analysis plan for components one and two that lays out the potential information that will be gleaned from the data and the specific variables that will be compared between Medicaid and free standing CHIP programs
- A reconsideration of a larger number of states to be included in the case studies and a reduction in the range of key informants to be interviewed
- An analysis plan for the third component that indicates some of the domains that might be included from the data and strategies to reduce and compile the qualitative data.

3) A revised budget that includes data analysts and other appropriate research staff to complete the scope of the work in Part 1 and eliminates the subcontract with the Children’s National Medical Center (CNMC) for Part 2 without increasing the cost of the project.
Summary

Statement of the Problem

Improving access to prenatal care is viewed as a key strategy for decreasing the incidence of low birthweight and infant mortality in the United States. However, a significant portion of the Nation's women, particularly low-income and minority women, still fail to obtain adequate prenatal care. In fact, approximately 32 percent of African-American women who start prenatal care by the fourth month of pregnancy receive less than adequate care. One factor that may affect prenatal care utilization is patient satisfaction with care. Studies of prenatal care characteristics that affect women's satisfaction have had a host of methodological problems, and only two studies have considered the relationship between satisfaction and prenatal care utilization. The information gained from this study can be used in the design of interventions or in the development of policy changes to increase the use of prenatal care by pregnant women, particularly African-American women.

Research Questions or Hypotheses

The following hypotheses will be tested:
1. The characteristics of prenatal care are related to a woman's satisfaction, independent of the woman's personal characteristics.
   a. Some care characteristics (e.g., patient-practitioner communication, waiting time at the site of care) will have a stronger relationship to satisfaction than others; and
   b. The relationship between care characteristics and satisfaction does not differ between African-American women who receive medicaid assistance and African-American women who do not receive medicaid assistance.
2. Satisfaction with prenatal care is associated with subsequent prenatal care utilization, independent of the woman's personal characteristics (including her barriers to prenatal care).

Study Design and Methods

Information on care characteristics and satisfaction will be obtained through face-to-face interviews. Information on subsequent prenatal care utilization will be obtained through retrospective medical record review. Questionnaires for the interviews will be developed specifically for the study; medical record data will be abstracted from the clinical prenatal and delivery records maintained at the health care delivery sites that will be participating in the study. During the interview, each study participant will be asked about the characteristics of her prenatal care experience and her satisfaction with that care. Following delivery, each woman's medical chart will be abstracted to obtain information on prenatal care utilization.

Population and Sampling Plan

The study sample will comprise 500 African-American women obtaining prenatal care at one of two health centers that are part of a large managed care organization. In 1994, this health plan began serving the medicaid population in addition to its traditional commercial and medicare clients. Approximately half of the sample will consist of clients receiving medicaid assistance; the other half will be clients not receiving medicaid assistance. Women will be recruited at each of the two sites on the day of their prenatal care appointment. To qualify for the study, the following criteria must be met: Women must be 18 years of age or older, length of gestation must be less than 29 weeks, and women must consent to participate. Following her prenatal care visit, each woman will complete a face-to-face interview (35–40 minutes in length) with an experienced interviewer in a private space at the health care site. To ensure that the study reflects a cross section of the experiences of African-American women who use prenatal care, the study will include women of varying gestations and with varying numbers of visits at the time of interview.

Analysis Plan

Plans for data analysis include the use of univariate, bivariate, and multivariate statistical techniques, including model fitting and determination of the validity and reliability of the study measures.

Pre-Award Evaluation

Evaluator 1

Originality and Importance

This study should contribute substantially to an understanding of the factors that lead some women to seek and sustain prenatal care. The study will seek to examine those characteristics or attributes of prenatal care that increase satisfaction and to explore the relationship between satisfaction and subsequent utilization of prenatal care. The published literature is clear about the positive effects of prenatal care on perinatal outcomes. This study will also address a major void in the literature: factors that predict sustained use of prenatal care. The answer to this question could help identify preventive strategies that might ultimately have an impact on high rates of infant mortality and low-birthweight births.

Regional and National Significance

The proposed study is an extremely important one. Issues related to satisfaction with and utilization of prenatal care are important to the Maternal and Child Health Bureau's programs, and this project has both regional and national significance.


Scientific and Technical Merit

This submission is a revision of an application reviewed during the June 1996 cycle, when it was recommended for disapproval. The revision has been judged by the reviewers to be quite responsive to the concerns raised in their prior review, with noticeable improvements in the organization and presentation of the information. A 3-year investigation is proposed.

The investigators have revised the conceptualization of the problem. The study now focuses on characteristics of care related to satisfaction with prenatal care among African-American women, the contribution of satisfaction with care to subsequent prenatal care utilization among those who initiate care, and the possible differences in these two relationships according to payer status (medicaid versus non-medicaid). This focus of the research is also described more clearly. On the basis of a pilot study funded by the Agency for Health Care Policy and Research (AHCPR), the care characteristics have been revised to retain only those expected to vary in the study sites. Generally, these are appropriate changes that address the reviewers' earlier concerns.

The original proposal for a comparison between Mexican-American women and African-American women has been replaced by a comparison of medicaid and non-medicaid participants among a sample of African-American women. This change not only addresses the issue of inadequate sample size in the Mexican-American component, but also proposes to answer an interesting question on differences in determinants and consequences of satisfaction between women who receive medicaid assistance and those who do not.

Recruitment problems have been addressed by restricting recruitment to the Humana clinic sites and to the use of research staff as recruiters. This further eliminates the problem of determining risk status as a criterion for inclusion, because Humana treats both high-risk and low-risk clients. Further, the use of research staff addresses concerns about confidentiality, namely the concern that a woman's response to questions about satisfaction with care will become known to her provider. Questions about recruitment still remain. For example, how will African-American racial status be determined? In addition, the study design calls for enrolling the "next" non-medicaid client after enrolling a medicaid client. If the selected woman declines, how will a replacement control be identified? Although the application indicates that one researcher will be able to interview both women, it is not clear that recruitment will be optimized if a 35- to 40-minute interview is needed for women scheduled essentially at the same time for appointments.

The previous reviewers raised concerns about the potential for bias, especially recall bias, given the inclusion criteria described in the application and the choice of women who had made two visits since enrollment. The revised inclusion criteria would include all African-American women who are age 18 or older at any visit before their 28th completed week of gestation. The number of visits at the interview and the length of gestation at time of interview will be considered in the analysis. Questions concerning the timing of the interview and subsequent measures of satisfaction have been addressed by more rigorous description of the interview and the medical-record abstraction protocol.

The statement of the hypotheses has been revised, and the current statement is clear and presented in terms of relationships between characteristics of prenatal care, personal characteristics of the client, and the impact of these two factors on client satisfaction with care and subsequent utilization of care. The investigators have been careful to focus on the issues of measuring satisfaction at an early point in prenatal care (less than 29 weeks) and on subsequent utilization. The power and the sample size considerations are much improved. Data from the AHCPR-funded study carried out by the investigators have contributed to estimation of correlations on which sample size is based. Refusal rates are estimated at 8–10 percent, which seems acceptable. Finally, the methods of statistical analysis have been revised in accordance with the changes in the hypotheses. The approach to analysis is sound.

The time schedule seems appropriate, and confidentiality of clients seems well considered. The investigators are capable and have the necessary experience to carry out the study.

The revised application is vastly improved and the investigators have been responsive to the concerns identified in an earlier review. The recommendation is for approval, with two conditions: the investigators need to describe in more detail how the control subjects are going to be selected, and the budget must be reduced by 15 percent.
The Epidemiology of Abruptio Placentae

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Swedish Medical Center

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Project Number  R40MC00187

Project Period  9/1/2000-8/31/2002

Costs

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Summary

Statement of the Problem

Abruptio placentae, the premature separation of the normally implanted placenta, is a life threatening obstetric complication of pregnancy. The etiology of abruptio placentae is unknown although results from previous studies suggest some risk factors, several of which may be amenable to modification. Briefly, results from several small studies suggest that low maternal intake of folate and other B vitamins may be associated with an increased risk of abruptio placentae. There is also some evidence suggestive of an association between maternal iron deficiency anemia and increased risk of abruptio placentae. We are working to build on this body of work by utilizing a maternal second trimester serum repository, and a hospital discharge diagnosis database to study the epidemiology of abruptio placentae in a population of 13,000 women giving birth at Swedish Medical Center. The ultimate goals of our research are to increase the ability to identify pregnant women at high risk of experiencing abruptio placentae, and to further understand the mechanisms by which abruptio placentae occurs. Results from our research have a very high potential for yielding etiologic and clinical information that may prove to be effective in the identification of subgroups of women at greatest need for specific preventive interventions and specialized clinical care.
**Research Questions or Hypotheses**

We are evaluating the relation between risk of abruptio placentae and biological markers of low folate, vitamin B6, vitamin B12, and iron (as measured by serum iron and transferrin receptor). In addition to addressing the primary aims, data collected for this on-going study will allow for a reevaluation of the association between abruptio placentae risk and other putative risk factors. Risk factors under consideration include maternal hypertensive disorders, maternal age, grand multiparity (parity ≥ 5), prior history of stillbirth and other adverse pregnancy outcomes, low educational attainment, and multifetal gestation.

**Study Design and Methods**

Within a large prospective cohort study population, we are conducting a nested case-control study to address our research aims.

**Population Description and Sampling Plan**

Maternal serum biological markers and data from medical records are being assessed for approximately 240 abruptio placentae cases and 960 controls as part of our aim to better characterize the epidemiology of abruptio placentae.

**Analysis Plan**

Because the distributions of the biological markers under consideration have not been thoroughly described in the literature, we will commence with an exploratory, descriptive analytic approach, which will summarize and compare the distributions of the markers in cases and controls. Our subsequent primary analyses will include stratified and multivariate logistic analysis of the dependence of risk of abruptio placentae on marker levels. The analyses will focus on evaluating the relation of maternal nutritional and medical characteristics with risk of abruptio placentae. Results from the proposed study could have practical significance in developing alternative, practical preventative interventions for abruptio placentae and other adverse pregnancy outcomes (e.g., preeclampsia and preterm delivery). Folate, other B vitamins and iron could be easily manipulated in the diet either by supplement use or by specific choice of foods if evidence from this and other studies indicates a benefit.

**Pre-Award Evaluation**

**Evaluator 1**

**Originality and Importance**

This work is made possible by the presence of a serum repository that was set up in 1993. Dr Williams and others have used this serum repository and other data from medical records and linked vital records to study the biochemical antecedents and genetic markers of preeclampsia. This database provides an extension of that research to a different endpoint, AP. AP is the second most important cause of perinatal mortality.

**Regional and National Significance**

If successful, results of this study would be of regional and national significance.

**Scientific and Technical Merit**

The literature review is carefully prepared, critical, convincing and provides a clear statement of the public health importance of AP.

Clear exposition of the primary dependent variable, primary independent variables and potential confounding variables. The choice of these variables was substantiated by the literature review and although many are suggested, the investigators are
aware of the problems of so many variables. The assays for each tests are carefully described and standard tests appear to be used. (This reviewer is not the best judge of which tests should be used!!). The investigators have a great deal of experience in the execution of case-control studies of this kind and have established the procedures and support needed to carry them out efficiently and effectively. The study design is appropriate considering the incidence of AP.

The selection of controls by stratified random sampling is appropriate and has been done before by these researchers. Sample size estimates are appropriate. Exclusions include 15% that can't be linked to vital records, 5% who are excluded with multiple births and repeat pregnancies, and 5% for whom the diagnosis of AP present or absent can not be made.

Power studies suggest that a 2 - 2.5-fold increase in risk of AP can be detected with the sample size provided. This varies somewhat depending on the prevalence of the exposure covariates. Further, three-fold increases in the effect modifiers can be detected with power slightly below 80%. Data analysis plans are well described. Both linear and logistic regression models are planned which provide for additive and multiplicative models.

There may be some problems with some of the confounders that may be intermediate in the process. It is assumed that the investigators are experienced enough to be able to handle this.

These investigators have excellent biosketches, and have worked together on previous studies. An appropriate team of project coordinators, data analysts, programmers, abstractors and laboratory technicians support them.

The PI effort, the Co-PI effort at .25 is appropriate. The Project Coordinators at 1.2 FTE's seems a bit high but the justification is reasonable. The abstractors seem appropriate for the sample size. The lab tech is appropriate. I thought that these samples were already frozen in the serum bank- There is justification for the freezer but I'm in no position to argue. Someone should ask. The laptops are ok. Supplies seem appropriate except that $1000 per file cabinet seems a bit high. Someone familiar with the costs of drug tests should review the cost of sample in this study. It is not possible for this reviewer to determine whether these costs are excessive on not. It would seem the costs of this grant are high, Seek and ye shall find.

Evaluator 2

Originality and Importance
No statement of originality and importance.

Regional and National Significance
No statement of regional and national significance.

Scientific and Technical Merit
This is a well written proposal whose strength is the potential use of a repository of samples of 41,977 pregnant women during the second trimester. These samples were collected for clinical purposes and the remaining specimens were kept for future use. There is a large clinical database from which the investigators will obtain the information for this study by chart abstraction. The sample size will consist of 360 "cases" of abruptio placentae and 720 controls. Cases will be defined on the basis of clinical symptoms of AP since there is no "gold standard" for this diagnosis. The criteria will include: 1) antepartum hemoglobin after 20 weeks gestation, 2) uterine pain or tenderness, 3) fetal distress or death, 4) retroplacental blood clot. The data obtained from the medical abstraction will be reviewed by co-investigators, D. Luthy, MD and A. E. Bastaursi, PhD who will classify AP into three classes based in severity of signs and symptoms. These classes I, II, and III will be characterized based on severity of bleeding, severity of uterine tenderness, tetanic contractions, and maternal hemodynamic alterations. In our opinion, this exercise might not be as productive to the investigators for several reasons and it is our concern. First, there are 15 medical institutions (hospitals) from which these charts need to be requested, it is not known if the protocol has been approved in all those places. Second, retrospective review of clinical data might not include the type of information the investigators are defining such as: tetanic contractions, severe uterine tenderness, etc. Third, who among the two reviewers will have a "final decision" in terms of assigning a classification? What if the opinions are conflicting? There is no pilot information about the feasibility of obtaining such information. This is crucial since all
correlations and statistical analyses will depend on who is defined as case," and if cases are not selected appropriately this might be a major bias. The same issues apply to "controls." These issues need to be clarified before the project is underway.

The scientific merit, assembly of investigators and consultants, and costs are appropriate except for a -80' freezer justified in the basis of needed space for samples.
Three-Generation Intervention Among Adolescent Mothers

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Project Number R40MC00122

Project Period 1/1/1996-6/30/2002

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Year 2010 Objectives
9.7, 15.33, 16.8, 19.4

Study Design
Experimental

Time Design
Longitudinal

Care Emphasis
Interventional

Population Focus
Infants, Toddlers, Adolescents (pregnancy-related), Parents/Families/Mothers/Fathers

Race/Ethnic Focus
African-American

Priority Research Issues
3.1.3, 6.3.2

Summary

Statement of the Problem

In 1990, nearly 1 of 8 live births (12.8 percent) was to an adolescent mother. Adolescent parenthood alters the developmental life course of adolescents and increases the risk of behavioral and developmental problems among their children. The adolescent tasks of emerging autonomy, career development, and formation of mutually supportive relationships are interrupted with the birth of a child and the responsibilities of parenthood. In the past, pregnant adolescents often married and lived with their husbands, but current trends indicate that adolescent mothers often remain with their families and share caregiving with the baby's grandmother. African Americans have a tradition of extended families, which may partially protect them from the negative consequences often associated with single parenting. Grandmothers are often conceptualized as providing support, nurturing, and sociological, financial, and legal stability; however, little is known about the challenges presented by multigenerational caregiving.

The previous study (MCJ-240621, Growth and Development: Longitudinal Followup, September 1, 1992–August 31, 1997) demonstrated the efficacy of home visiting in promoting parenting and early development among drug-abusing mothers and families of infants with failure to thrive. This research extends the work of that study into a three-generational
Research Questions or Hypotheses

This research project study seeks to study the following issues:

1. Through qualitative methods of interviews and focus groups, we can identify the ethnotheories of adolescent mothers and grandmothers regarding parenting, adolescent development, and child rearing.
   a. This information can be used to develop an intervention guide based on ecological, family systems, and personal-social theories.
   b. The information can also be used to produce a videocassette directed toward enhancing relationships between adolescent mothers and grandmothers.

2. Adolescent mothers and their families who receive a 1-year community-based intervention program will accomplish adolescent tasks (educational/career preparation, relationships with grandmother, and risk behavior, including contraceptive use and fertility) and parenting tasks (preventive health care, household/mealtime routine, mother-infant interaction during feeding, and child-oriented home environment). In addition, children of mothers who receive the intervention will demonstrate better growth, development, and mother-infant interactions during feeding.
   a. When confronted with a potential conflict, mothers and grandmothers who receive the intervention will be better able than those in the control group to reach a compromise that demonstrates concern for the long-term relationship more than the immediate problem.

3. Based on Bronfenbrenner's person-process-context models, secondary hypotheses will be tested to examine the mechanisms underlying the impact of the intervention.
   a. Consistent with the psychosocial perspective, mothers with relatively well-developed social skills who report high levels of self-esteem and family support and low levels of depressive symptoms and parenting stress and who view their child as having an easy temperament will be most likely to benefit from the intervention.
   b. Consistent with the family systems perspective, adolescent mothers who have a supportive, open relationship with the baby's grandmother will be better able than those without such a relationship to negotiate caregiving roles with other family members to ensure that their children are adequately cared for and to develop both their adolescent and parenting roles.
   c. Consistent with the ecological perspective, adolescent mothers who remain in school and/or access community services (e.g., family support programs) will be better able to enhance their adolescent and parenting roles and promote their child's development than will adolescent mothers who are not involved in these services.

Study Design and Methods

This research extends previous work demonstrating the efficacy of home visiting in promoting parenting and early development among drug-abusing mothers. This study encompasses a two-phase, three-generational project involving adolescent mothers, infants, and grandmothers.

Phase 1 is a qualitative examination of the ethnotheories of adolescent mothers and grandmothers regarding parenting, decision making, and social problem solving, with an emphasis on the mealtime context. This phase culminates in the development of an intervention guide to be used in the second phase and in the production of a videocassette directed toward enhancing communication and conflict resolution between adolescent mothers and grandmothers.

Phase 2 is conducted in partnership with community family support organizations and includes a three-generational developmentally oriented intervention based on three theoretical perspectives—ecological, family systems, and psychosocial. The 1-year intervention, designed to promote the developmental outcomes of adolescent mothers and their infants, consists of biweekly home visits, monthly support groups, and coordination with community services. The intervention includes the videocassette produced in the first phase and emphasizes social problem-solving skills, open and direct communication, and emotional support, using mealtimes as a primary context.

Baseline data are collected at delivery and outcome data are collected midway through the intervention, at completion of the intervention, and 1 year later. Multimethod assessment procedures are used, including observation, self-report, and
performance on standardized measures. Maternal domains include adolescent tasks (educational preparation and risk behavior) and parenting tasks (preventive health care, household/mealtime routine, and mother-infant interaction during feeding). Infant domains include growth, development, and mother-infant interaction. Grandmother domains include the relationship with the mother and infant.

**Population and Sampling Plan**

Phase 1: Ethnotheories. For the ethnotheory phase of the project, 20 adolescent African-American mothers of infants under 12 months of age will be recruited from two urban clinics that provide services through the Special Supplemental Nutrition Program for Women, Infants and Children (WIC). Eligibility criteria for WIC services are based on financial resources and nutritional status. Two WIC clinics were chosen as recruitment sites to ensure representation of adolescent mothers of low-income status, including those who have not returned to school.

Phase 2: Intervention. In the second phase, 180 adolescent mothers and infants from the full-term nursery at the University of Maryland Hospital (UMH) will be recruited. UMH is a university-based teaching hospital that serves a large portion of inner-city Baltimore. African-American women under 18 years of age account for about 20 percent of the approximately 2,100 births annually at UMH. Recruitment will extend over 18 months at the rate of 10 per month.

Maternal eligibility criteria for phase 2 include the following: African-American women under age 18 who are giving birth for the first time, who have no recognized psychiatric disorders, who intend to provide primary care for their baby, and who are living with a grandmother or "grandmother-figure." The study has limited the recruitment to adolescent mothers who are living with a grandmother at the time of delivery in order to study the communication that occurs as adolescents enter parenthood. Infant eligibility criteria include full term (37 weeks), birthweight appropriate for gestational age, and absence of identified congenital or disabling conditions.

**Analysis Plan**

Phase 1: Ethnotheories. The qualitative data will be entered into a computer as both text and numeric files. Textual data will be analyzed using the text search and retrieval program DtSearch. Analysis of the data will involve pattern searching, content analysis, and the derivation of summarization figures on key themes, including: (1) Parenting roles for mothers; (2) meaning of parenting for mothers; (3) decision-making models regarding parenting roles; (4) local models and perceptions relating to adolescent/young adult female role development, parenting responsibilities, and child development; (5) local patterns of communication and information sharing regarding parenting; (6) influence of personal child-rearing history on decisions regarding parenting; and (7) influence of others (e.g., fathers, grandparents) on decisions regarding parenting.

Phase 2: Intervention. The initial step in the analysis will be to examine equivalence across the intervention and control groups. Because the groups are assigned using a randomization procedure, no differences are expected. However, if there are differences in demographic variables, they will be used as covariants in the analysis. Initial analyses will include correlations, means, and standard deviations for all variables. Repeated measures multivariate analysis of covariance (RM ANCOVA) will be used to assess changes in the primary adolescent and child variables that can be measured in a continuum over time (hypothesis 2). Maternal dependent measures are: Relationship with other family members, household and mealtime routines, and interactions during mealtime. Child dependent measures are: Development, interactions during mealtime, and behavior. Intervention group is the independent variable. The within-subject factor is time, and an interaction between groups (intervention vs. control) by time would indicate that the two groups responded differently over time and would suggest an effect of the intervention. Logistic regression equations will be used to examine changes in binary outcomes over time, controlling for baseline values. Maternal categorical variables include educational achievement, risk behavior, and preventive health care. Child categorical variables include growth (adequate vs. insufficient/excess growth).

Hypothesis 2a involves the problem-solving skills of mothers. Because the scores are categorical, chi-square analysis will be used to examine problem-solving skills at each data collection point and logistic regressions will be used to examine changes in problem-solving skills over time. The independent variable will be intervention status. Multivariate analyses of variance using intervention group as the independent variable will be used to assess the direct effects of the intervention on mother and child outcome variables (hypothesis 2) and the mechanisms underlying the impact of the intervention (hypothesis 3). The research team will regress intervention status and the intervening variables and their interactions on the outcome variable under investigation. Structural equation modeling (SEM) also will be used to examine the theory behind hypotheses 3a, b, and c by determining
whether the intervening psychosocial, family systems, and ecological variables are related to the dependent variables of adolescent role, parenting role, and child development.

**Pre-Award Evaluation**

**Evaluator 1**

**Originality and Importance**
In 1990, almost 13 percent of live births were to adolescent mothers. Many of these women and their offspring are at risk for negative life outcomes. The development of effective interventions targeting this population has major national public health implications.

**Regional and National Significance**
This proposal addresses a topic that is of regional and national significance.

**Scientific and Technical Merit**
As noted in this application, most interventions for adolescent parents have focused on the adolescent mother, ignoring the relationship between the adolescent and her own mother. Yet, maternal grandparents are often central figures, organizing the family, supporting the adolescent, and sometimes assuming the role of primary caregiver for the infant. Given that these relationships can sometimes be detrimental (rather than supportive) to the adolescent mother and her infant, it is important to understand how to assist the entire family system to move toward optimal relationships that enhance the development of the infant.

This is a well-documented and well-written proposal. Its strengths stem from the investigators' expertise in conducting home-based interventions with African-American adolescent mothers and their families. The investigators also have extensive experience with innovative methods of data collection and have the extensive community-based networks necessary to conduct the proposed study. A major strength of the proposed research is the random assignment of adolescents to the intervention and control groups. The proposed work builds on successful intervention studies conducted by the investigators. The experience of the research team in conducting similar studies bodes well for their ability to conduct this complex intervention research. The study design is well conceptualized and the research measures are state-of-the-art and appropriate for the study questions. Study hypotheses are conceptually driven and clearly stated. The application is comprehensive, clear, and easy to read. Although this is an excellent proposal, a few issues need to be addressed before the study is implemented. Investigators discuss numerous strategies to minimize threats to the research design, including examiner bias, comparison group adequacy (i.e., validation of receipt of intervention), chronology bias (age of mother), adequacy of timing of observations, continuity of measurement (measures that may become outdated because of developmental changes in the child), and attrition. Although this list suggests that the investigators have thought through many potential problems, can the planned home-based assessments of controls threaten the validity of the design? In other words, the intensive nature of the proposed home assessments may actually operate as a modified intervention for controls. This may be particularly problematic since the single most important independent variable is intervention status. The investigators plan to study African-American families. The application states that studying children within one cultural context minimizes the need for controls for processes that vary across different environmental/cultural contexts. The application also notes the rich history of African-American parenting and child-rearing values/traditions that may be somewhat distinct from those of the majority culture. This perspective is a potential strength of the proposed research, but, unfortunately, culturally relevant aspects of the conceptual framework are not developed in the application. In addition, the literature on African-American families is not reviewed. The qualitative examination of ethnotheories provides a strong mechanism for tapping culturally based parenting and problem-solving strategies. However, a more elaborated discussion of the cultural aspects of the proposed intervention is needed. In addition, a clear statement is needed concerning the group of families for whom the intervention is appropriate. It is assumed that the intervention will be specific to African-American families, with no generalization to families from other cultural groups. Although the list of intervening variables for maternal psychosocial characteristics is quite comprehensive, it appears that similar information about the grandmother will not be collected. This is surprising, given this study's emphasis on family systems and the discussion regarding the idea that adolescent pregnancy is viewed as an "off time" occurrence for both
adolescents and their parents. Variations in grandmothers' abilities to cope with the adolescent mother and the grandchild suggest important individual differences. Thus, the assessment of variables, such as depressive symptoms, self-esteem, social skills, social support, etc., could add important insights into the relational strengths and impasses experienced between the adolescent mothers and the grandmothers.

The complexity and variety of roles that grandmothers assume in families of adolescent mothers is not adequately reflected in the proposed intervention. The range of caregiver roles of the grandparents is not clearly defined or addressed. Would the intervention strategies be the same across differing family constellations? For example, would the desired intervention be identical in families in which (1) the grandparent, rather than the adolescent mother, is the primary caregiver; (2) the adolescent takes primary responsibility for the infant, and the grandparent provides support when needed; or (3) a father figure is prominent in the adolescent's life? Would the desired intervention outcomes be the same for families with different distributions of child care roles and responsibilities?

There is also some question as to whether an intervention focusing on problem-solving is really powerful enough to intervene in the relationship between the adolescent and her mother. What if this relationship is highly conflictual or otherwise troubled? How will the investigators make sure that, by intervening in the family system, they are not causing harm, upsetting the balance of the system without providing a sufficiently intensive intervention to assist the family in dealing with the emotional issues generated by the intervention? How will home visitors be trained to make sure they can competently address hostile or seriously conflicted family situations that may emerge from being exposed to certain aspects of the intervention? These issues needed to be addressed in the application.

Although the longitudinal data analysis plan is well delineated, it is not entirely clear how the data collected from the 100 interviews from the first phase of the study will be coded and interpreted. Given the research team's extensive amount of experience with this population, it would be helpful to propose some preliminary themes for exploration.

This is a very strong, clearly written application that addresses an extremely important research topic. It uses a randomized design to study the effectiveness of a potentially important intervention. The recommendation is for approval with the following conditions: 1. Clarify the extent to which the proposed study sample of adolescent mothers overlaps with those participating in the other studies being conducted by the investigator.; 2. Elaborate on the cultural framework focusing on African-American families with a clear statement of the group targeted by the intervention. For what groups of families will the intervention be appropriate/generalizable?; 3. Address issues of complex, varying roles of grandparents in the families, and the ramifications of these roles for the proposed intervention.; 4. Address issues relating to home visitor competence in dealing with conflicted or troubled family situations.
Welfare Reform and the Perinatal Health of Immigrants

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Project Number  R40MC00126


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Summary

Statement of the Problem

America's new immigrants may be the first to experience the public health effects of recent welfare reform through the Personal Responsibility and Work Opportunity Reconciliation Act of 1996. While that legislation ended the guarantee of cash welfare assistance to all income-eligible families, the changes it mandated in the medicaid program disproportionately affect immigrants. The consequences of this new law for maternal and infant health may be dramatic, especially in urban areas where large proportions of new mothers are immigrants. Subsequent legislation may also influence the perinatal outcomes of these families. For example, the State Children's Health Insurance Program (SCHIP), enacted as part of the 1997 Balanced Budget Act, may improve infant health through expanded health coverage—but the extent remains to be seen. Within the framework provided by the 1996 and 1997 legislation, each State's legislature has significant leeway in shaping the health policy that will affect its residents. The consequences of welfare reform for immigrants, therefore, may vary considerably from one State to another. To discern the effects of legislation on the maternal-child health of immigrants, over a 4-year period we will track the implementation of these laws and the perinatal health outcomes for immigrants in four States with large immigrant populations—California, Texas, Florida, and New York. Investigators from the disciplines of obstetrics and gynecology, pediatrics, public policy, and health economics will utilize three approaches to study the effects of legislative changes: (1) Analyzing each State's policy environment, (2) compiling vital data sets in four States from time
intervals before and after the new law's implementation, and (3) interviewing service recipients in three of these States. In the 30 years following the passage of the Nation's first medicaid bill in 1965, perinatal and maternal mortality rates dropped dramatically. Although many have assumed that the two events were linked, a conflicting body of research has failed to clarify the relationship between medicaid expansions and perinatal health. To date, most studies of this relationship have not included information regarding postpartum or infant care. Many such studies relied on aggregate vital data and thus failed to link prenatal care patterns with adverse outcomes (such as infant mortality). Most importantly, these studies lacked adequate control populations, and researchers were, therefore, unable to isolate their observations from time-varying factors such as the crack cocaine epidemic or advances in neonatology.

Two elements of our study design promise more reliable conclusions. Current changes in medicaid most directly affect immigrants; therefore, our study will use American-born women of similar ancestry as a control group. By comparing outcomes for immigrant women before and after welfare reform to outcomes for indigent American-born women during the same time intervals, we will be better able to isolate any changes caused by the new legislation from time-dependent factors affecting all poor women. Client-level data from interviews with women will provide information on the interaction between entitlement status; patterns of prenatal, postpartum and infant care; and infant health outcomes.

In addressing the legislative policies that affect immigrant women's perinatal health, welfare reform legislation will be analyzed simultaneously with SCHIP, which is a Federal Block Grant available to States to provide medical assistance to children who are not eligible for any other insurance coverage, including medicaid. The manner in which each State will utilize SCHIP dollars may influence the degree to which other legislatively mandated programs affect immigrant women. In order to gather data on legislative mandates and programs that have not been fully implemented, several strategies will be utilized.

**Research Questions or Hypotheses**

The hypotheses and specific aims of the study are as follows:
1. The welfare reform act will affect the health of immigrant women and their newborns.
   a. Describe changes in the categorical and income guidelines for medicaid eligibility associated with welfare reform and subsequent legislation such as SCHIP;
   b. Determine rates of preterm birth, low birthweight, intrauterine growth restriction (IUGR), low Apgar scores, and congenital infections among women whose medicaid status is altered by welfare reform;
   c. Determine the change in the adequacy of prenatal care use by immigrant women as related to medicaid access;
   d. Determine the change in the number and timing of postpartum visits, well-baby checkups, and immunizations as related to medicaid access;
   e. Describe through case studies whether resources that are available for the care of all pregnant women and newborns are affected by any financial encumbrance experienced by States and municipalities as they seek to replace Federal funds.
2. Maternal-newborn outcomes will vary according to the medicaid policies of the State in which women reside.
   a. Among recent immigrant women whose medicaid status is altered by the bill, determine how rates of preterm birth, low birthweight, IUGR, low Apgar scores, and congenital infections vary between States;
   b. Determine if there are differences by State in the adequacy of prenatal care use by immigrant women as related to medicaid access; and
   c. Determine if there are differences by State in the frequency of well-baby checkups and vaccinations as related to medicaid access or to related programs such as SCHIP.

**Study Design and Methods**

The research design involves a three-tiered strategy for the collection of data. First, we will conduct interviews with health officials and administrators to examine new regulations and State policies as they are implemented in four States. Second, we will analyze vital data sets in two of these States through a series of cross sections of birth certificate data before and after the implementation of welfare reform policies. Third, we will interview postpartum women in sentinel hospitals in New York, Florida, and California and interview them again after 5 to 7 months to determine if postpartum and newborn care has occurred.

**Population and Sampling Plan**
The study will focus on Latina immigrant women, primarily women from Mexico, Central and South America, and the Caribbean. In 1994, infants of foreign-born women constituted 18.5 percent of the 3.95 million births in the United States, with 70 percent of births to women of Hispanic origin occurring in California, Florida, and New York.

The commissioner of health and social services of each State, the CEO of sentinel hospitals (i.e., hospitals with high percentages of immigrant and indigent women), and chairs of obstetrics in each State will be interviewed by a single investigator. A uniform instrument was designed for these contacts. Case studies developed from the data gathered in these interviews will illustrate the unique approaches designed in a given State or municipal setting.

A series of cross sections of birth certificate data before and after policies that are related to welfare reform go into effect will be analyzed to assess whether broader patterns of change in perinatal care and outcomes among immigrants can be detected. These data have provided much of the currently available information regarding the impact of entitlements on health outcomes. Although these sources may not have the requisite specificity to sustain detailed analysis, they can be used to measure changes in utilization of prenatal services and perinatal outcomes by immigrant and indigent populations.

In the analysis of the interview data, medicaid eligibility will serve as the exposure variable, and adequacy of prenatal care, birthweight, Apgar score, and postpartum maternal and infant care are examples of measurable outcomes. Based on power estimates for possible differences in such outcomes among U.S.-born eligible and ineligible immigrant women, we have planned a sample size of 2,400 women from each of the three States for a total of 7,200 women. Completed interview forms will be sent to the data center (SUNY-Downstate) where they will be reviewed for completeness, accuracy, and consistency. Standardization of data gathering will be achieved by using uniform data-gathering instruments and procedures. Interviewers will be trained by the data center staff and will be observed conducting interviews to ensure adherence to study protocol. Confidentiality of the participating study subjects will be ensured through multiple protocols for storing documents, using unique identifiers, and maintaining separate storing spaces for contact data and medical/interview data.

**Analysis Plan**

The manner in which these three sets of data will be used to reach our goals is illustrated below:

I. Client Data Collection for Hypothesis I: PRWORA will affect the health of immigrant women and their newborns.
   - **Predictor Factors**: Medicaid and benefits status
   - **Source of data**: Patient interview/patient eligibility
   - **Co-variates**: Drug use, smoking, cultural factors, etc.
   - **Source of data**: Preterm birth; IUGR; adequacy of prenatal, postpartum, or newborn care; etc.
   - **Outcome Factors**: Patient interview/patient eligibility
   - **Source of data**: Chart review
   - **Co-variate Factors**: Drug use, smoking, cultural factors, etc.
   - **Source of data**: Interview/chart review
   - **Outcome Factors**: Chart review
   - **Source of data**: Birth certificates

II. Client Data Collection for Hypothesis II: Maternal-newborn outcomes will vary according to the medicaid policies of the State in which women reside.
   - **Predictor Factors**: State medicaid regulations
   - **Source of data**: Medicaid official interview to determine eligibility criteria
   - **Co-variates**: Drug use, cultural factors, smoking etc.
   - **Source of data**: Interview/chart review
   - **Outcome Factors**: Preterm birth; IUGR; adequacy of prenatal, postpartum, or newborn care; etc.
   - **Source of data**: Chart review

III. State Vital Data Sets Review for Hypothesis II: Maternal-Newborn Outcomes Will Vary According to the Medicaid Policies of the State in Which Women Reside
   - **Predictor Definition**: Locale
   - **Source of data**: Birth certificates
   - **Intermediate Variable Definition**: Birthplace (country)
   - **Source of data**: Birth certificates
   - **Outcome Definition**: Change in payment source of outcomes
   - **Source of data**: Birth certificates

Data gathered from the client interviews will be analyzed according to general linear models (for continuous variables), logistic regression models (for discrete variables), or multinomial logit models (for discrete outcomes with more than two levels). Based on court orders in each State and current iteration of State policy priorities, it is likely that pregnant women in California and New York will remain eligible for State-only or federally matched medicaid in each State regardless of their immigration status. Florida will provide medicaid coverage to pregnant immigrants to the extent permitted by Federal law.
with newly ineligible populations potentially eligible for State-funded programs. A direct comparison of the perinatal outcomes for immigrants in California, Florida, and New York, however, would not account for local trends that might confound the data. Low-income, U.S.-born women (whose eligibility for medicaid is unlikely to change in either State as a result of the 1996 welfare reform legislation) will serve as an effective control group for poor immigrant women who may lose their health benefits. The existence of this control group will help account for local trends that may affect birth outcomes in each of the three States. We will, therefore, use a differences-in-differences estimate. This method will allow us to relate the change over time of the treatment group (immigrants) to that of the control group (U.S.-born women) in each of the study States and then to compare those differences to assess the effects of the 1996 and 1997 legislation.

Pre-Award Evaluation

Evaluator 1

Originality and Importance
This application proposes an investigation of the impact of welfare reform on the perinatal health of immigrants in four locations: Brooklyn, NY; Houston, TX; Miami, FL; and San Francisco, CA. The focus of the study is on changes in the health of immigrants who may be denied Medicaid. The application addresses an issue of high scientific, medical, political, and ethical importance.

Regional and National Significance
There is little doubt that welfare reform will drastically change the political landscape of the United States. It is also likely that such reform will result in increased adverse perinatal outcomes. If such is the case, the results could not only be disastrous for the infants involved, but for many health care institutions in urban areas likely to bear the brunt of any adverse financial consequences. Documentation of such changes in outcomes would be of major scientific and of practical importance for the Maternal and Child Health Bureau and other Federal agencies. In general, the study will provide information that has the potential to impact policy related to Medicaid and financing of antenatal care.

Scientific and Technical Merit
This application has many strengths. The investigators (PIs) are extremely qualified and experienced at conducting research of this type. The proposal is well written and presents clearly the problem and the potential policy implications of the research they propose. The literature review is extensive including presentation of data that indicate that immigrants often have better outcomes in the face of less prenatal care.

The logistics of conducting the study and data to be collected have been well thought out and draw on experiences in conducting similar types of studies. Hypotheses are clearly stated and concepts well defined. The principle investigator presents proposed tests and measures as well as data gathering procedures. Preliminary data intake forms are also included. Representative plans for data analysis is clearly presented.

Weaknesses are present. The investigation intends to look at a lot of things. Although there is some evidence that prenatal care is associated with better perinatal outcomes, this link is not as firm as these investigators postulate. Moreover, even assuming such a link exists, it is not clear that all potential outcomes to be measured can in fact be linked in some way to welfare reform. At the same time, noticeably absent from the list are some important perinatal outcomes that could be readily obtainable from local databases at the sentinel hospitals- the 5 most important such outcomes are: 1) admission to an intensive care setting (for mother or child); 2) assisted ventilation; 3) intra-ventricular hemorrhage; 4) major congenitally acquired infection (e.g., HIV, syphilis); and 5) fetal and neonatal deaths. Why not get an electronic download from local NICU databases? Similarly, some of the other outcome variables (e.g., immunization rates) need to be defined in time (e.g., vaccines by age 12 months).

A related issue is that the investigators will be looking at such outcomes on a "micro" level ("high grain" with N: 9600) as well as on a "macro level" ("low grain", using vital statistics data sets). The relationships between these two analytic strategies need to be made more explicit. The investigators also need to address the issue of how they intend to handle those
situations where the results of the "micro and macro" analyses are in conflict.

With respect to Study II, the investigators intend to ask various officials for information regarding how their entities will cope with welfare reform. Some of the information regarding how they plan to request is likely to be considered privileged because it relates to how a given entity games the system in order to survive. Moreover, given the tremendous weight these investigators place on this part of the project, it is of concern that there are no letters of commitment from the relevant administrators. The fact that chairs of obstetrics departments have endorsed the project does not necessarily mean that these other informants will necessarily collaborate.

Letters of support from the participating institutions are included. There will be two hospital sites in each of the four cities. The second hospital in each of the four participating cities has not yet been determined, however.

The investigators propose to use US-born women receiving Medicaid (who will not lose their benefits as a result of the welfare reform legislation) as the control group of foreign born women. While the use of these women as a control group is the best one can do, in interpreting and reporting data it will be important to keep in mind that it is not perfect and some secular trends could occur differentially in the US- and foreign--born women.

Could the change result in changes in care patterns? Could some hospitals (especially referral centers) see a change in the baseline risk of adverse outcomes among their patients that could influence comparisons?

The investigators propose to compare changes in outcome in states where undocumented immigrants continue to receive Medicaid with states where such coverage is denied. They indicate that it is likely that pregnant women in New York will remain Medicaid eligible and that the "status quo is likely to remain unchanged for at least several months." What would be the impact on the study analyses if women in all states (including New York) became ineligible during the study period?

Given personnel, there are limitations on the number of interviews that can be performed on a given day or in a given week. How will the investigators select women to be interviewed if there are too many patients available?

A limitation of the study is the lack of detailed information related to Medicaid in Florida and Texas vital statistics. The investigators have dealt with this by using women equal to or more than 20 years of age without a high school diploma as a proxy. These analyses will result in less precise evaluations. The investigators are aware of the limitations.

All senior investigators listed for the project are highly qualified and have exemplary track records as clinicians, multi-center project coordinators, and researchers. Resources and facilities are adequate.

The budget includes $25,700 for office furniture ($14,700 in main budget and $11,000 in subcontracts) that should be excluded. In year 2, the NBER has included additional money for office furniture (amount not specified) that should be deleted. The request for $7500 to recruit personnel at the New York site (main budget) seems high. The need for seven additional phone lines at the New York site completely paid by the grant does not seem justified. Overall, the budget could stand reductions of 15 to 25 percent.

Issues related to human subjects have been carefully considered. The investigators are aware of the importance of confidentiality in performing the study.
**WIC Families Who Smoke: A Behavioral Counseling Study**

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(858) 8614 fax
hovell@projects.sdsu.edu

**Project Number** R40MC00185

**Project Period** 1/1/2000-12/31/2003

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**Year 2010 Objectives**
23.17, 27.9

**Study Design**
Experimental

**Time Design**
Mixed

**Care Emphasis**
Interventional

**Population Focus**
Infants, Toddlers, Preschool-age children, Parents/Families/Mothers/Fathers

**Race/Ethnic Focus**
No Stated Race, Ethnic Focus

**Priority Research Issues**

**Summary**

**Statement of the Problem**

Exposure to environmental tobacco smoke (ETS) among children is causally associated with an increased risk of lower respiratory tract infections such as bronchitis and pneumonia, fluid in the middle ear (otitis media), respiratory tract infections, Sudden Infant Death Syndrome (SIDS), and increased prevalence and severity of asthma. Healthy People 2010 and U.S. EPA objectives are to reduce to less than 10% and 15% respectively, the proportion of children age 6 and younger who are regularly exposed to ETS. Although Healthy People 2010 reports a decrease in children’s ETS exposure from 27% in 1994 to 20% in 1998, more must be done to reach Healthy People and U.S. EPA targets. Cigarette smoking is the leading preventable cause of death in the United States. Use of tobacco products accounts for more than 430,000, or 20% of all U.S. deaths each year. Smoking substantially increases health risks such as cardiovascular disease, chronic lung disease, lung cancer and other cancers, and low birth weight for babies of women who smoked during pregnancy. Healthy People 2010 Objectives call for a reduction in cigarette smoking to a prevalence of no more than 12% among people 18 years and older. A small decline in smoking prevalence is reported —from 29% in 1987 to 25% in...
1990 —to 23.5% in 1999. Recent data indicate that 23.1% of White, non-Hispanic women, 20.8% of Black, non-Hispanic women, and 12.3% of Hispanic women are current smokers.

If effective in reducing children’s ETS exposure and increasing mothers’ and other parents’ quit rates, the intervention we are testing could be incorporated into standard care for the federal Special Supplemental Nutrition Program for Women, Infants, and Children (WIC) sites nation-wide that serve over seven million low-income women, infants, and children.

Research Questions or Hypotheses

This study is testing a behavioral counseling intervention designed to reduce children’s ETS exposure and to help parents quit smoking among families recruited from WIC. We hypothesize that there will be a greater decrease in parent-reported ETS exposure and in children’s urine cotinine concentrations among children from families assigned to the intervention than for controls. We also hypothesize that a greater proportion of parents who participate in the counseling program will quit smoking. We expect to find statistically significant positive relationships among parent-reported and biological and environmental measures of ETS exposure.

Study Design and Methods

A two-group repeated measures design with random assignment is being used. After three baseline measures, families with a child reportedly exposed to a minimum of ten cigarettes per week from the mother in the home or the car are assigned at random to experimental counseling or "usual care” control condition. The experimental group receives ten in-home and four telephone counseling sessions over six months. Counseling is provided for all mothers, and fathers and other smokers living in the home are encouraged to participate. Counseling incorporates behavioral contracting, shaping, and problem-solving negotiations. Outcome measures are obtained at three baseline measures each spaced one week apart, 3, 6, 12, and 18 months. Measures include a detailed interview concerning smoking and exposure rates, key Social Learning Theory variables, and children’s health; and children’s urine samples for cotinine analysis. An environmental measure of nicotine in the home is collected for a random sample of 40% at the third baseline and 6 months (with inactive "bogus pipeline" monitoring for the duration of each family’s 18 months participation). Self-reported smoking cessation is verified with cotinine analysis, supplemented by anabasine and anatabine assays for participants using NRT.

Population Description and Sampling Plan

One hundred fifty families (with a mother who exposes her non-breastfeeding child under age four to a minimum of three cigarettes per day in the home or car) will be recruited. Families will meet WIC eligibility criteria of income less than 185% of poverty level. Although the study is not designed for formal analysis of racial/ethnic differences in outcome, possible differences will be explored in secondary analyses.

Analysis Plan

Statistical analyses will be performed using the intention-to-treat model. A repeated measures design (two groups by seven repeated tests) will be employed. Differential rates of change in parent-reported exposure and urine cotinine between groups will be assessed as a function of group by time interaction. A generalized estimating equation (GEE) approach using SAS (6.12) and STATA (7.0) will be employed to model the effects of group, time, group by time interactions, covariates, and to test specific hypotheses.

To determine the difference in proportion of mothers and other adults in the home who quit smoking, group differences will be assessed within the GEE framework, using a logit link-function to model the dichotomous dependent variable (i.e., quit/non-quit). Similar to the approach discussed above, the group by time interaction will be tested to assess differential rates of change between experimental and control groups.

A multiple regression approach will be used to examine whether differences in parents' reports of exposure are related to urine cotinine and environmental measures after adjusting for covariates (e.g., demographics, time of measurement). Partial regression coefficients will be tested to examine hypotheses about the relationships between parent-reported and biological and environmental measures.

Pre-Award Evaluation
Evaluator 1

Originality and Importance
This is a strong project that intends to evaluate the efficacy of an intervention program to reduce ETS exposure in young children by focusing on two mechanisms: attending to parent's pattern of behavior when smoking while supplementing this with smoking cessation counseling. This clearly meets MCH priorities and attempts to innovatively reduce exposure to potential carcinogens via multiple methods of intervention.

Regional and National Significance
The proposal, if successful, would have both regional and national significance by demonstrating the efficacy of using cost-efficient behavioral and pharmacological interventions in reducing a prime health risk to children.

Scientific and Technical Merit

Statement of the Problem
The statement of the problem is clear and is a real strength of the proposal. The investigators logically draw the connection between ETS and children's health risk and well as the problems associated with the assessment of ETS exposure. Use of innovative techniques and multiple methods of assessment and the need for this research are clearly stated.

The literature review is excellent and the investigative team has contributed much of what we know regarding the measurement of ETS exposure and the effectiveness of ETS interventions.

One potential weakness is the discrepancy between a family-centered approach that is being advocated while nevertheless clearly focusing on a target parent. Even if intervention with the target-parent is successful, it may be that a lack of focus on the family system, especially with respect to family dynamics, may lead to a less than efficacious outcome.

Hypotheses and Specification of Variables
The hypotheses are clear, well stated, and are justified by previous research. Albeit written in very small font.

Explanation of Concepts
The concepts are well defined and are supplemented with appropriate figures and tables.

Test and Measurements
One of the real strengths of this proposal is the multiple methods used by the investigators when assessing such crucial information as ETS exposure and extent of smoking behavior. Combining biological measures with self-report measures, using environmental monitors (along with bogus pipeline effects) gives the research team a real chance to understand the nature of the phenomena.

There are a couple of weaknesses with the measurements as I understand them. First, the assessment of children's health outcomes seems a bit weak (based on self-report of respiratory difficulties such as coughs, etc.) and there is no real evidence presented for the reliability and validity of this measure. Likewise, there is likely to be a confound when assessing health care utilization, which must surely depend upon access to health care.

Similarly, the real possibility of bias is present when you have counselor's rate the enthusiasm of the participants in the intervention as well as rate intervention compliance and process integrity. The counselor's will clearly know whether or not progress in both ETS control and cessation of smoking is taking place; I find it hard to believe that such judgments can be made in an unbiased fashion. If this variable is used as a covariate to try to control for compliance, it runs the real risk of exaggerating treatment effects due to this bias.

Study Design
The study design is exceptionally well thought out. I do think the investigators area bit optimistic in their projections of dropout and attrition rates, however. Their previous work dealt primarily with mothers of asthmatic children (thus highly motivated) and did not attempt to reduce the amount of smoking (only re-direct it so that it would have less of an effect on
children). Since this study intends to work with families who may not have a clearly visible motive to continue and will ask them to attempt a much more difficult behavior change, attrition may be higher than that anticipated.

Population Description and Sampling Plan
The population description and sampling plan are adequate.

Plan for Data Analysis
The data analysis plan is excellent. I did notice that the investigators, when estimating power, miscalculated the expected effect sizes. If the counseling group is expected to have a 35% success rate in extinguishing smoking, and if the control group is expected to have a 10% success rate, then isn’t the odds ratio \( \frac{.35}{.65} \cdot \frac{.90}{.10} = \frac{4.85}{.35} \text{ and not } 3.5 \)? Of course, this would suggest that power is much higher than anticipated and should not be a problem.

Finally, the cost analysis is not well specified at this time. More detail is needed on how the cost-benefit analysis will be attempted and what residual cost savings will be obtained via a successful smoking cessation study.

I also am curious as to how successful this project would be from a cost-benefit standpoint compared to a study that simply placed room air-filtration devices into the relevant places.

Time scheduling. I do wonder why it is that the investigators have allowed 2 years for subject recruitment when the study itself only requires \( n=150 \) families from a very large population. I suspect that it may have more to do with the ability to deliver the treatment in a timely fashion, but this is not justified very well, in my view.

Resources and Environment
Adequate.

Qualifications and Experience
This is an excellent research team which has been quite successful in the past in the area of research and is likely to be successful in the future.

However, I wonder to what extent the success of the treatment depends upon the presence of counselors, though, who are currently finishing master’s degrees and may choose to leave in the middle of the project. Given the bilinguality of the individuals involved, they may not be easy to replace in terms of both training in counseling, bilinguality, and research training.

Budget
There are no real budget problems.

Human Subjects
There does remain at least two human subject concerns with this proposal, one of which is marginally recognized by the investigators and one which is not. The first concerns the possibility of coercive behavior on the part of the target parent with respect to the non-targeted smokers in the family. Although the researchers recognize this potential, they merely suggest the possibility of family discord. Given the drug withdrawal symptoms that accompany a smoking cessation attempt, the risk of being at least a distal cause of a family breakup or an episode of domestic violence is not farfetched. Although I do believe that the treatment as offered by the proposal is fairly benign and not highly likely to end in the result mentioned, it should be mentioned as one possible outcome of the treatment and not underestimated.

Second, because the treatment involves supplementation with NRT, there are some possible medical complications that could arise. The research team simply proposes to have the target parent check with their primary care physician, but it is not clear that all participants (WIC parents) will have timely and cost-free primary care. This issue must be resolved as a human subject’s matter if the treatment itself is a cause of a need for medical care.

**Evaluator 2**
**Originality and Importance**
No statement of regional and national significance.

**Regional and National Significance**
No statement of regional and national significance.

**Scientific and Technical Merit**
The investigators do not clearly define Spanish speaking. Given the diversity of Spanish-speaking countries, there may be a confounding effect in terms of ethnicity. Moreover, it is possible that some of the non-Spanish speaking households may also be of Latino origin. The investigators should more clearly and carefully delineate the two distinct populations. Similarly, it is curious that issues of cultural identity have been totally overlooked both in the conceptual model but also in the previous work of the investigators. Is one to assume that smoking behaviors are not in part related to cultural ideologies and practices?

Ironically, one of the objectives of the proposed investigation is to examine the impact of this clinical intervention on the missing from the interview protocols are impact of other family members smoking cessation. Yet, conspicuously information on the transient nature of household residents. Clearly, previously published research has indicated that families who live in economically distressed communities are more likely to have transient and unstable household residents, including fictive and non-fictive kin who are embraced in the household. It would seem, therefore, that information on household composition, as well as smoking behaviors of these residents, be collected more systematically.

Given current national and international economic situations, this 5-year study poses interesting challenges for the investigators. For example, challenges related to subject attrition are not sufficiently addressed. How will the investigators seek to maintain their subject population? Stated somewhat differently, the sample size may be too small as no power calculations have been provided nor has a model of subject attrition been introduced or discussed.

It is also somewhat disconcerting that the investigators target Spanish- and non-Spanish speaking households (assumed to be English speaking), yet, there are no proposed inter- or intra-group hypotheses. In other words, given the two-group repeated measures experimental design that is being employed, valuable data are simply being ignored. It should also be noted that the authors state "We plan to recruit equal numbers of Latin, African-American, and non-Latino White target parents. While we will most likely not have adequate statistical power to find differential experimental effects, we will explore ethnic differences in outcomes as well as process measures." Why has the investigator not systematically designed to study to capture the richness of the diverse populations that exist in San Diego County? These data and outcomes related to this study are issues that are of significance to our nation now. Is another study to systematically replicate the tentative findings of this already well-conceptualized investigation necessary? Can it not be addressed within the current proposal?

Given the geographical diversity of San Diego, it is surprising to not present any contextual hypotheses. For example, are the proposed intervention efforts more/less successful for those residents who live in closer proximity to the US-Mexico border?

In summary, this proposal seeks five-years of funding to test the efficacy of an intervention designed to reduce environmental tobacco smoke exposure (ETS) and parents' smoking among low-SES English and Spanish-speaking families recruited from the Federal Special Supplemental Nutrition Program for Women, Infants, and Children. Seven specific hypotheses are proposed for this two-group repeated measures design which will randomly assign subjects to a condition of experimental counseling or a usual care control condition. The experimental group will receive 10 in-home counseling sessions over a 6-month period. While minor criticisms have been offered, the proposed investigation is through and involves a highly productive and skilled research team.
The Maternal and Child Health Bureau (MCHB) periodically reexamines its applied research agenda by convening advisory groups that broadly represent the national MCH community. The most recent meeting, which took place in June 1994, generated a research agenda composed of 266 issues and questions identified as critically important to MCHB’s mission in the year 2000 and beyond. The agenda was first published in 1996 in *Proceedings of the Fourth National Title V Maternal and Child Health Research Priority Conference*.

The issues and questions contained in the 1994 research agenda were evaluated in early FY 1999, and underlying themes were identified and extracted. The extracted themes were supplemented by (1) recommendations of the 1999 Special Projects of Regional and National Significance (SPRANS) Report; (2) known program areas for which various MCHB divisions have responsibility; (3) Health Resources and Services Administration (HRSA), MCHB, and the Nation’s Year 2010 goals and objectives as declared in their respective strategic plans; and (4) assumed state Title V program needs and concerns (e.g., needs assessment, performance evaluation, etc.). In view of the extracted themes and supplemental considerations, a set of broadly demarcated research agenda areas was constructed, keyed to HRSA, MCHB, and the Nation’s Year 2010 goals and objectives. Each of the 11 broadly demarcated areas was further explicated using issues and questions derived from the original research agenda. An MCHB advisory committee composed of division and office representatives scrutinized these issues and questions further. From the larger array of issues and questions, this committee selected a subset of 15 to be considered a first priority during FY 2000–03. These are presented on page 3. If a project application that is recommended for approval by the Maternal and Child Health Research Review Committee addresses one of the 15 priorities, a 0.5 point adjustment is applied to the funding score, which raises the chances of its being funded. The issues and questions remaining under the 11 broadly demarcated areas have also been designated as critical to HRSA and MCHB. Field-initiated applications addressing this larger array of issues and questions will be accepted for review and considered for funding but will not be given the special funding consideration mentioned above. In summary, the 15 priority issues and questions selected represent a balance of competing programmatic needs and concerns as expressed by MCHB offices and divisions and articulated by the HRSA and MCHB strategic plans.

Individuals interested in examining the entire array of issues and questions are encouraged to request the new research application guidance material from the HRSA Grants Application Center, (CFDA#93.110RS), 1815 North Fort Myer Drive, Suite 300, Arlington, VA 22209, tel: (877) 4772123, email: Hrsgac@hrsa.gov.

### I. Quality, Cost, Organization, Access to, and Use of Primary Care, Specialty Care, and Public Health Services

5.2.5. Study alternatives for the organization, regionalization, and delivery of comprehensive, continuous health services for typically developing and for special health care needs children, including ways that the primary health care needs of these children can be integrated with the provision of specialized services as exemplified under the concept of “medical home.”

6.3.2. Investigate the factors, from both the micro and the macro levels, that promote adolescents’ timely access to and utilization of health services, with attention to understanding what modifications in service delivery systems, provider training, and youth health education would help adolescents engage the health care system more appropriately.
II. Response of State Governments and State MCH Units to Federal and State Legislation Creating, Expanding, or Reducing Services.

8.1.3. Study the processes and complexities involved in having states, communities, and individuals within states take full advantage of Medicaid and Balanced Budget Act provisions, including those of the State Children’s Health Insurance Program (CHIP) and the authorization for 12 months of continuous eligibility for Medicaid and CHIP.

8.1.7. Study how changes in federal and state welfare laws and in states’ interpretation and implementation of these laws affects immigrants’ access to and use of MCH services. How does the implementation of these laws in turn affect trends in the use of services (e.g., trimester when prenatal care started) and trends in morbidity and mortality rates (e.g., neonatal death rates) for high-immigrant states and specific immigrant groups within states?

III. Development, Testing, and Validation of Screening and Diagnostic Instruments, Including Generic Methodologies to Conduct Needs Assessments and Evaluate Performance by States.

2.6.5. Develop and evaluate new screening and diagnostic technologies for diseases and conditions newly identified as “genetic.”

8.1.8. Develop and test generic methodologies to perform needs assessments and evaluate performance at the state and community levels.

IV. Causes of Class, Ethnic, Racial, and Urban-Rural Disparities in Physical, Mental, and Dental Health; Developmental Competencies; and Access to and Use of Services.

3.1.3. Examine the effects of barriers such as racism, prejudice, and residential segregation on infant, child, and adolescent health status and health services.

V. Determinants of Behaviors Associated with Positive and Negative Maternal and Child Health Outcomes and with Preventive, Health Enhancement, and Curative Health Actions.

2.1.3. Conduct population-based studies on how women decide to seek prenatal care and how this process is arrested or delayed in women who do not receive prenatal care or start later than medically recommended.

VI. Longitudinal Studies of Health and Normative Development in Minority Children, Children with Special Health Care Needs, and Children of Low Socioeconomic Rural, Migrant, and Homeless Backgrounds.

4.3.2. Conduct longitudinal studies on the normative development of children in minority and other at-risk population groups.

VII. Child, Parent, and Family Coping and Resilience Associated with Significant Injuries and Chronic and Catastrophic Disease Conditions.

1.11.2. Conduct studies on how parents adapt to having a child with a disability, taking into consideration specific features of the disability as well as parent and family factors existing before and after the birth of the affected child.

VIII. Effects of Family, Community, and Service Systems Contexts on Children’s Physical and Mental Health and Development.

8.1.11. Investigate the processes involved in the transition to employment and adult health care for typically developing adolescents and for adolescents with special health care needs, with particular emphasis on the role that the health care system may play in facilitating or hindering such transitions.
IX. Development, Evaluation, and Validation of MCH Clinical Treatments, Outreach Strategies, Program Interventions, Care Guidelines, and Case Management Approaches.

9.1.12. Support randomized controlled studies of the efficacy and cost-effectiveness of the various MCHB-developed and promoted Bright Futures guidelines.

X. Pregnancy, Low Birthweight, Nutrition, and Breastfeeding.

2.4.11. Continue to investigate the suspected connection between infections and preterm onset of labor.

3.8.2. Investigate the determinants of breastfeeding in groups classified according to race, ethnicity, and social class.

XI. Intentional and Unintentional Injuries, Child Neglect and Abuse, Family Violence, Suicide, and Emergency Medical Services.

8.1.13. Study the extent to which children who need emergency medical services receive them, with particular attention to care received (or not received) in hospital emergency departments.

(excerpt from MCH Research Exchange, March 2000)
Healthy People 2010 Objectives by Active Projects 2000-2001

1-1. Persons with health insurance
1-2. Health insurance coverage for clinical preventive services
1-4. Source of ongoing care
1-5. Usual primary care provider
1-6. Difficulties or delays in obtaining needed health care
1-9. Hospitalization for ambulatory-care-sensitive conditions
1-12. Single toll-free number for poison control centers
1-13. Trauma care systems
1-14. Special needs of children

3-3. Breast cancer deaths
3-4. Cervical cancer deaths
3-11. Pap tests
3-13. Mammograms

5-8. Gestational diabetes

6-2. Feelings and depression among children with disabilities
6-7. Congregate care of children and adults with disabilities
6-9. Children and youth with disabilities included in regular education programs
6-12. Environmental barriers affecting participation

7-1. High school completion
7-2. School health education
7-3. Health risk behavior for college and university students
7-4. School nurse-to-student ratio
7-11. Culturally appropriate community health promotion

8-11. Elevated blood lead levels in children
8-20. School policies to protect against environmental hazards
8-22. Lead-based paint testing
8-27. Monitoring environmentally related diseases

9-1. Intended pregnancy
9-2. Birth spacing
9-6. Male involvement
9-7. Adolescent pregnancy
9-8. Abstinence before 15 years
9-9. Abstinence among adolescents aged 15 to 17 years
9-10. Pregnancy prevention and sexually transmitted disease protection
9-11. Pregnancy prevention education

13-17. Prenatally acquired HIV infection

14-1. Vaccine-preventable diseases
14-2. Hepatitis B in infants and young children
14-4. Bacterial meningitis in young children
14-18. Antibiotics prescribed for ear infections
14-19. Antibiotics prescribed for colds
14-22. Universally recommended vaccination of children 19-35 months of age
14-23. Vaccination coverage for children in daycare, kindergarten, and first grade
14-24. Fully immunized children 19-35 months
14-25. Providers who measure childhood vaccination coverage levels
14-26. State/community population-based immunization registries for children
14-27. Vaccination coverage among adolescents
14-30. Adverse events from vaccinations
14-31. Active surveillance for vaccine safety

15-1. Nonfatal head injuries
15-2. Nonfatal spinal cord injuries
15-3. Firearm-related injury deaths
15-4. Proper firearm storage in homes
15-5. Nonfatal firearm-related injuries
15-6. Child fatality review
15-7. Nonfatal poisoning
15-8. Deaths from poisoning
15-9. Deaths from suffocation
15-10. Emergency department surveillance systems
15-11. Hospital discharge surveillance systems
15-12. Emergency department visits
15-13. Deaths from unintentional injuries
15-14. Nonfatal unintentional injuries
15-15. Deaths from motor vehicle crashes
15-17. Nonfatal motor vehicle injuries
15-18. Nonfatal pedestrian injuries
15-19. Safety belts
15-20. Child restraints
15-23. Bicycle helmet use
15-24. Bicycle helmet laws
15-25. Residential fire deaths
15-29. Drownings
15-31. Injury protection in school sports
15-32. Homicides
15-33. Maltreatment and maltreatment fatalities of children
15-34. Physical assault by intimate partners
15-35. Rape or attempted rape
15-36. Sexual assault other than rape
15-37. Physical assaults
15-38. Physical fighting among adolescents
15-39. Weapon carrying by adolescents on school property

16-1. Fetal and infant deaths
16-2. Child deaths
16-3. Adolescent and young adult deaths
16-4. Maternal deaths
16-5. Maternal illness and complications due to pregnancy
16-6. Prenatal care
16-7. Childbirth classes
16-8. Very low birth weight infants born at Level III hospitals
16-9. Cesarean deliveries
16-10. Low birth weight and very low birth weight
16-11. Preterm birth
16-12. Weight gain during pregnancy
16-13. Infants put to sleep on their backs
16-14. Developmental disabilities
16-15. Spina bifida and other neural tube defects
16-16. Optimum folic acid
16-17. Prenatal substance exposure
16-18. Fetal alcohol syndrome
16-20. Newborn bloodspot screening
16-21. Sepsis among infants with sickle cell disease
16-22. Medical home for children with special health care needs
16-23. Service systems for children with special health care needs

18-1. Suicide
18-2. Adolescent suicide attempts
18-5. Eating disorder relapses
18-7. Treatment for children with mental health problems
18-8. Juvenile justice facility screening

19-3. Overweight or obesity in children and adolescents
19-4. Growth retardation in children
19-5. Fruit intake
19-6. Vegetable intake
19-7. Grain product intake
19-8. Saturated fat intake
19-9. Total fat intake
19-10. Sodium intake
19-11. Calcium intake
19-12. Iron deficiency in young children and in females of childbearing age
19-13. Anemia in low-income pregnant females
19-15. Meals and snacks at school

21-1. Dental caries experience
21-2. Untreated dental decay
21-8. Dental sealants
21-9. Community water fluoridation
21-10. Use of oral health care system
21-12. Dental services for low-income children
21-13. School-based health centers with oral health component
21-14. Health centers with oral health service components
21-15. Referral for cleft lip/palate
21-16. State-based surveillance system

22-6. Moderate physical activity in adolescents
22-7. Vigorous physical activity in adolescents
22-8. Physical education requirement in schools
22-9. Daily physical education in schools
22-10. Physical activity in physical education class
22-11. Television viewing
22-12. School physical activity facilities

23-1. Public health employee access to Internet
23-2. Public access to information and surveillance data
23-3. Use of geocoding in health data systems
23-4. Data for all population groups
23-5. Data for Leading Health Indicators, Health Status Indicators, and Priority Data Needs at Tribal, State, and local levels
23-7. Timely release of data on objectives
23-8. Competencies for public health workers
23-10. Continuing education and training by public health agencies
23-11. Performance standards for essential public health services
23-12. Health improvement plans
23-13. Access to public health laboratory services
23-14. Access to epidemiology services
23-15. Model statutes related to essential public health services
23-16. Data on public health expenditures
23-17. Prevention research

24-1. Deaths from asthma
24-2. Hospitalizations for asthma
24-3. Hospital emergency department visits for asthma
24-5. School or work days lost

25-1. Chlamydia
25-8. Heterosexually transmitted HIV infection in women
25-9. Congenital syphilis
25-10. Neonatal STDs
25-11. Responsible adolescent sexual behavior
25-12. Sexual behavior messages on television
25-14. Screening in youth detention facilities and jails
25-16. Annual screening for genital chlamydia (HP Goal is for women under 25 years)
25-17. Screening of pregnant women
25-18. Compliance with recognized STD treatment standards

26-6. Adolescents riding with a driver who has been drinking
26-9. Substance-free youth
26-10. Adolescent and adult use of illicit substances
26-11. Binge drinking
26-14. Steroid use among adolescents
26-15. Inhalant use among adolescents
26-16. Peer disapproval of substance abuse
26-17. Perception of risk associated with substance abuse

27-2. Adolescent tobacco use
27-3. Initiation of tobacco use
27-4. Age at first use of tobacco
27-6. Smoking cessation during pregnancy
27-7. Smoking cessation by adolescents
27-9. Exposure to tobacco smoke at home among children
27-11. Smoke-free and tobacco-free schools
27-14. Enforcement of illegal tobacco sales to minors laws
27-15. Retail license suspension for sales to minors
27-16. Tobacco advertising and promotion targeting adolescents and young adults
27-17. Adolescent disapproval of smoking

28-2. Vision screening for children
28-4. Impairment in children and adolescents
28-11. Newborn hearing screening, evaluation, and intervention
28-12. Otitis media
28-13. Rehabilitation for hearing impairment
28-17. Noise-induced hearing loss in children
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<td>Factors Associated with Nutritional Intake in Adolescents</td>
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<td>Trauma</td>
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<td>Responsiveness of CHIP to Children With Special Health Care Needs</td>
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<td>Adolescent Attitudes About Pregnancy, Economic Impact of Breast-Feeding Promotion Intervention, Improving Anemia Screening in Inner-City Children, Neighborhood and Family Effects on Adolescent Health Behaviors</td>
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<td>WIC Families Who Smoke: A Behavioral Counseling Study</td>
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