Title: Influence of Prenatal and Early Childhood Home Visiting by Nurses on Development of Chronic Disease: 29-Year Follow-Up of a Randomized Clinical Trial

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New Mothers Study - COMIRB # 20-0794

Influence of Prenatal and Early Childhood Home-Visiting by Nurses on Development of Chronic Disease: 29-year Follow-Up of a Randomized Clinical Trial

I. PURPOSE OF THE STUDY AND BACKGROUND

Purpose of the study. This study consists of a 29-year follow-up of participants (N=742) in a randomized clinical trial of the Nurse-Family Partnership (NFP), a program of prenatal and infant/toddler home-visiting by nurses for low-income women with no previous live births, focusing on emergent chronic disease in mothers and first-born offspring. Previous assessments were conducted at registration, at the 36th week of gestation, and at the child's 6th month and years 1, 2, 4.5, 6, 9, 12, and 18. NFP nurses are charged with improving: 1) pregnancy outcomes; 2) children's health and development; and 3) women's health and economic self-sufficiency. They do this by promoting women's health behaviors, care of their child, planning subsequent pregnancies, completing their educations and finding work. Nurses explicitly promote women's self-efficacy/mastery in managing challenges, foster informal social support (including involving fathers), and link families with health and human services. The goal is to continue surveillance of health outcomes among mothers and firstborn offspring enrolled in this second NFP trial, which focused on very low-income, primarily African American (89%) women and their offspring. Eighty five percent of the randomized mothers and offspring were assessed at the most recent 18-year follow-up. NFP effects have been found on a range of maternal outcomes through child age 18, including Pregnancy-Induced Hypertension (PIH), closely spaced subsequent pregnancies, marriage, sense of mastery, use of government benefits; and among mothers of females, reduced BP and self-reported kidney and heart problems. Nurse-visited offspring, through age 18, had lower rates of preventable mortality; among those born to mothers with limited coping capacity, lower rates of low birthweight and compromised cognitive functioning, receipt of Social Security Disability; and, among females, lower rates of obesity.

At the 29-year follow-up, we expect to complete assessments on approximately 80% of those randomized. **Findings from earlier follow-ups have led to our general hypothesis that, over the life-course, the intervention will lead to reductions in the emergence of cardiovascular disease (CVD), chronic kidney disease (CKD), type 2 diabetes (T2D), and premature mortality among both mothers and their first-born offspring.** We will a) conduct anthropometric assessments; b) draw blood to measure cardio-metabolic and immune-inflammatory factors; c) collect random urines to measure the microalbumin/creatinine ratio; d) evaluate arterial stiffness using SphygmoCor Xcel and a standard BP instrument; and e) classify timing and causes of death from National Death Index (NDI) records. To help with interpretation, we will conduct interviews to assess history of diagnoses, medications, menopause, hospitalizations, disability, sedentary and physical activity, sleep, diet, substance use, depression, anxiety, mastery, duration and quality of partnered relationships, education, work, and incarceration; and review hospitalization records, and state records of government-benefits use. We will estimate Nurse-Visited (NV) - Control (C) differences in these outcome domains for both mothers and first-born offspring. Given that previous follow-ups of the Memphis sample for determinations of maternal and offspring mortality have involved all four of the original treatment conditions in this study, we will assess maternal and offspring mortality in all four of those treatment conditions for this phase of follow-up. Moreover, given that maternal mortality due to natural causes will increase as the mothers age, we plan to follow this sample through 2026. The rates of mortality among offspring also will increase over this age-range, so we will assess offspring mortality over the same years. Earlier phases of this study (protocol 04-0518—now closed) examined neighborhood adversity for treatment groups 1 and 3, which involved sending participants' baseline addresses in these groups at the time of registration in this trial to Geolytics, a firm we used to calculate neighborhood adversity scores. Registration in this trial took place in 1989 and 1990. We now wish to include measures of neighborhood adversity in this study four all four treatment groups. Neighborhood adversity can be treated as a baseline factor that may either moderate treatment effects on mortality or account for variance in our estimates of mortality by treatment condition. We now realize the value in obtaining

approval to gather data on neighborhood adversity for allreatment groups through Geolytics.

Our specific aims are:
Aim 1: Estimate NV-C differences in markers of chronic disease and mortality. The NV group is hypothesized to have: *H1: lower measures of obesity; H2: lower risks for macrovascular disease reflected in measures of functional arterial stiffness; H3: fewer markers of chronic kidney disease (CKD); H4: better metabolic outcomes; H5: lower levels of immune/inflammatory markers; and H6: lower mortality rates.*

Aim 2: Examine modifiers of the intervention on outcomes in H1-5. *H7: Given results through age 18, NV effects on H1-5 outcomes will be greater for mothers of females and female offspring.*

Aim 3: Explore mediators of NV on selected outcomes: *H8: NV effects on maternal outcomes will be mediated, in part, by earlier NV beneficial effects on prenatal health behaviors, PIH, preterm delivery in first and subsequent births, closely spaced subsequent pregnancies, maternal sense of mastery, stable family structure, family economic resources, and hypertension at 12 and 18 years postpartum. H9: NV effects on offspring outcomes will be mediated, in part, by NV beneficial effects on prenatal health behaviors, PIH, preterm delivery, breastfeeding, qualities of parental care, lower screen-time, stable family structure, family economic resources, and obesity at ages 12 and 18.*

Background

Significance

Addressing the extraordinarily high rates of chronic disease and premature mortality among low-income African Americans, in spite of recent reductions in white-black disparities, is a public health imperative.[1,2] In the US, non-Hispanic (NH) blacks, compared to NH whites, have higher rates of CVD mortality;[3] T2D;[4] and kidney failure.[5] These differences emerge in the context of large racial disparities in socioeconomic position (SEP)[6] and modifiable individual risks indexed by diet, physical activity, smoking, BMI, blood pressure, blood glucose, and total cholesterol.[6-11] Disparities begin with compromised health and development during pregnancy and early childhood.[12-15] Women's first pregnancies and births set in motion significant changes in their immune,[16] endocrine,[17,18] cardiovascular,[19] and neurologic systems,[20] including the development of maternal protective behaviors designed to promote offspring survival.[21-24] Under conditions of concentrated adversity, these changes create risks for subsequent maternal health,[24] including maternal risk for gestational hypertension,[25] and future CVD risk.[26-30] Note that there is a relationship between LBW and the development of subsequent hypertension, a relationship most pronounced among black women.[31] Important early influences on children's risk for chronic disease include exposures to prenatal tobacco, [32] nutritional factors,[33] hypertensive disorders of pregnancy,[34,35] low birthweight,[36] socioeconomic adversities,[37-39] and "toxic" stress, including child abuse and neglect. [40,41]

The NH black-white difference in individual risks is most pronounced among black females. [8] And SEP adversities and child maltreatment increase the risk for CVD most among females,[8,40,41] a finding replicated in an animal model.[42] but not consistent across epidemiologic studies.[12] Sex-based differences in response to stress begin in pregnancy,[43,44] with female newborns expressing heighten androgen activity in response to uncontrollable significant stressors.[44] Pregnant women bearing female fetuses have heightened risk for PIH and pre-eclampsia.[45-47] PIH is a unique risk for CVD over the life-course for mothers,[48] and for offspring.[49] These early exposures appear to have both direct effects on maternal and offspring biologic development, and indirect effects mediated by changes in subsequent behavior and context, amplifying effects of early exposures.

Epidemiologic studies provide clues for the development of preventive interventions, but lack the scientific rigor needed to guide policy and practice more definitively. That rigor will come from long-term follow-ups of RCT's. Starting risk-reduction early in life has considerable promise, [50,51] but trials conducted to date have not yet revealed the potential of early interventions to alter adult risks for chronic disease. Some RCT's have tested the effects of diet and physical-activity interventions among children and youth, but most are challenged with small samples and attrition bias, and have not yet followed participants into adulthood.[52-54] Two trials of childhood interventions have followed participants into adulthood, but they also have been challenged with either small samples and/or attrition bias. [55,56] To our knowledge, there are no adult follow-ups of RCT's of prenatal and infant/toddler interventions designed to reduce adversities that compromise cardio-metabolic functioning.

One of the difficulties with such trials is that improving at-risk individuals' behavior is challenging.[11] The Nurse-Family Partnership–NFP, a program of prenatal and infant/toddler home-visiting by nurses for low-income mothers bearing first children, explicitly leverages new mothers' and fathers' developing motivations to protect their offspring.[20-24] Nurses guide mothers and other caregivers to improve pregnancy outcomes, early child health and development, maternal health and economic self-sufficiency.[57] Replicated effects found in a series of RCT's have been found in these outcome domains across separate NFP trials with different populations.[57-75] One of these trials with 89% AA families in Memphis, TN (N=742), serves as the foundation for the current proposal; it has found program effects on a range of maternal and offspring outcomes of clear public health importance,[63-72] including hypertension among mothers of females and obesity in female offspring at child-ages 12 and 18.[72]

The proposed follow-up builds upon trials of other interventions and expands the list of outcomes to include state-of-the-art measures of obesity and fat distribution, arterial stiffness, CKD, metabolic outcomes, immune/inflammatory markers, and mortality–for both mothers and their firstborn offspring. By examining the impact of a comprehensive program of prenatal and infant/toddler home-visiting by nurses on maternal and offspring adult chronic-disease risk in an RCT, the current study holds considerable promise for addressing this critical public health challenge.

Sampling Design of Original Clinical Trial

Original Sample Characteristics. We invited 1,290 women from the obstetrical clinic of the Regional Medical Center in Memphis to participate (Table 1). We recruited women <29 weeks pregnant if they had no previous live births, no specific chronic illnesses thought to contribute to fetal growth retardation or preterm delivery, and at least 2 sociodemographic risks (unmarried, <12 years of education, unemployed). Eighty-eight percent (1138/1289) completed informed consent and were randomized to 1 of 4 treatment conditions.[63]

Treatment Conditions

Table 1 summarizes services provided and numbers of participating families randomized into each of 4 treatment conditions in this trial. The study was designed to follow 742 families in 2 treatment conditions after delivery (Treatments 2 and 4). Details of the allocation procedures are found in our original publication.[63]

Table 1. Services provided in each treatment condition

Services	Treatment 1 N=166	Treatment 2 N=514	Treatment 3 N=230	Treatment 4 N=228
Transportation for prenatal care	X	X	X	X
Screening and referral for children		X		X
Prenatal/postpartum home visiting			X	X
Infant and toddler home visiting				X

Treatment 1 - Transportation during Pregnancy. The 166 families in this treatment condition received free round-trip taxicab transportation for scheduled prenatal care appointments. This group did not receive any postpartum services or assessments (with the exception of maternal death records described below).

Treatment 2 - Transportation during Pregnancy and Screening during Infancy. The 514 families in this condition received: 1) free transportation for scheduled prenatal care; and 2) developmental screening and referral services for the child at the 6th, 12th, and 24th months of the child's life.

Treatment 3 - Transportation and Nurse-Visitation during Pregnancy Only. The 230 families in this condition received: 1) free transportation for scheduled prenatal care; and 2) intensive nurse home-visitation services during pregnancy and one postpartum visit in the hospital before discharge and one postpartum visit in the home. This group did not receive any other postpartum services or assessments (except death records).

Treatment 4 - Transportation and Nurse-Visitation during Pregnancy and Infancy. The 228 families in this condition received: 1) free transportation for scheduled prenatal care; 2) intensive nurse home-visitation services during pregnancy and through the child's second birthday; and 3) developmental screening and referral services for the child at the 6th, 12th, and 24th months of the child's life.

Note that the trial was structured to follow Treatments 2 and 4 after delivery to minimize study costs, and these two groups have been followed through offspring age 18. In planning the current follow-up, we conducted pilot work and found that our success in tracing T1 and T3 participants would be significantly less

than those in T2 and T4, so we chose not to attempt to follow them.

Program Plan and Implementation

NFP nurses in T4 had three goals: 1) to improve the outcomes of pregnancy by helping women improve their prenatal health; 2) to improve children's subsequent health and development by helping mothers and other caregivers provide competent care of the child; and 3) to improve women's health and economic self-sufficiency by helping them develop self-care practices, plan subsequent pregnancies, complete their educations, and find work. Nurses systematically involved fathers and other supportive family members/friends and linked families with needed health and human services. They promoted women's protection of their personal health, providing guidance on topics such as diet, exercise, hygiene, use of substances, advocating for themselves with providers of office-based care, and risky behavior and social relationships.[57] Nurses supported mothers' and other caregivers' efforts to care well for their children, including promoting breast feeding, healthy diets, "back to sleep," safe bedding, regular sleep times, reducing hazards in the home, and supporting regulated and responsive care of the child.[57] The program is structured, but nurses adapted it to the needs and of individual families, helping mothers accomplish program goals that aligned with their aspirations. Nurses completed a mean of 7 visits during pregnancy and 26 between birth and child age 2.[63]

Sample Retained at Most Recent Phase of Follow-Up

Table 2 shows elements of the CONSORT diagram for participants in the trial through the first-born offspring's 18th birthday and those available for the 29-year follow-up. Recall that for the postnatal phase of the trial, we followed families assigned to treatments 2 (n=514) and 4 (n=228) for primary assessments. We reviewed medical records on participants for the prenatal phase of the trial, and well-child, emergency-department, and hospital records through child age two. We interviewed participants and conducted tests at intake, 36 weeks of gestation, and child age 6 months, and 1, 2, 4.5, 6, 9,12 and 18 years of the first-born child's life. At the 18-year follow-up, we completed assessments on 618 mothers and 629 youth, for completion rates of 83% of the mothers and 85% of the children originally randomized, and 86% of the mothers and 90% of the children who had not died prior to the 18-year assessment. Obtaining high rates of sample retention is crucial for ensuring accurate estimates of intervention effect. We will conduct maternal assessments on all cases where the mother had not miscarried, the child had not died in the first two years of life, and the mother had not died or refused by age 18. In the current phase, we will conduct assessments on first-born offspring, irrespective of their mothers' refusal or mortality status. 657 mothers and 687 offspring are available for the year-29 follow-up. Note that we completed an update of participants' current addresses in the spring of 2018. They are displayed at the bottom of Table 2. Among mothers, 84% of those available and found for the 29-year follow-up live in the Memphis metropolitan area, and an additional 3% live within a 3-hour drive of Memphis. Among the 687 offspring available and found, 81% live in the Memphis metropolitan area, and an additional 3% live within a 3-hour drive. It is important to note that all participants in this study received services beyond "usual care." Our experience with mothers and children enrolled in this trial has been that they experience participating in this study as helpful to them, given that health conditions identified in the course of conducting assessments are referred for further evaluation and treatment. We will follow this same procedure in the 29-year follow-up.

Table 2. Sample Recruitment, randomization, attrition, and completed assessments at 18 Years and sample availability for 29-year follow-up

Eligible Subjects Invited to Participate	1289				
Number Refused	151				
Number Randomized	1138				
Treatment Group Assignment	**1[a]**	**2**	**3[a]**	**4**	**Total (TX 2 & 4)**
Number Allocated to Each Treatment	166	514	230	228	742
Not Available for 29-year follow-up					
Miscarriages (first born) not followed	6	19	6	8	27
Stillbirths (first born) not followed	0	5	3	2	7
Offspring deaths before age two (not followed)		7		1	8
Maternal deaths through 18 years postpartum		15		3	18
Post-randomization maternal refusals/drops		14		11	25

Offspring Deaths (after age 2)		9		2	11
Post-randomization offspring refusals/drops		1		1	2
Mothers Available for 29 year follow up		**454**		**203**	**657**
Current mother address in Memphis metro area		380		163	543
Current mother address < 3 hrs. drive Memphis		13		8	21
Current mother address > 3 hrs. drive Memphis		50		29	79
First-Born Offspring Available for 29 year follow FU		**473**		**214**	**687**
Current study child address in Memphis metro area		378		178	556
Current study child address < 3 hrs. drive Memphis		16		6	22
Current study child address > 3 hrs. drive Memphis		79		30	109

[a] Sample not followed after birth by design

Summary of NFP Effects from Pregnancy through Child Age 18 on Maternal Outcomes in Memphis Trial

Table 3 summarizes key Control-NV effects found for mothers over the 18-year period following registration in the program during pregnancy. We summarize offspring effects below.

Prenatal/Newborn Health. Nurse-visited women (T3+T4) had fewer first pregnancies compromised by Pregnancy-Induced-Hypertension (PIH) than did women in the control group (T1+T2).[63] While this difference was only statistically significant when T3 and T4 were contrasted with T1 + T2, the pattern held for the two groups followed after delivery, T2 and T4. Nurse-visited women overall had lower rates of preterm birth, and those with low psychological resources (LPR) measured at registration had fewer low birth weight newborns than did their control-group counterparts.[72] This reduction was significant when the contrast was limited to the two groups followed after delivery (T2 vs T4). Note also differences in self-reported prenatal health behaviors at 36 weeks of gestation for mothers of females.

Short Inter-Pregnancy Intervals. Nurse-visited women (T4) had greater intervals between their first and second births,[63-65] and had fewer closely spaced subsequent births over the 12-year period following birth of the first child,[68] an important contributor to maternal health.[76]

Table 3. Program effects on selected maternal outcomes through age 18

Outcome and Age of Assessment	Sample	Comparison	Nurse	Comp vs. Nurse	
Prenatal/Newborn Health		**Mean/Rate**	**Mean/Rat**	**p-**	**Effect size***
Pregnancy-Induced Hypertension, %[1]	Whole-T1+2 vs T3+4	20.0	13.0	.009	OR=0.65
Preterm delivery[1]	Whole	13.3	7.3	.020	OR=0.51
Low birthweight, %[1]	LPR[8]	19.8	9.5	.010	OR=0.42
High birthweight - %	Mothers of F's	5.3	0.0	.005	Not est
Health behavior index, % – 36 wks.[2]	Mothers of F's	67.8	80.2	.038	OR=1.18
Inter-Pregnancy Intervals					
Time to first subsequent birth (0-72 mo.) [3]	Whole	30.23	34.38	.01	ES=0.26
Count of closely spaced subsequent births–age 0-12[4]	Whole	0.51	0.34	.019	IR=0.67
Maternal Economic & Behavioral Resources					
Count of Substances Used – child age 9	Whole	0.17	0.10	.075	IR=0.62
Role Impairment due to Substance Use–ages 9 & 12	Whole	0.25	0.00	.04	Not est.
Sense of mastery – 36 wks preg to 18 yrs[5]	Whole	99.62	100.95	.009	ES=0.13
% live with partner – across time[6]	Whole	32.8	36.8	.09	OR=1.20
% married – across time[6]	Whole	10.7	14.9	.03	OR=1.37
Public Benefits costs (summed-birth-age 18 yrs)[7]	Whole	$192,836	$175,525	.03	ES=-0.13
Maternal Death over 21-year Period after Birth					
All-cause mortality, %	Whole-T1+T2vs T3+4	3.7	1.3	.008	Not Est.
External-cause mortality, %	Whole-T1+T2vs T3+4	1.7	0.2	.02	Not Est.
Measured Maternal Obesity & Hypertension, and Self-Reported Health Problems – through Child Age 18					
Systolic BP – age 18	Mothers of F's	128.85	123.50	.024	ES=0.30
Diastolic BP – age 18	Mothers of F's	90.03	87.02	.044	ES=0.34
Systolic BP – age 12	Mothers of F's	118.40	112.11	.010	ES=0.31
Diastolic BP – age 12	Mothers of F's	82.51	77.73	.010	ES=0.33
Stage 1 Hyperten (Sys≥120 or Dias ≥80) % – age 18	Mothers of F's	84.1	66.3	.002	OR=0.79
Stage 1 Hyperten (Sys ≥120 or Dias ≥80) % – age 12	Mothers of F's	63.5	45.8	.025	OR=0.72
Thyroid Problems (self-report), %- age 18	Whole	6.6	2.6	.030	OR=0.38
Kidney Problems (self-report), % - age 18	Whole	2.5	0.5	.037	OR=0.18
Memory problems (self-report) % - age 18	Mothers of F's	2.1	0.0	.038	Not Est.
High Cholesterol (self-report), % - age 18	Whole	8.3	14.4	.023	OR= 1.87

[1] Derived from labor, delivery, and newborn medical record; [2]derived from interview, responded "yes definitely" to all questions: 1) "I picture myself feeding the baby", 2) "I do things to try to stay healthy that I would not do if I were not pregnant", 3) "I eat meat and vegetables to be sure my baby gets a good diet", and 4) "I give up certain things to help the baby"; [3]2-, 4.5-, and 6-year postpartum interviews;[4]derived from 2-, 4.5--, 6-, 9-, and 12-year postpartum interviews; [5]36 wks. pregnancy, 6-, 24-, 54 mo. postpartum, plus 6-,9-12-, and 18-years after birth; [6] 2,4.5,6,9,12, and 18 year interviews;[7]sum of annual estimates following birth of first child; [8]LPR – sample defined by mothers being in lower half of distribution for psychological resources (intellectual functioning, mental health mastery/self-efficacy).[61]

Maternal Economic and Behavioral Resources. By child age 9, nurse visited (T4) women reported, as a trend, using fewer substances,[66] and at age 12, fewer behavioral impairments due to substance use than control-group women (T2).[68] Over the 18-year period following birth of the first child, nurse-visited (T4) women reported a greater sense of mastery than did women assigned to the control group (T2).[71] By child age 18, nurse-visited (T4) women reported higher rates of marriage, cohabitation, and received fewer public benefits (discounted) for Supplemental Food and Nutrition, Medicaid, and cash assistance welfare than did those assigned to the control group (T2), an effect mediated by their having fewer closely spaced subsequent births.[71]

Maternal Death over 21-year Period Following Birth of First Child. Nurse-visited women assigned to receive visitation during pregnancy alone (T3) or to receive NFP visits during pregnancy through child age 2 (T4), were less likely to have died from all causes than were women in the control group (T1+T2), an effect particularly pronounced for death due to external causes (drug overdose, suicide, injury, and homicide). [69] These effects were in the same direction for women visited during pregnancy and through child age 2 (T4), but not statistically significant.

Measured Maternal Obesity, Hypertension, and Self-Reported Health Problems. By the first offspring's 18th birthday, nurse-visited (T4) women were less likely to have stage-1 hypertension (at the year 12 and 18 assessments) than women in the control group (T2), effects limited to mothers of females.[72] In addition, nurse-visited (T4) women reported fewer thyroid problems, kidney problems, and among mothers of females, fewer memory problems.[72] The presence of hypothyroidism among women with chronic kidney disease increases the risk for serious heart disease. [77] The one exception to this pattern is that nurse-visited women reported more problems with high cholesterol, an effect essentially limited to those who gave birth to males (not shown). [72]

Hypothesized Pathways of Program Effects on Maternal Chronic Disease

Figure 1 summarizes how the effects reported in Table 3 are thought to reduce risks for the development of CVD, CKD, and T2D, in mothers. The bold lines show those effects that are established; the lighter lines represent hypothesized relationships; and the dotted lines represent hypothesized relationships between earlier effects and outcomes to be measured in the 29-year follow-up. Program effects on aspects of prenatal health (reductions in PIH, PTD, and LBW) are thought to play a role in reducing maternal hypertension and reported thyroid problems, which in turn will contribute to reductions in measured risks for CVD, T2D, CKD, and mortality in this 29-year follow-up. Note for example that in the control group (T1+T2), 30% of the women who died during the first two decades following birth of the first child had PIH; the corresponding rate among those who died in the T3 nurse-visited condition was 25%, and 14% in the T4 condition. This suggests that part of the reduction in maternal mortality may be explained by or at least correlated with the improvement in conditions for prenatal health that led to PIH in the control group. Moreover, the reduction in short inter-pregnancy intervals is expected to help explain the treatment effect on risks for maternal morbidity and mortality. The reduction in short inter-pregnancy intervals was a major contributor to the reduction in mothers' reliance on public benefits. Intervention effects on economic and social/behavioral resources have implications for the development of chronic disease among mothers, as well as their offspring, especially girls, given that economic adversity is particularly predictive of risks for CVD among females.[12] Note also that the reduction in behavioral dysregulation on the part of nurse-visited children shown in Table 4 below is also likely to play a role in reducing maternal stress, which contributes to inflammation and risk for chronic-disease. We have not attempted full-blown mediation analyses of the inter-relationships among the outcome domains in Figure 1, as the model is complex, with different domains of maternal functioning likely to play a role in both mediating the effect of the program over time and moderating adverse influences on the development of chronic disease.

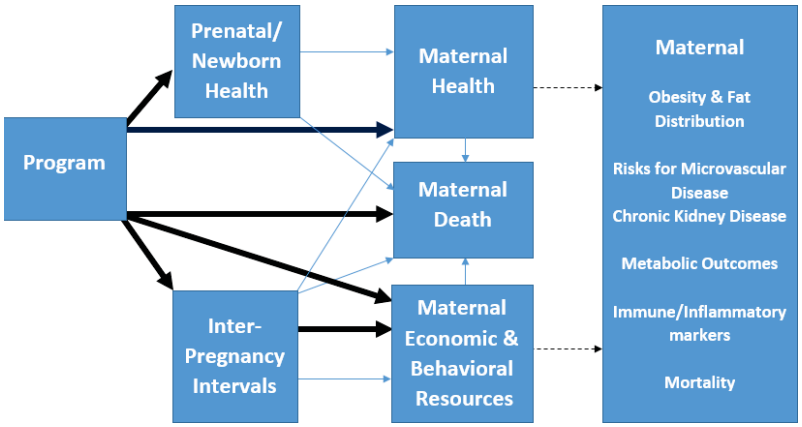

Figure 1. Model of NFP Program Effects on Maternal Risks for Chronic Disease in Memphis Trial

Summary of NFP Effects on Offspring Outcomes in Memphis Trial

Table 4 summarizes key Control-NV effects found for first-born offspring through age 18.

Maternal Caregiving Dysfunction/Investment. Nurse-visited women (T4), especially those with LPR measured at registration, exhibited significantly better care of their children than did their control-group counterparts (T2). [63,65] These effects included fewer beliefs about infants and caregiving predictive of child abuse, home environments that were more conducive to children's emotional and cognitive development, [63,65] and among girls, higher rates of breastfeeding in the first two years of life.[72]

Offspring Injuries/Ingestions in Medical Record. Nurse-visited (T4) children born to mothers with LPR were

less likely to have healthcare encounters of all types for injuries/ ingestions in the first 2 years of life than children in the control group (T2).[63] Moreover, they had far fewer days of hospitalization for injuries/ingestions during that time;[63] all fractures and head trauma, markers for maltreatment, were in the control group.[63]

Offspring Language, Achievement and Cognition. Nurse-visited (T4) children born to mothers with LPR had better language development and math achievement over the first 18 years of life than their control-group counterparts (T2).[63,65-67,70] At age 18, they also scored better on a test of working-memory.[70] Nurse-visited mothers/caregivers reported that T4 offspring were receiving SSI disability income less frequently than did those in the control group (T2), an effect concentrated among those born to LPR mothers.[70]

Table 4. Program effects on selected caregiving and child outcomes through age 18

Outcome and Age of Assessment	Sample	Comparison	Nurse	Comp vs. Nurse	
Maternal Caregiving Dysfunction/Investment					
Beliefs predictive of child abuse, 6 & 24 mo.	Whole LPR[1]	100.5 102.5	98.7 100.2	.003 ≤.01	ES=-0.23 ES=-0.29
Emotional/cognitive stimulation (Home total score) 12 & 24 mo.	Whole LPR[1]	30.9 30.3	32.3 31.5	.003 ≤.05	ES=0.24 ES=0.21
Ever Breast Fed, % - 24 mo.	Mothers of F's	12.3	24.3	.0086	OR=2.28
Child Injuries/Ingestions in Medical Record					
Incidence of encounters (all types) 0-24 mo.	LPR[1]	0.67	0.41	≤.01	IR=0.61
Incidence of days hospitalized—0-24 mo.	LPR[1]	0.26	0.02	.01	IR=0.08
Child Language, Achievement, & Cognition					
Receptive Language (PPVT) – ages 6 & 18y	LPR[1]	79.91	82.79	.03	ES=0.21
Math Achievement (PIAT), ages 6, 12 & 18 y	LPR[1]	82.89	86.70	.001	ES=0.31
Working Memory – age 18y	LPR[1]	7.90	8.51	.045	ES=0.23
% SSI Disability – 18y	LPR[1]	11.3	4.0	.011	OR=0.33
Child Emotional/Behavioral Regulation, Mental Health, Substance Use					
Dysregulated Aggression- MSSB - age 6	LPR[1]	101.10	98.58	.04	ES=-0.25
Incoherent Stories- MSSB - age 6	LPR[1]	29.84	20.90	.006	ES=-0.34
Total Behavior Problems - Borderline/Clinical, CBCL, % 6y	Whole	5.4	1.8	.04	OR=0.32
Count of Failed Conduct Grades–males (grades 1-6)y	Whole	0.10	0.06	.044	IR=0.56
Used alcohol, cigarettes, or cannabis, % - age 12	Whole	5.2	1.6	.024	OR=0.29
No. days used substances-last 30 days - age 12y	Whole	0.18	0.03	<.001	IR=0.17
Ever Sent to Juvenile Detention, % - age 12y	Whole	9.4	7.2	.080	OR=0.52
Internalizing Disorders Borderline/Clinical, %– age 12y	Whole	31	22	.044	OR=0.63
No. hrs./day screen time video/computer–age 12y	Females	0.49	0.28	.028	ES=0.21
Count of convictions - age 18y	Females	.22	.09	.0504	IR=0.42
Child Death over 21-year Period after Birth					
All-cause mortality rate, %	Whole	2.7	0.9	.11	Not est
Preventable-cause mortality rate, %	Whole	1.6	0.0	.04	Not est
Child Obesity					
Obese, % (CDC standard – 18 y)	Females	30.2	21.2	.035	OR=0.70
Obese,% (CDC standard – 12 y)	Females	31.8	15.9	.003	OR=0.50

[1]LPR – Sample defined by Mothers being in lower half of distribution for Psychological Resources

Offspring Emotional/Behavioral Regulation, Mental Health, Substance Use. Nurse-visited (T4) children born to LPR mothers exhibited less dysregulated aggression and incoherent stories in response to examiners' story stems at age 6 than did their counterparts in the control group (T2). [65] Overall, nurse-visited (T4) children were identified as having fewer behavioral problems in the borderline/clinical range on the Achenbach child behavioral checklist at age 6 than did children assigned to the control group (T2). [65] By age 12, nurse-visited (T4) children were less likely to be using substances, to have been sent to juvenile detention, and to have internalizing disorders in the borderline/clinical range.[67] By age 18, nurse-visited (T4) females reported fewer convictions than did their control-group (T2) counterparts,[70] a sex-moderated effect replicated in a prior trial of the NFP.[62]

Offspring Death over 21-year Period after Birth. Over the 21-year period following their birth, nurse-visited (T4) offspring were less likely to have died for preventable causes than those in the control group (T2).[69]

Hypothesized Pathways of Program Effects on Offspring Chronic Disease

Figure 2 summarizes how the Nurse-Control differences in caregiving reported in Table 4 over the 18-year period following birth of the first child are hypothesized to reduce risks for the development of CVD, CKD, and T2D in first-born offspring. In this figure, the bold lines show those effects that are established; the lighter lines represent hypothesized relationships; and the dotted lines represent hypothesized relationships between earlier effects and outcomes to be measured at 29 years. The findings in Table 4, in general, suggest that the long-term effects of the program on offspring health are likely due to improvements in offspring neurobiological functioning and reductions in over-nutrition set in motion during gestation [78,79] that are amplified over time by improved maternal caregiving, increased inter-pregnancy intervals, improved family economic resources, improvements in offspring development and behavior, and reductions in obesity, all of which will reduce stress and inflammation, that iteratively contribute to reductions in offspring developing risks for chronic disease.

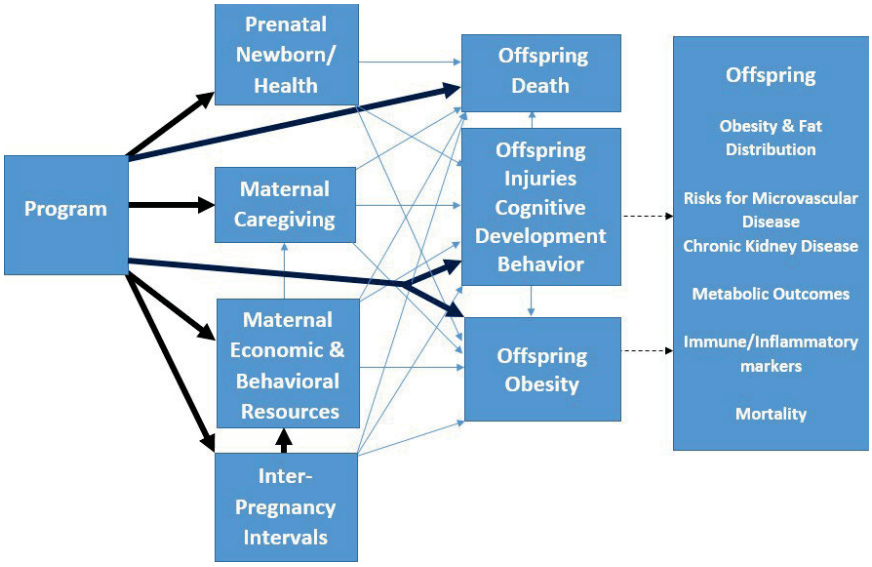

Figure 2. Model of NFP Program Effects on Offspring Risks for Chronic Disease in Memphis Trial.

We are particularly interested in understanding the interplay of contextual and behavioral factors that contribute to sex differences in risks for emerging chronic disease over the course of development, including sex differences in offspring reactivity to various forms of stress[40-44] and increased parental caregiving investments in female offspring under conditions of adversity and the absence of fathers in households.[80-83] We have not yet attempted full-blown mediation analyses of the interrelationships among the outcome domains in Figure 2, as the model is complex, with different domains of maternal and child functioning likely to play a role in both mediating the effect of the program and moderating adverse influences on the development of chronic disease.

I. CHARACTERISTICS OF THE RESEARCH SAMPLE

1. **Number of subjects**. Recruit approximately 1344 people who participated in the New Mothers Study.

2. **Gender of Subjects.** Recruited participants will be approximately 75% female and 25% male.

3. **Age of Subjects**. We will recruit men and women who are > 18 years of age.

4. **Racial and Ethnic Origin**. We anticipate that the racial and ethnic distribution of the study subjects will be approximately 89% African American and 11% Caucasian.

5. **Inclusion Criteria**. Participated in the New Mothers Study as mothers or their firstborn offspring

6. **Exclusion Criteria**. Not a participant in the New Mothers Study

7. Vulnerable Subjects. This study focuses on participants from the New Mothers Study and there is a possibility the potential participants could be incarcerated, pregnant, lack capacity to consent, or disabled.

II. SUBJECT IDENTIFICATION, RECRUITMENT, AND CONSENT

The recruitment and assessment plans are adjusted to ensure the safety of participants and data-gathering staff in light of the COVID-19 pandemic. We will inform study participants at the stage of recruitment that the assessment will take place in two parts – a telephone interview (Part One) and a second, face-to-face assessment, to be conducted at a later time (Part Two). For in-office interviews and health assessments, to assess subject COVID status and insure appropriate steps are taken to minimize subject and staff risk: a phone pre-screen will be administered prior to the visit; an in-person screen will be administered at the start of the visit; and necessary sanitization procedures will be followed.We will conduct the Part Two interview by phone or by HIPPA-compliant Zoom with a limited number of subjects who are unable or unwilling to travel to the Memphis office to complete the face-to face Part Two interview. For this limited number of Part Two interviews that will be virtual, no in-office health assessment will take place. For participants who are currently incarcerated, a prisoner interview will include portions of the Part 1 and the Part 2 interview, will last approximately one hour, will take place in a private room at the prison either via secure video conferencing, or by phone, or in person, and will be administered only after staff obtains verbal consent from the prisoner at the start of the interview session.

Information regarding research safety during the COVID-19 pandemic:

To ensure appropriate safety precautions when conducting in-person study procedures, the process for conducting in-person visits outlined in the University of Rochester Guidance for Human Subject Research will be followed. The study team will continue to monitor the guidance provided by UR/URMC for updates and revisions to ensure all study activities are conducted according to current safety guidelines. Since guidance will change over time, appropriate changes to COVID risk assessment and office sanitization tasks will be implemented as needed.

1. **Method of Subject Identification and Recruitment**. Over the past 28 years, we have continuously traced the sample between assessment phases (through regular birthday and holiday cards and use of internet), and have built in intrinsic incentives to optimize participation. These incentives include having the same primary local study leader (the wife of a local minister) develop trust within the community and be responsible for engaging the sample; referring participants for further evaluation and treatment when health problems are identified; and remunerating participants adequately for their travel and time. We will employ the same procedures for this next phase of follow-up. To reconnect with study participants, several methods for re-contact will be used. Letters will be sent announcing this new phase of the study. Phone calls using contact information provided by subjects at the previous phase of the study will be used, along with emails provided to us in the previous study phase. Study participants will be traced as needed through telephone directories and the internet. In addition, we will use social media, e.g. Facebook. Study participants either will call the study office to indicate their desire to participate in the follow-up or the interviewing staff will call the study participants to determine their interest in continued participation. To facilitate confidentiality, all use of social media for reconnecting with study participants will be administered and maintained by study staff, and individuals who are not study staff will not be able to post information on such study-related social media platforms. When social media platforms are used, we will not collect information from participants, including health information or information that might be used to identify them. The e-mail address associated with any social media used for recruitment will be: NewMothersStudy@urmc.rochester.edu or Evelyn_Collins@urmc.rochester.edu . Language in the study's chosen social media will be as follows: "The Memphis New Mothers Study would like to contact you because we have a new opportunity for you to participate. Please contact us today at: (901) 452-6180."

   If we learn that a study participant (either mother or firstborn child) is in prison, either from newspaper listings or through their personal contacts, the project coordinator will be responsible for both recruitment and consent procedures. We will follow the procedures approved by IRB and used successfully in the 18 year follow-up. The project coordinator will write to the prison's warden to explain the nature of the current study, outline the study participant's previous involvement in this research, and ask for the warden's email permission to request one interview with the study participant. If the warden gives his/her approval, he/she will be provided with a list of names of subject prisoners, and will be asked to give the recruitment letter

and a copy of the verbal consent document to the study participant for his/her review. If the study participant prisoner indicates that he/she wants to participate, he/she will be instructed by the warden to let the warden know of their decision, and the warden will contact the New Mothers Study project coordinator and make arrangements for the scheduling and setup of the interview. There will be no physical assessment with any prisoner participants.

2. **Process of Consent**. Trained staff will administer all consenting procedures. Initial consent for Part 1 will be obtained over the phone prior to the interview. If the participant verbally agrees to participate, and the study team member assesses that the participant demonstrates comprehension of the information, the study staff member will proceed with collection of interview data. If the study team member concludes that the participant is unable to give verbal informed consent, the Part 1 interview will not go forward and plans will be made to bring the individual to the study site for both Part 1 and 2 consent and data collection - with the participant accompanied by a Legally Authorized Representative (LAR). For Part 2, consent will be obtained in a private office where, prior to data collection, participants will be informed of the nature of voluntary participation, time commitment, possible risks, and remuneration. Occasionally, particularly if they are physically disabled, subjects may be given an option for study staff to visit their homes to complete the visit activities; in these cases, consent will be obtained in a private space in the home. The study staff member will review the informed consents, including review of the interview and physical assessments with the study participant. In all instances, if the study participant agrees to participate in the Part 2 assessment and is deemed competent to provide consent, study staff will proceed with the interview and other data gathering procedures. If, during the Part 2 physical health assessment, the study nurse determines that any of the physical measures cannot be completed during that office visit, study subjects will have the opportunity to return to the office for a brief follow-up visit to complete those physical measures. That brief follow-up visit will take about 30 minutes and subjects will receive a small honorarium for their time. First-born study children will now be adults (~30 years of age) and will have had experience with prior interviews/assessments that are similar. Interviewers trained in the consenting/assenting process will assess subjects' comprehension of the information provided. Note that we will enroll some decisionally-challenged participants if their LAR agrees that participation aligns with the participant's values and with the understanding that the procedure will be terminated or certain sections skipped if the participant experiences discomfort.

   For a small subset of participants with whom the Part Two interview will be completed by phone or by HIPPA-compliant Zoom, a newly created Part Two written consent form will be mailed to these subjects along with written release forms for administrative records. A stamped, return-addressed envelope will be sent along with the forms to facilitate mailing for subjects. No virtual Part Two data collection will take place with these subjects until signed forms have been returned by US mail to the Memphis New Mothers Study office.

   For prisoner participants, verbal consent will be administered. All questions will be answered to the participant's satisfaction prior to study staff asking for their decision about whether or not he/she chooses to participate. The interview will not take place without study staff obtaining verbal consent. All prisoner subjects will be informed that participation in this study will not have any effect on any court decisions, parole, or probation.

3. **Subject Capacity/Representative Comprehension**. In order to ensure adequate knowledge and comprehension on the part of potential study subjects, each potential subject will be asked to describe his/her understanding of the purpose of the study and what his/her participation will include following a subset of COMIRB-recommended questions to determine capacity for consent. All questions will be answered to the potential subject's or LAR's satisfaction before informed consent is obtained. Adequacy is required to continue with the consenting process. Those individuals found to be decisionally-challenged will be guided through the interview portions of the assessment, with the LAR serving as an interpreter. The study staff member will work with the LAR to ensure that the participant is comfortable and capable of

answering questions about particular topics. In the case of decisionally-challenged participants,, the participant's LAR is designated in order of preference as one of the following:

a. The person identified above is:
   - An adult
   - Who has exhibited special care and concern for the patient
   - Who is familiar with the patient's personal values AND
   - Who is reasonably available to serve as a surrogate

b. The person can make health care decisions for the patient in accordance with the patient's individual healthcare instructions, if any, and other wishes, if known to the health care decision maker. If the patient has not given individual healthcare instructions, and the patient's specific wishes are not known, the health care decision maker can make a determination of the patient's desires or best interests in light of the patient's personal values and beliefs to the extent they are known.

c. This person may include, in order of descending preference, the patient's spouse, the patient's adult child, the patient's parent, the patient's adult sibling, any other adult relative of the patient or another adult who satisfies the requirements listed above.

4. **Prisoner status**. If a study participant is in prison, the study staff will not be scheduled to administer verbal consent and conduct the interview until the warden relates the study participant's express agreement to the New Mothers Study project coordinator. Before the interview, the study staff will review the verbal informed consent with the study participant specifically approved for use with incarcerated subjects. The study staff will remind the participant that participation will not affect consideration for probation or parole in any way, that she or he is under no obligation to participate in the study, and that she or he has the right to refuse to answer questions or to terminate the interview at any time. If the participant agrees to participate in the study, the study staff will proceed with the consenting process.Release forms will not be used.

   - Care will be taken in enrolling prisoners as those incarcerated are a vulnerable population. The recruitment and consent procedures we have outlined earlier are designed to protect all incarcerated subjects in our study from being coerced to participate in any way. If a study participant is incarcerated in a prison outside the Memphis area, the same process will take place for them as for the prisoners in the Memphis area. Prior to the start of an interview, those participants will be asked if they have any questions regarding the interview, and will provide verbal consent. Additionally, a private room for conducting the interview will be made available at the prison.

5. **Consent Forms**. See consent form.

6. **Documentation of Consent**. Informed consent will be obtained by research study personnel. For Part 1 consent will be obtained verbally and for Part 2 it will be obtained and documented on Research Subjects Review Board-approved consent forms. Consent for Part Two virtual (phone or HIPPA-compliant Zoom) interviews will be obtained and documented on Research Subjects Review Board-approved consent forms. For the Part 2 additional brief office visit opportunity, consent will be obtained verbally. Consent forms will be kept in locked office files (originals will be sent to Colorado study office and copies maintained at the Memphis site). All prisoner participants will be consented using a verbal consent form.

7. **Costs to the Subject**. There are no costs to the subject. Any procedures that are for study purposes will be billed to the grant.

8. **Payment for Participation**. Participants will be remunerated with $50 at the completion of Part 1 data gathering process. They will receive $200 if they complete the Part 2 interview and assessments. In addition, they will receive a possible $25 incentive if they complete the Part 2 interview on the first scheduled appointment. Further, if it is determined by a study nurse that a study subject needs to return for

an additional brief visit to the study office to obtain a measure of PWV (pulse wave velocity), body composition, or to obtain their blood or urine sample, the participant will be compensated with an additional $30. For subjects who are uncomfortable or unwilling to provide a blood and/or urine sample (or if we are unable to obtain) for various reasons during their office visit, we will ask those subjects to provide lab results from within their past year's medical records. Such results may include the following: Urine – Markers of Chronic Kidney Disease (CKD) including Glomerular Filtration Rate (eGFR) and the microalbumin/creatinine ratio. Blood – Metabolic Outcomes including Glycosylated Hemoglobin (HbA1C), dyslipidemia (TC, LDL, HDL, TG), and the AST/ALT ratio). Cab or public transportation to the study office also will be covered on an as needed basis. Round trip mileage for those who drive themselves will be reimbursed at the current IRS mileage reimbursement rate if the round trip is over 50 miles. Travel from locations that are not a reasonable distance from the office will be covered by study funds as well as overnight hotel stays if warranted, determined on a case by case basis. For incarcerated participants, payment of $150 will be given to them unless receiving payment is in violation of penal institution policy. If receipt of payment is in violation of penal institution policy, incarcerated participants may elect to have their payment given to a family member or other designee.

The Part Two virtual interviews may be administered in two parts, which could take up to 1.5 hours in total if completed during one data collection meeting by phone or HIPPA-compliant Zoom. Subjects who complete this interview in one session will be paid $125 plus an additional $25 for keeping their first appointment. Subjects who require two separate sessions to complete the interview will be paid $50 for the first session plus an additional $25 for keeping their first appointment, and then another $75 for completing the second interview session,

III. METHODS AND PROCEDURES

Data Collection. Tables 5 and 6 summarize the measures to be gathered in this 29-year follow-up. All data will be gathered by staff masked to original treatment assignment.

Part 1: Overview: once verbal consent is obtained the participant will be interviewed by the study staff member using interview 1. In addition, contact information will be obtained that can be used to contact them for the Part 2 interview/assessment. All interview data will be entered into Redcap. On occasion we may email a link to the redcap questionnaire to the study participant directly for them to complete. Once the interview is completed the participant will be paid $50 for their participation and will be reminded that we will be in contact with them for the part 2 interview.

Table 5. Part 1 Telephone or Computer Interview Content (RedCap)

Alterations due to COVID-19 Experience Health Employment Childcare Access to food and services Comfort with office visit	**Household Composition** Name of residents Age Relationship Housing type Number of rooms Mortgage and rent payment	**Education and Training** High school Training Licensure College Graduate school Armed Services
Residence History State location Receipt of benefits	**Employment History** Job Type Earnings Elder care/Handicapped children	**Tobacco Use** Cigarettes, Cigars, Pipe, Hookah, Smokless Tobacco Products and Vaping
Healthcare Providers Medications, Insurance, self-report height and weight	**Hospital Admissions – self-report**	**Births and Children** Since last data collection point Birth outcomes
Social Security Benefits		

Reason for benefits

The interview includes all the areas listed in table 5.

Part 2

Overview: Once we are able to see people face-to-face safely study staff will contact participants to schedule an appointment for the Part 2 assessments. Following informed consent the Part 2 assessments will commence collecting the data indicated in table 6. These assessments consist of completion of several questionnaires (interview 2) and physical assessments. These include weight, height, bioelectrical impedance analysis (BIA), waist and hip circumference, blood draws, urine sample, BP, augmentation index (AI), pulse wave velocity (PWV) and the questionnaires included in the part 2 interview. The questionnaires will be administered in a private space and entered into Redcap.

Rarely, subjects will be given an option for study staff to visit their homes to complete the visit activities, particularly if they are physically disabled. Study activities completed at home will remain the same as the in-person visit, with an exception of BIA, PWV and AI.

Anthropometric assessments: We will conduct anthropometric assessments to measure obesity and fat distribution, given that they are well established risks for CVD, CKD, and T2D. To assess obesity, fat, and fat distribution, we will measure, in centimeters, height in bare feet (including sitting height) using a stationary stadiometer with headpiece; waist (after exhaling, just above iliac crest); and hip circumference (at point of greatest protrusion of gluteal muscles). Waist and hip circumference will be measured with a flexible ribbon of non-stretchable cloth. The Tanita-780U Multifrequency Segmental Body Composition Analyzer will be used in the study office to derive an estimate of segmental fat mass in arms, trunk, legs, and total body. Prior to BIA, the Tanita Questionnaire will be administered to assess factors which may impact the BIA measurement. For assessments conducted outside of our offices, we will use the Omron hand-held body fat analyzer.

Macrovascular disease assessments: We will measure risks for macrovascular disease using a sphygmomanometer, SphygmoCor Xcel. We will obtain 3 independent brachial-cuff BP measurements, standardized for the instrument, size of cuff to arm circumference, cuff placement, prior resting time (at least 30 minutes into the session and after 5 minutes of rest), and then one minute apart, after which the system will average the successfully completed assessments to provide a brachial BP, body position, and Phase I and IV sounds.[84] The SphygmoCor Xcel device will be used to estimate carotid femoral Pulse Wave Velocity (cfPWV) and the Augmentation Index (AI). These measures of arterial stiffness are proximal risks for the diseases addressed in this study.

In addition we will use sphygmomanometer, SphygmoCor Xcel. We will obtain 3 independent brachial-cuff BP measurements, standardized for the instrument, size of cuff to arm circumference, cuff placement, prior resting time (at least 30 minutes into the session, and then one minute apart, discarding the first and taking the average of the second and third readings), body position, and Phase I and IV sounds.[84] The SphygmoCor Xcel device will be used to estimate carotid femoral Pulse Wave Velocity (cfPWV) and the Augmentation Index (AI). These measures of arterial stiffness are proximal risks for the diseases addressed in this study.

Table 6. Part 2 Face-to-Face Assessment

Physical Measurements	Interview measures
Obesity, Fat and Fat Distribution	**Illness History & System Review**
Height (standing & sitting), weight, waist & hip circumference	Diagnoses, signs & symptoms, chronic conditions, hospital encounters
Body Composition (segmented & % body fat, visceral fat, muscle mass) (Tanita-780 Multifrequency)	Current Medications
	Disability–Injury/physical/mental Illness
Cardio-Metabolic Risks – Blood	**Eating**
TC, HDL, (calculated) LDL	Diet (% energy scale; eating at America's table); 3-factor eating questionnaire

Triglycerides	**Substance Use**
Glycosylated hemoglobin	TAPS; rehabilitation for substance use
GF-1; FSH	
	Physical Activities & Sleep
Kidney Function–Blood/Urine	Physical activity: IPAQ, Sedentary activity,
U. Albumin; creatinine	SF-20 Physical functioning, role functioning, health perceptions, pain
eGFR	Sleep: (PSQI)
Immune-Inflam. Markers - Blood	**Arrests and Incarceration**
hs-CRP, IL-6, ICF-1	**Raising children (Bavolek)**
Fibrinogen	**Adverse childhood experiences**
TNF-alpha receptor 2	**Depression, Anxiety, Mastery**
Risks for Macrovascular Disease - Arterial Measures	Depression (PROMIS)
Pulse wave velocity; Augmentation Index (SphygmoCorXCEL)	Anxiety (PROMIS)
Resting BP	Mastery (Pearlin)
Mortality – NDI: Cause, date	**Marriage & Partnered Relationships**
	Duration, Support, Cohabitation, Commitment, Satisfaction, Partner hostility and warmth
	Births, pregnancies, and outcomes, partner involvement

Subjects will be asked to give biospecimens: We will draw blood to measure cardio-metabolic factors (see table). We will collect urine samples from all subjects to measure the microalbumin/creatinine ratio. Subjects will undergo a blood draw of approximately 50 ml of blood (up to 50 ml are permitted according to established IRB guidelines), which will be collected by a trained phlebotomist/nurse and processed using standard methods provided by the Medpace Reference Laboratories. Aliquots will be frozen at -80ºC for future analysis of immune, endocrine, and metabolic markers. The study staff will measure the specific gravity (dilution) and temperature of the sample using a handheld refractometer and record the time of collection. Blood and urine samples will be aliquotted and stored at -80ºC using protocols provided by the Medpace Reference Laboratories. Samples will be shipped on a weekly/bi-weekly basis on dry ice to the Medpace Reference Laboratories for analysis and storage for future use.

Administrative data: We will review National Death Index (NDI) records to obtain dates and causes of death. We will send identifying information for all mothers enrolled and children born alive to NDI; this includes maternal and child names, social security numbers, dates of birth, and gender. NDI is the “gold standard” for ascertainment of mortality and cause of death in the US. Estimates of NV-C differences in all of these outcome domains will be interpreted in light of data derived from participant interviews conducted at this phase of follow-up, assessments conducted at earlier phases, and medical/hospitalization records. Other administrative data that will be obtained include medical records, Medicaid, TANF, SNAP and birth certificates.

Neighborhood Adversity Data: We would like to include measures of neighborhood adversity in this study. Neighborhood adversity can be treated as a baseline factor that may either moderate treatment effects on morality or account as a baseline factor that may either moderate treatment effects on mortality or account for variance in our estimates of mortality by treatment condition. We plan to include data on maternal and offspring neighborhood adversity for study participants in treatment groups 1 and 3. A previous study, protocol #04-0518, which is now closed, examined neighborhood adversity for participants in all three original trials. We will send participants’ baseline addresses in these groups at the time of registration in this trial to Geolytics, the firm we used to calculate neighborhood adversity at earlier phases of this study (the 04-0518 study mentioned). There was approval to evaluate neighborhood adversity scores in T2 and T4 in that protocol, but not T1 and T3. We would like to examine neighborhood adversity scores for all four treatment groups in this phase of the study.

Interviews: The majority of subjects will be interviewed in person for Part Two; a small number of Part Two interviews will be conducted virtually. Subjects who complete virtual interviews for Part 2 will not be in the Memphis office and therefore will not be participating in the physical assessment. Registered nurses (RN) will interview participants directly on the components that are health related (systematic health histories, including

signs, symptoms, health care provider diagnoses of chronic diseases, history, medications, surgeries, hospitalizations). Other components of the interview may be conducted by other trained study staff. Some of the measures consist of repeated measures of outcomes examined in earlier phases of the trial. Others, focusing on key behaviors for this phase of follow-up are new measures appropriate to the life stages of the participants and the outcomes being examined. These include measuring physical activity and sedentary activity levels which influence disease risk, dietary assessments, and the PSQI for measurement of sleep. The study staff will also collect information on use of substances, depression, anxiety, sense of mastery, duration and quality of partnered relationships, education, work, and incarceration. We will assess the availability and source of medical care. This information will be used to make judgements about referrals (addressed below) in light of abnormal physical assessments and lab results.

Sharing results of clinically relevant laboratory results and physical assessments with participants**.** We will share results of key physical health measurements at the time of assessment in the study office. Serious conditions reflective of imminent risk will be referred for emergency care (e.g. elevated BP). We will send the results of the clinically relevant urine and blood assays to subjects once results are analyzed, and encourage them to seek care if values exceed clinical cut-offs. If participants have no providers, we will refer them to their State Health Insurance program for help in gaining access to care.

All biological analyses will be done in the Medpace Reference Laboratories. Overview: The following will be analyzed: Lipid Profile (TC, HDL, LDLc, TG), Chemistry Panel (AST, ALT, Serum Albumin and Serum Creatinine), eGFR (calculation), ALT/AST ratio (calculation), HbA1c, Urine Albumin/Creatinine, FSH, hsCRP, Fibrinogen, IL-6, TNF-alpha receptor 2 and IGF-1 (total).

Data Processing. Blood and urine samples will be processed for storage on site in Memphis, stored at -80 Celsius, and shipped weekly/bi-weekly to the Medpace Reference Laboratories, where the MedPace team will conduct standard assessments for the clinically relevant analytes as they are received. MedPace will only have unique codes which are not the same as study IDs and they will not have access to individual identifiers. They will send results to the University of Rochester as they are analyzed through Box; the UR team will be responsible for creating a work file for analysis and one of the RNs on the Rochester team will notify participants of the results of their clinically relevant blood and urine assays (e.g. lipid panel, HbA1c). Specimens for less commonly assayed analytes (those used for research purposes only - IL-6, TNF-alpha receptor 2, IGF-1) will be stored and assayed in batches.

All interview data will be entered into REDCap by study staff and/or study participants. Physical assessment data will be entered into REDCap by the Memphis study staff, These data will be accessed by UR data management staff for the construction of data files. Signed consents to review medical and/or hospitalization records will be sent to the UR data processing team where they will process requests for records. Upon receipt of medical records, the UR team will code lengths of stay and I-CD 10 diagnoses. Biomarker and assessment results will be interpreted in light of self-reported diagnoses, medications, and medical/hospitalization records. Original singed consents and releases will be forwarded to and stored in Denver.

Analysis

Approach to Addressing Specific Aim One

For Hypotheses 1-5, we will examine NV-C adjusted mean differences in the individual measures specified in each of the primary outcome domains, (as well as values that exceed clinical thresholds) employing statistical models described below in the Statistical Models and Methods section. For Hypothesis 6, we will employ survival analysis to examine differences.

H1: Measures of Obesity, Fat, and Fat Distribution. We will compare NV and C participants on standard measures of BMI, waist and hip circumference, as well as segmental fat mass in arms, trunk, legs, and total body. Note that for assessments conducted outside of the Memphis office, we will resort to % total body fat.

H2: Risks for Macrovascular Disease. We will compare NV and C participants on measures of arterial stiffness: peripheral systolic and diastolic BP (averaged over the two assessments), cfPWV, and AI.

H3: Markers of Chronic Kidney Disease (CKD). We will compare NV and C participants on the estimated Glomerular Filtration Rate (eGFR) and the microalbumin/creatinine ratio.

H4: Metabolic Outcomes: We will compare NV and C participants on measures of Glycosylated Hemoglobin (HbA1C), dyslipidemia (TC, LDL, HDL, TG), and the AST/ALT ratio.

H5: Immune/Inflammatory Markers: We will compare NV and C participants on immune/ inflammatory markers [hsCRP, fibrinogen, interleukin 6 (IL-6), tumor necrosis factor alpha-receptor 2 (TNF-2), and insulin-like growth factor-1 (IGF-1 – free and total].

H6: Mortality. We will compare NV and C participants on rates, ages, and causes of death.

The interpretation of outcomes specified in H1-6 will take into consideration the presence of existing disease and disabilities, based upon interviews, records of medication, diagnoses, and hospitalization records.

Approach to Specific Aim Two (Examine Moderators of Intervention Effects)

As elaborated below, we will examine all outcomes in this study in statistical models that employ sex of offspring as a classification factor and maternal psychological resources cross-classified with Treatment condition (NV-C). We have hypothesized (H7) that intervention effects (H1-5) will be more pronounced among females and mothers who gave birth to females, so analyses of NV-C differences will focus on these groups. We have elaborated methods to address this aim under the statistical methods and models below.

Approach to Specific Aim Three (Explore Mediators of NV Effects)

We have hypothesized (H8) that NV effects on maternal primary outcomes will be mediated by earlier NV effects on the index of prenatal health behaviors, pregnancy outcomes (PIH in first births, preterm delivery), closely spaced subsequent pregnancies, sense of mastery, stable family structure following offspring birth, government benefit payments to the family, and hypertension at 12 and 18 years postpartum. We also have hypothesized (H9) that NV effects on offspring outcomes (H1-6) will be mediated, in part, by NV effects on the index of prenatal health behaviors, PIH, preterm delivery, breast feeding, maternal caregiving dysfunction (an index composed of maternal beliefs associated with child maltreatment and observed qualities of the home environment in the first 2 years of life), screen time at age 12, duration and quality of relationships, government benefit payments to the family, and obesity and prehypertension at ages 12 and 18.

Data from current participant interviews on sedentary and physical activity, sleep, diet, use of substances (especially cigarette smoking), depression, anxiety, sense of mastery, chronic pain, stable/supportive partnered relationships, educational achievement, paid employment, health insurance, and incarceration will be used as sources of data to explore other potential mediators of NV effects. Among offspring, we will gather reports of pregnancies and births since last interview dates. These sources of data will be explored as possible additional mediators on NV effects.

Statistical Models and Methods of Analysis

The primary analyses will make use of general linear model methods and their extensions.[89-94] The focus will be on (1) full model specification to account for all sources of variation, and full examination of interactions among model factors, including examination of homogeneity of regressions to understand interactions between classification effects and covariates; (2) generalized models to analyze dichotomous outcomes with binomial error distributions and count data assumed to have negative binomial distributions; (3) generalized linear mixed models (including repeated measures and growth-curve models) to account for correlated data and to examine differences in change over time; (4) semiparametric methods to model relations between variables without requiring a specific functional form;[95] (5) survival analyses including Kaplan-Meier, competing risks and Cox hazard models; [96-99] (6) mediation analyses using structural equation models to examine causal processes, including the direct and indirect effects of treatment on outcomes. [100,101]

The primary classification factors for examination in our models, as determined by our hypotheses and earlier work, include treatments (Control vs. Nurse Visited - T), maternal psychological resources (low versus high based on a median split – P), sex of offspring (S), and follow-up time (A) for outcomes assessed at multiple time points (e.g. obesity) – T|P|S and T|P|S|A. Covariates will be selected using a post-double-selection lasso (least absolute shrinkage and selection operator) procedure.[102-104] This procedure will select covariates that are most related to intervention status (i.e. differences at randomization) or related to the dependent variable. Candidate covariates will include an index of household poverty, obesity, and maternal

pre-pregnancy BMI.

Statistical Power/Smallest Detectable Differences for Proposed Follow-Up

Given that sample size is fixed, we show below calculations of the smallest detectable treatment-control differences for the 29-year follow-up. Calculations for representative outcomes were carried out with the following assumptions: a Type I error of .05, Type II error of .20 (power of .80), 2-tailed tests, 10 percent of the variance accounted for by other terms in the model for normally distributed variables and N=600. Disproportionate sample sizes in Control and Nurse-Visited groups are taken into account.

Smallest Detectable Program Effects. Table 6 displays the smallest detectable treatment differences. The study has sufficient power to detect small to moderate effect sizes for normally distributed variables for tests of treatment main effects (.24 SD) and moderate effect sizes (.33 SD) for tests conditioned by a single factor that is evenly distributed between two levels (e.g., offspring sex). For outcomes that are dichotomous, our calculations of smallest detectable treatment differences are calculated in the binomial logistic-linear model and shown for a range of base rates likely to be found in our outcomes. It is important to note that we have detected program effects of this magnitude in earlier phases of the trial and that we have seen that some intervention effects are larger as the mothers and offspring age. We will not make adjustments for multiple comparisons of the primary outcomes (Hypotheses 1-5), but will interpret findings with a critical eye concerning chance effects.

Table 7. Smallest detectable treatment effects for treatment main effects and for subgroups defined by sex

Base Rate for OR	Smallest Detectable Treatment Contrasts for ORs	Smallest Detectable Treatment Contrasts for ORs
	Whole Sample N=600	**One Half of Sample (e.g., Mothers of Females) N=300**
10%	.33	.14
20%	.49	.33
30%	.55	.42
40%	.59	.46
	Smallest Detectable Treatment Contrasts for ESs	**Smallest Detectable Treatment Contrasts for ESs**
	.24	.33

Note OR = T_4 odds/T_2 odds; ES = (T_4 mean *minus* T_2 mean)/pooled standard deviation

Tests of Hypotheses

Hypotheses 1-6 (primary): The NV group is hypothesized to have: H1: lower measures of obesity, (BMI, waist to hip ratios, segmental and % body fat, visceral fat); H2: lower risks for macrovascular disease, reflected in measures of functional arterial stiffness (peripheral BP, cfPWV, AI); H3: fewer markers of CKD - higher eGFR and lower microalbumin/creatinine ratios; H4: better metabolic outcomes (lower levels of HbA1C, TC, HDL, LDLc, TG, AST/ALT ratio); H5: lower levels of immune/inflammatory markers (hsCRP, fibrinogen, IL-6, TNF-alpha receptor 2, IGF-1); and H6: lower mortality rates. We will test Hypotheses 1-5 by examining each of the primary outcomes listed above as dependent variables in our primary T|P|S model, plus covariates from the post-double-selection lasso results. Outcomes also measured at earlier time points will include an additional classification factor for first-born offspring age at assessment (A). We will examine treatment–control difference summing across levels of maternal psychological resources and sex. In addition, we will examine planned contrasts for males and females, and mothers of males and females. Outcomes for hypotheses 1-5 are normally distributed and will be examined in the general linear model or mixed linear model for repeated measure outcomes. Secondary analyses will examine some outcomes in their dichotomous form for those values that cross clinical thresholds (e.g., obesity), which will be analyzed in the logistic model or generalized linear mixed model for repeated measure outcomes. [90] Hypothesis 6, related to mortality 6, will be examined in survival analysis by treatment condition without additional classification factors consistent with our earlier report on mortality.[99,69]

Hypotheses 7: NV effects on H1-5 outcomes will be greater for female offspring and mothers who gave birth to females. Planned contrasts in the above aforementioned models for all primary outcomes, with the exception of mortality (given low base rates), will focus on female offspring and mothers of females.

Hypothesis 8: NV effects on maternal outcomes (H1-6) will be mediated, in part, by NV effects on prenatal health behaviors, preterm delivery in first and subsequent births, and PIH in first births; closely spaced subsequent pregnancies, maternal sense of mastery, stable/supportive partnered

relationships, family economic resources, and hypertension at 12 and 18 years postpartum. H9: NV effects on offspring outcomes (H1-6) will be mediated, in part, by NV effects on prenatal health behaviors, preterm delivery, PIH, breast feeding, screen time at age 12, improved partner relationships, family economic resources through age 18, and obesity and prehypertension at ages 12 and 18. Tests of mediation will follow the empirical and theoretical model shown in Figures 1 and 2. We will employ mediation analyses using structural equation models to examine causal processes, including the direct and indirect effects of treatment on outcomes.[100,101] To illustrate, we have hypothesized that NV will have an indirect effect on maternal arterial stiffness through its effect on PIH, preterm delivery, and the count of short inter-pregnancy intervals. To test one aspect of this hypothesis, we will regress maternal arterial stiffness on the count of closely spaced subsequent children (child density) within the control group; we also will regress child density on the treatment contrast. If the paths from the control sample to child density and from density to arterial stiffness are both significant, we will have met the joint significance test criterion. We will next calculate the indirect effect, based on these same two path coefficients, and compare the resultant z' to Mackinnon's table of critical values. If the z' is equal to or higher than the appropriate critical value, we will conclude that density of subsequent children mediates the effect of nurse visitation on maternal arterial stiffness. We will use this approach for each hypothesized mediator separately and jointly to develop a map of mediation.

Challenges in the Conduct of This Work

Missing Data. Missing data in this trial have been remarkably low. We are sensitive to the potential pitfalls of analyzing only cases with complete data.[105] We have complete data on all relevant background characteristics, which we will examine to address potential attrition bias. We also will compare our analyses to the same analyses employing inverse proportional weighting. We will perform sensitivity analyses to ensure that results are similar under various assumptions. We will determine whether imputation is valid and has sufficient added value with our data to justify the complexity involved in reporting these analyses.

Increased Difficulty in Tracing and Engaging Participants. The most significant challenge to this work is attrition bias. While this problem is minimized for the mortality outcome, it is a challenge for those that depend on direct assessments. The best solution is to invest sufficient resources into locating and engaging participants. Note that this study: 1) employs the same local study leader (the wife of a local minister) who will continue to engage the sample; 2) refers participants for further evaluation and treatment for health problems; and 3) remunerates participants adequately for travel and time. These factors reduce participant attrition.

Conducting Assessments among those Outside of the Memphis Region. We have chosen measures that, for the most part, can be assessed in both home and office, except for body fat and arterial stiffness, which creates possible cross-context challenges with validity and reliability, which we will examine as part of this study.

Multiple Comparisons. If we were to make Bonferroni-like adjustments to our statistical tests in this study, the cost of conducting such studies with adequate power would be prohibitive, given the large number of outcomes examined over time. Our approach has been to make specific hypotheses for primary outcomes, look for coherence across outcomes, and to emphasize the importance of replication.[106] This is a sensible strategy that in the long-run minimizes costs and accelerates scientific discovery.

IV. RISK/BENEFIT ASSESSMENT

1. **Risk Category**. Minimal risk.

   Potential Risk. Risk to participants for this study are expected to be minimal; these minimal risks will be minimized by using appropriate space and equipment, attending to all protocols/procedures, and providing adequate personnel selection, training, and supervision. The collection of questionnaire data has inherent risk to confidentiality, however prior to and during study implementation study personnel will be trained to follow protocols to minimize that risk. All study personnel will follow HIPAA regulations and be trained and certified in Human Subjects Protections by the relevant university or institution. We expect that most study activities will pose little discomfort or risk to subjects. If needed, this study will be able to refer to local support services. A blood draw is planned. In no instance will we collect more than

the allowable volume of blood (50 ml), based on consideration of body weight. Risks from blood draws are minimal and may include fainting, dizziness, ill feeling, and bruising during and/or after the blood draw and there is a low risk of infection. To minimize the risk trained nurses/phlebotomists will perform blood draws while participants are sitting or lying down. Collection of urine samples is done as a part of the standard of care and is not likely to cause distress. Measurement of weight and blood pressure is done as part of the standard of care and is not likely to cause distress. Bioelectrical impedance analysis is similar to standing on a scale and not likely to elicit additional distress beyond what weight measurement might. SphygmoCor EXCEL is not likely to elicit additional distress as it is a painless procedure. Anthropometric measurements of obese individuals may cause mild distress. To minimize this distress, the proposed assessments will be detailed during the consent process and confidentiality will be assured. Information will be provided to participants regarding the handling and the identification process involved with the data. Information that identifies subjects and subject number will be kept in the secure servers. Only study staff who have contact with participants will have access to this information. Note that the safety of the Tanita Body-Composition analyzer has not been established for pregnant women, so women who are pregnant or may be pregnant will not have this procedure conducted.

The potential risks to the participants involve the breach of confidentiality. To the extent that the data gathered are divulged to those who are not involved in the data gathering and processing, the subjects are at risk for a breach of their confidentiality. The potential for this problem is reduced by the use of identification codes rather than names on the data collection forms, keeping the data and consent forms in locked file cabinets, and instituting procedures whereby breach of confidentiality by the data gathering and clerical staff is grounds for immediate termination. Individuals with access to the research data are the study staff located at the Memphis site, data management staff based in Rochester, NY, and the Colorado and Rochester-based programming and analysis staff, along with study PIs. All computers will be password protected. Data files will be encrypted during transfer between organizations (e.g. Rochester and Colorado) and stored on servers only accessible to those mentioned above and who have undergone Human Subjects Training. Note that the Tanita body-composition analysis will not be conducted with pregnant women or women who may be pregnant.

Respondent Boredom/Fatigue. The time for data- collection may seem long to some participants. Based on our experience at the 18 year follow-up, total expected time required for the assessment is approximately 2.5 hours which will be acceptable to participants given that prior follow-up assessments have been of comparable length. Nevertheless, some participants may experience boredom or fatigue.

Abnormal BP measurements may indicate a serious health problem.

Protection against Risks. Risks to the participants will be fully explained during the informed consent process and repeated as needed during data collection activities. All study personnel will undergo extensive, standardized training and certification with ongoing quality control monitoring. We will adhere to strict data storage and confidentiality procedures to ensure the privacy and confidentiality of the participants. Only trained phlebotomists/nurses will collect blood samples and only trained study team members will have contact with the subjects. To address concerns about psychological issues (including anxiety and depression), all individuals will be informed about mental health services that are available and will be encouraged to discuss concerns that they may have with their mental health with their clinicians. Wherever possible, the study will make use of existing resources. Interviewers/researchers will be familiar with clinic resources and will be trained in the administration of the questionnaire measures. If patients are highly distressed or show signs of serious depression or psychiatric illness during the study, they will be referred for help through their local county mental health services. Disclosure of child abuse or neglect revealed during the study or observed by study staff will be referred to Child Protective Services in the county in which the child (or parent) lives. Reporting of child abuse or neglect may have psychological and legal ramifications for the family; we will manage any potential disclosures in cooperation with local child welfare services. If an individual reports being

a victim of domestic violence, they will be referred to domestic violence services in the county in which they live. If study staff is concerned about any information shared by a prisoner participant regarding the possibility of self-harm or harm to others, study staff will inform the prison warden or his/her designee via telephone call and will document this call.

Boredom/fatigue risk. This risk will be reduced by: 1) respecting participants' time and contribution; 2) creating a comfortable, welcoming environment; 3) providing a clear explanation of procedures and length of time required during the recruitment, scheduling, and consenting processes; 4) providing transportation and remuneration to participants to reduce associated stress; 5) varying the activities within the assessment; 6) providing a break/refreshment time in the middle of the session; and 7) offering the opportunity for additional breaks or terminating the assessment.

If the blood pressure readings are abnormally high, defined as average systolic BP (SBP) readings greater than or equal to 180 mmHg and/or an average diastolic (DBP) readings greater than or equal to 110 mmHg), participants will have their blood pressure re-checked and assessed by a RN. Participants will be provided with a handout indicating their blood pressure measurements and advised to follow up with their primary care provider or the emergency department as soon as possible. If the subject does not have a primary care provider a referral will be provided.

2. **Potential Benefits to the Subjects**. The participants themselves will receive no direct benefit from this study, although those with potential health problems identified during the course of the assessment will be encouraged to seek further evaluation and treatment through existing health and human services in their community.

Confidentiality of Data and Computer Records for all Coordinating Sites. It is important to note that this study will be conducted in collaboration with the University of Rochester (FWA00009386), and the Medpace Reference Laboratories; and, directly obtained participant data will be collected under the oversight of University of Rochester investigators in a Project controlled office in Memphis, Tennessee. The Medpace Reference Laboratories will not have access to individual identifiers. In all sites, staff given access to the data will have all human subjects training up to date and have read and agreed to everything in the confidentiality agreement. A log will be kept of any staff granted access to the data. We will take the following steps to protect the confidentiality of our data and computer records:

- All study staff will receive extensive training in maintaining participant confidentiality.
- Identification codes rather than names will be used on all data collection forms and data transfers.
- The handling of data generally will be limited to the numerical values and statistical summaries.
- The identifiers linking identification codes with individual names are only available to the Memphis staff, Rochester staff and PI and co-PIs. They will be kept in a secure database on an encrypted server.
    - < PHI is stored in File Maker Pro 18 which is maintained by the University of Rochester School of Nursing. This same software has been used to store participants PHI for past phases of the Memphis New Mothers Study. FileMaker Pro: University of Rochester, School of Nursing runs a FileMaker Pro (FMP) 18 server that is used for protecting Protected Health Information (PHI) (including name, phone number, email address, home address, and Social Security Number (SSN)). This database will hold the link between participant ID and actual identity and is designed to ensure that authorized users have minimal data access as possible in their roles.
        - Only those who need to assess PHI information will have access granted by their login name privilege set. Usernames and passwords are managed by Rochester study office and a list of usernames and allowable PHI access will be obtained on a log in Rochester study office.
        - The FileMaker server is housed in the UR Medical Center's internal network, which is protected from the public Internet by firewalls, along with the UR Medical Center's electronic

health record and other restricted assets. The server runs Cylance anti-virus and is backed up nightly with 30 days' retention with replication to a off-site facility.

- Consents and any data collection forms that are in paper format will be stored in a locked file drawer, in a room that is locked when it is unoccupied.
- Data collection forms will be shredded when they are no longer relevant (e.g., after entered into REDCap).
- To ensure that data are not co-mingled with data from other projects, data will be stored in its own subdirectory with access only granted to individuals approved to work on this project.
- The data received will not be used for purposes other than what is described in this application, or consented to for future research by study participants.
    - Personal computers will be logged off at the end of each work day to prevent inadvertent access to the network and to data stored on the computer hard drive.
    - A screensaver password will be engaged during the day to prevent people from accessing data while individuals are out of the office.
    - An access control list through arrangements with network administrators will be used to limit the number of people who have permission to access the network subdirectory where sensitive data are stored.
    - Consideration may be given to storing sensitive data only on the secure network when it is being analyzed. More permanent storage would then be on an encrypted drive on a server at the University of Rochester. .
    - Sending sensitive data via email will be minimized.
        - Email within the University of Rochester and University of Colorado is automatically encrypted
    - All data transfers will be done via Box (from Memphis to UR; from UR to Colorado; from Medpace to UR). See flow chart at end of document.

- Confidentiality of Data and Computer Records Specific to Denver
    - < Physical Control. Paper associated with study PHI will be stored in a locked cabinet in our locked file room which is accessible to a very limited number of people who must use their ID badge to electronically unlock the door. During non-work hours the building itself is locked and an ID badge is required for admittance. All output that is identifiable will be recycled using a protocol for sensitive data (i.e. put in a locked trash container in a secure room and ultimately shredded by a company that deals with sensitive data).
    - < Technical Control. Data will be stored on the University of Colorado network on a drive called "Sensitive" which has very limited access (i.e. one statistician and the data coordinator). Programs and output will be on the same "Sensitive" shared drive. No identifiable data will be stored outside of this Sensitive drive.
    - < Administrative control. As part of the university network the Office of Information Technology provides an enterprise level backup service for backup of data. Data on the server are backed up the night the file is first created; As the file is modified, each revision of that file is also backed up and is kept for 30 days; At day 31, the earliest revision is removed from the backup environment; The last copy of the file is kept (assuming no additional modifications) until it is deleted from the server; Secondary of backup data is retained off-site for disaster recovery purposes.

- Confidentiality of Data Specific to University of Rochester, the Memphis Study Office, and the Medpace Reference Laboratories. The use of the following modalities ensures secure transfer of data between Memphis where the data are gathered and University of Rochester where the data are processed and stored and the finished file sent to University of Colorado.
    - < University of Rochester School of Nursing's Windows File Server – This is the site where information private to Memphis/SON will be stored. Connection to it from a non-direct site requires use of the University of Rochester Medical Center (URMC) VPN (Cisco AnyConnect, which requires Duo multi-factor authentication). This server is in the University of Rochester's

Primary Data Center, which provides adequate physical security controls to meet its Electronic Medical Record requirements.

< Memphis Computers — All of the desktop and laptop PCs will be secured to meet URMC standards: managed full disk encryption (Microsoft BitLocker) plus anti-virus (Cylance).

< Memphis Network — We have a permanent VPN in place between the Memphis network and the URMC network to protect data in motion.

- REDCap — The University of Rochester manages a REDCap database instance. Access to the site requires HTTPS / TLS transport security. This service is also hosted in the University of Rochester's Primary Data Center.
- Box — University of Rochester has a HIPAA BAA with Box for storage of data and sharing with collaborating institutions / researchers. This is the University of Rochester's preferred method of transporting data electronically. BOX is the primary place where information is to be shared, between Memphis (Rochester employees), University of Rochester, MedPace, and University of Colorado. Box protects the data during transmission by HTTPS / TLS security. Strict, streamlined procedures will be followed regarding data transmission and its confirmation.
  - Memphis staff will upload data into Box at the end of each data collection day and send confirmation to Rochester staff on identification codes uploaded. Rochester staff will be responsible for confirming receipt of data by identification codes and the transfer of data from BOX to the University of Rochester file server. All files will be removed from BOX once files transfer is complete. A similar process was in place at the 18 year follow up between the Memphis office and the University of Rochester.
  - Memphis staff will ship blood and urine samples to the Medpace Reference Laboratories labeled by an identification number that is different from the main study identification number used in data collection. MedPace staff will transfer blood and urine results to the University of Rochester in Box. Rochester staff will be responsible for confirming receipt of data by identification codes and the transfer of data from BOX to the University of Rochester file server. All files will be removed from BOX once file transfers are complete.
  - University of Rochester will upload the final analysis file via BOX to the University of Colorado using the same process.
  - University of Rochester Box will have separate shares with the Memphis office, Medpace Reference Laboratories, and University of Colorado with separate permissions.

Data and Safety Monitoring Plan

Monitoring: We have created an independent Data Safety Monitoring Board (DSMB) consisting of Allison Kempe, M.D., Professor of Pediatrics at the University of Colorado, Zhaoxing Pan, biostatistician from The Children's Hospital Research Institute in Denver, and Sara Brewer. MPA, instructor, Department of Family Medicine, and chair of the DSMB. This group will meet as needed (and at least yearly) to review any reports of untoward events and to monitor their resolution. At the stage of analysis and interpretation of data from the next phase of follow-up, this group will meet with the principal investigators and members of our biostatistical team to review the findings to determine whether there are any negative side effects. Minutes will be kept of the meeting and following DSMB meetings, the results of the meeting concerning possible negative side effects will be documented by Ms. Brewer and sent to the PIs and appropriate NIH staff, or other appropriate institutions depending upon the nature of risk identified.

Management of Untoward Events

How an "Untoward Effect" May Be Discovered:

- Data analysis uncovers treatment effects with higher rates of adverse events or outcomes in the nurse-visited groups compared to the control groups. While statistically significant differences may not pose a problem for individuals, the possibility of adverse program effects needs to be considered carefully.
- Staff member discovers that participant personal health information has been revealed to individual or group who does not have permission for this information.

- Participant verbalizes or displays high level anxiety or fear to the interviewer or other staff member regarding research procedures.

How an Untoward Effect Will Be Reported:

- At the stage of data analysis, data analysts and investigators will keep a log of any test of treatment contrasts that produce statistically significant effects in the unexpected direction, or a pattern of trends in the unexpected direction. The Data Safety Monitoring Board group will meet with the principal investigators and members of our biostatistical team to review the findings to determine whether there are any negative side effects. Following the DSMB meeting, the results of the meeting concerning possible negative side effects will be documented by Ms. Sara Brewer (a member of our Data-Safety Monitoring Board) and sent to the PIs, the IRB, and appropriate NIH staff.
- Any breach of confidentiality is cause for termination. Breaches of confidentiality will be identified and reported to the DSMB and IRB by the PI whenever they occur. The DSMB will report these infractions to the IRB and NIH.
- Instances of extreme anxiety or fear will be noted in a confidential log and reported to the PI, who in turn will report this information to the DSMB. A record of these problems will be submitted to the IRB. Referral of Cases for Further Evaluation and Treatment: Should an Untoward Event occur, the data gathering staff in Memphis will discuss the untoward event with their supervisor, who will make an appropriate referral for further evaluation and treatment within the health and human service delivery system in Memphis. The Memphis leadership staff members have been with the study for nearly 15 years and are well-positioned to evaluate and make appropriate community referrals, given the types of untoward effects that may occur in this study.

Follow-up and Referral: The PI will be informed of all reported adverse outcomes, including who is referred for further evaluation and treatment and the outcomes.

Confidentiality: The PI will maintain information on monitoring untoward events, but will do so without specific patient identifiers.

Implementation of Monitoring Recommendations: The monitoring board will review cases and make written recommendations to the PI and investigative team regarding safety procedures and the procedures employed in the study to ensure participant safety. These recommendations will be reviewed at special meetings of investigators and research team members to institute any changes in procedures that would improve participant safety and that would ensure that they receive appropriate treatment and follow-up in a timely way.

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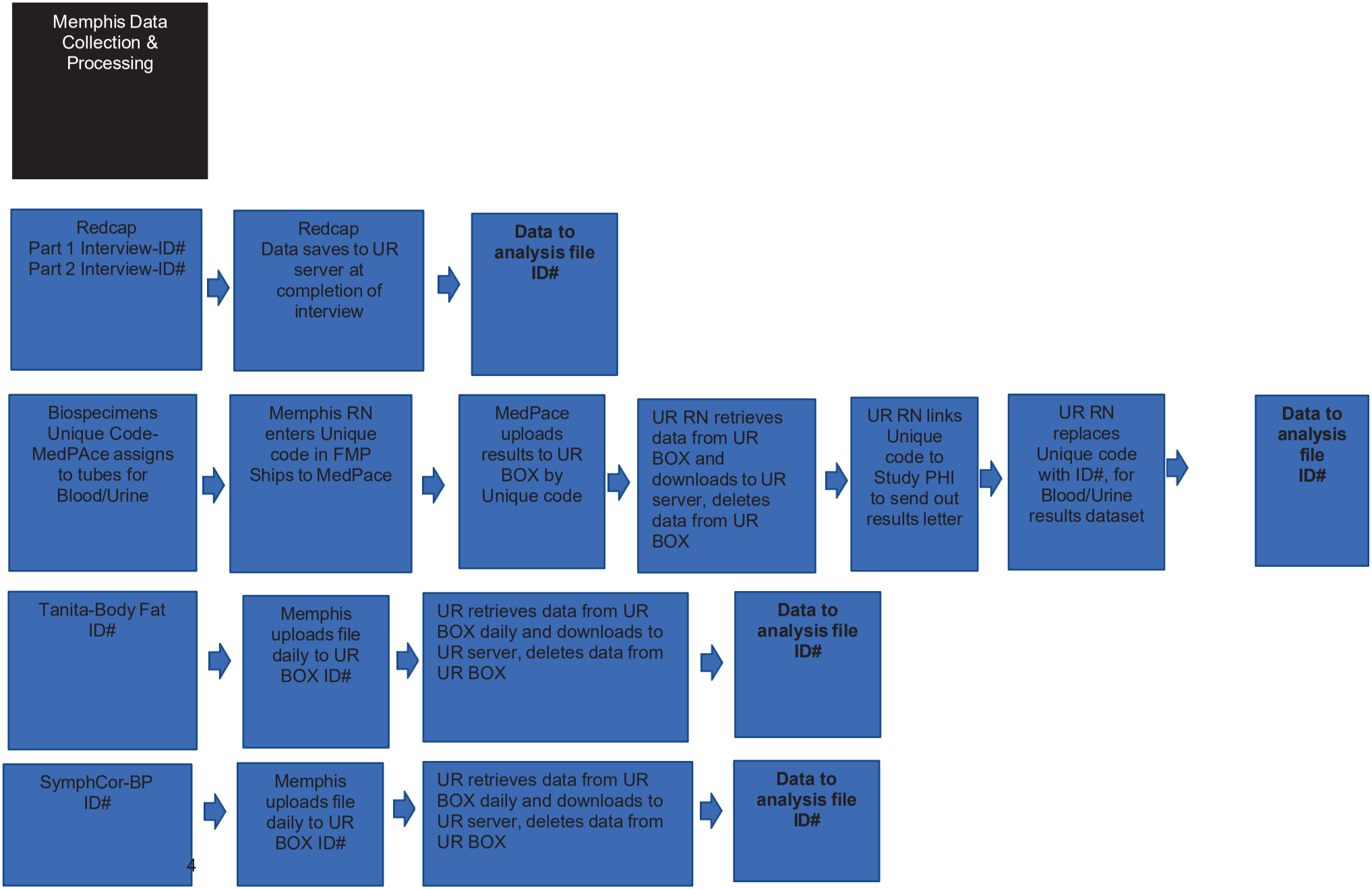
Memphis Data Collection & Processing
Redcap Part 1 Interview-ID# Part 2 Interview-ID#
Redcap Data saves to UR server at completion of interview
Data to analysis file ID#
Biospecimens Unique Code-MedPAce assigns to tubes for Blood/Urine
Memphis RN enters Unique code in FMP Ships to MedPace
MedPace uploads results to UR BOX by Unique code
UR RN retrieves data from UR BOX and downloads to UR server, deletes data from UR BOX
UR RN links Unique code to Study PHI to send out results letter
UR RN replaces Unique code with ID#, for Blood/Urine results dataset
Data to analysis file ID#
Tanita-Body Fat ID#
Memphis uploads file daily to UR BOX ID#
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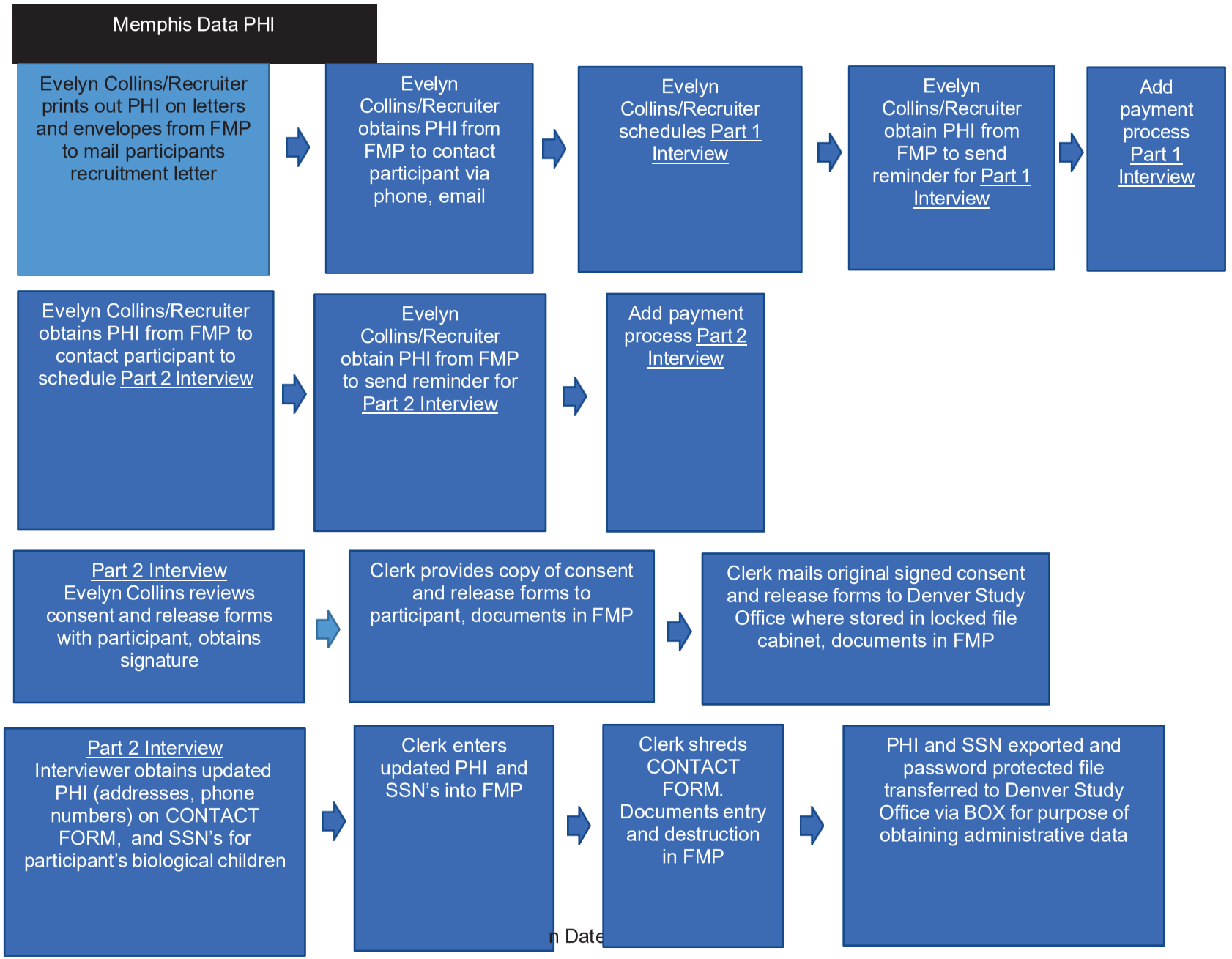
Memphis Data PHI
Evelyn Collins/Recruiter prints out PHI on letters and envelopes from FMP to mail participants recruitment letter
Evelyn Collins/Recruiter obtains PHI from FMP to contact participant via phone, email
Evelyn Collins/Recruiter schedules Part 1 Interview
Evelyn Collins/Recruiter obtain PHI from FMP to send reminder for Part 1 Interview
Add payment process Part 1 Interview
Evelyn Collins/Recruiter obtains PHI from FMP to contact participant to schedule Part 2 Interview
Evelyn Collins/Recruiter obtain PHI from FMP to send reminder for Part 2 Interview
Add payment process Part 2 Interview
Part 2 Interview
Evelyn Collins reviews consent and release forms with participant, obtains signature
Clerk provides copy of consent and release forms to participant, documents in FMP
Clerk mails original signed consent and release forms to Denver Study Office where stored in locked file cabinet, documents in FMP
Part 2 Interview
Interviewer obtains updated PHI (addresses, phone numbers) on CONTACT FORM, and SSN's for participant's biological children
Clerk enters updated PHI and SSN's into FMP
Clerk shreds CONTACT FORM. Documents entry and destruction in FMP
PHI and SSN exported and password protected file transferred to Denver Study Office via BOX for purpose of obtaining administrative data