This document was prepared by the investigators to provide supplemental protocol and statistical methods details regarding the randomized clinical trial registered under ClinicalTrials.gov Identifier: NCT02210832.

**History of Modifications**

Modification on Oct 1, 2013: To assure that Best Practices were implemented, a decision was made to have study staff make initial and follow-up referrals of all trial participants in the Best Practices and Best Practices +Financial Incentives conditions to the Vermont Quitline rather than train referring physicians to make those referrals.

Modification on August 15, 2019: In light of evolving guidance on the risk-benefits of breastfeeding among women continuing to smoke, we decided to expand our analyses of breastfeeding to also include the percent breastfeeding while sustaining smoking abstinence.

Modification on January 23, 2020: We replaced proposed low-birth weight as a birth outcome with small-for-gestational-age ($<10^{th}$ percentile) deliveries to reduce potential confounding with differences in gestational age based on information provided in the 2020 U.S. Department of Health and Human Services, *Smoking Cessation: A Report of the Surgeon General*. U.S. Department of Health and Human Services, Center for Disease Control and Prevention, National Center for Chronic Disease Prevention and Health Promotion, Office of Smoking and Health, 2020.

Modification on September 1, 2021. In completing the cost-effectiveness analyses we made updates to reflect guidelines and data sources published since our protocol was originally reviewed by funders

and local IRB in 2013. Our final analyses follow recommendations published in 2016 from the Second U.S. Panel on Cost-Effectiveness in Health and Medicine (Neumann et al. *Cost-effectiveness in Health and Medicine, 2nd edition.* New York: Oxford University Press. 2017). They state that cost-effectiveness analyses should include a provider and/or public payer perspective to better inform producers and payers about the intervention's costs of adoption. In updating our data sources, we incorporated methods used in the only other cost-effectiveness analysis in the peer-reviewed literature on the use of abstinence-contingent financial incentives with pregnant women who smoke (Boyd et al. Are financial incentives cost-effective to support smoking cessation during pregnancy. *Addiction*. 2016; 1111(2): 360-70). More specifically, we adopted their method of translating smoking abstinence into QALY gains, which permits QALYs to be derived directly from data available in the trial based on "absolute difference percent" (ADP) (see Stapleton JA, West R. A direct method and ICER tables for the estimation of the cost-effectiveness of smoking cessation interventions in general populations: applications to a new cystine trial and other examples. *Nicotine Tob Res*. 2012. 14(4): 463-71).

The protocol information provided below is what the local Institutional Review Board approved for this randomized clinical trial comparing Best Practices, Best Practices +Financial Incentives, and Never Smokers.

## Table of Contents

**Content** **Page Number**

Project Summary:……..…….……4

Research Design and Methods:…….....6

Statistical Methods:……13

Protection of Human Subjects:……...19

References:……..26

## Project Summary

Smoking during pregnancy is the leading preventable cause of poor pregnancy outcomes in the U.S. Most pregnant smokers continue smoking through pregnancy producing serious immediate and longer-term adverse health consequences for the infant. Smoking during pregnancy is highly associated with economic disadvantage and a substantive contributor to health disparities. Efficacious interventions are available, but cessation rates are low (<15%) and improvements in birth outcomes often modest or absent. Current treatments usually entail relatively brief, low-cost interventions (e.g., pregnancy-specific quitlines). There is broad consensus that more effective interventions are sorely needed. We have developed a novel behavioral economic intervention in which women earn financial incentives contingent on smoking abstinence. In a meta-analysis of treatments for smoking during pregnancy, effect sizes achieved with financial incentives were severalfold larger than those achieved with lower intensity approaches or medications. The intervention also appears to improve birth outcomes and increase breastfeeding duration. While highly promising, further research is needed in at least three areas. (1) The evidence on birth outcomes and breastfeeding is from studies that combined data across trials rather than a single prospective trial, (2) whether the intervention produces other postpartum improvements in health has not been investigated, and (3) the overall cost effectiveness of this approach has not been examined. To examine these unanswered questions, we are proposing a randomized, controlled clinical trial comparing the efficacy and cost effectiveness through one-year postpartum of current best practices for smoking cessation during pregnancy vs. best practices plus financial incentives among 230 pregnant, Medicaid recipients. We will also include a third condition of 115 pregnant nonsmokers matched to the smokers on sociodemographic and health conditions to compare the extent to which the treatments reduce the burden of smoking and to estimate how much more might be accomplished by further improvements in this incentives intervention without exceeding cost effectiveness. We hypothesize that best practices plus financial incentives will be more effective than best practices alone, that the incentives intervention will be cost effective, and that while

adding the incentives reduces a greater proportion of the health and economic burden of smoking than best practices alone, more can be done while remaining cost effective. Overall, the proposed study has the potential to substantially advance knowledge on cost-effective smoking cessation for pregnant women. Importantly, because of the strong association between smoking during pregnancy and economic disadvantage, the proposed study also has the potential to contribute new knowledge relevant to reducing the serious challenges of health disparities.

## Research Design and Methods

We proposed a parallel groups design involving three study conditions. Across two of the conditions we will employ a conventional randomized, controlled clinical trial research design comparing outcomes between two treatment approaches to smoking cessation during pregnancy. The third condition will represent a group of women who are biochemically-verified nonsmokers and matched to women in the smoking cessation conditions on characteristics that may influence health and health-care-utilization outcomes.

### Participants

Study participants will be 345 pregnant Medicaid recipients > 18 yrs of age who will be recruited from obstetric practices and the WIC office located in the greater Burlington, VT area using procedures developed in our prior trials (e.g., Heil et al., 2008; Higgins et al., 2004b). As noted above, 230 of these women will be smokers and 115 nonsmokers recruited from the same clinics. Pregnant women attending their first prenatal visit will be identified from the appointment schedules. The practices' receptionists will request that women complete a brief self-administered smoking screening form containing a multiple-choice question on smoking status that has been validated to enhance accurate reporting (Mullen et al., 1991). Women who endorse smoking in the 7 days prior to screening will be invited for an intake assessment that will provide a more thorough determination of study eligibility. For inclusion in the cessation trial, women must report being smokers at the time that they learned of the current pregnancy, report smoking in the 7 days prior to the first prenatal care visit, be confirmed as a smoker by urine cotinine testing, be < 25 weeks pregnant, reside in the county in which the clinic is located, speak English, and plan on remaining in the geographical area through 12-months postpartum. Two hundred and thirty eligible smokers who agree to participate and provide written informed consent will be randomly assigned to one of the two treatment conditions described below. Women who endorse no smoking in the 7 days prior to screening will be similarly invited for the same detailed assessment and biochemical verification of smoking status. To be eligible they must report

being nonsmokers at the time they learned of the current pregnancy, report no smoking in the past 6 month, and report smoking < 100 cigarettes in their lifetime, the conventional definition of a never smoker (Pomerleau et al., 2004). Recruiting never smokers will substantially reduce the likelihood of women in this condition converting to smoker status during the study. They must also meet other study inclusion criteria listed above and will be frequency matched to women in the two smoker conditions on the following characteristics that may influence outcomes: (1) maternal education (% < 12 years), (2) pre-pregnancy body mass index (% > 25, % > 30), (3) parity (% primigravida), (4) age (% < 20 yrs), (5) comorbidities (% diabetic, % hypertensive), and (6) recreational use of cocaine/opioids in past 12 months (% reporting yes). Initially, the distributions of these characteristics will be based on our previous trials but where necessary adjustments will be made as smokers are enrolled into the proposed trial. Because women will be recruited at the start of their prenatal care, we will not yet know infant sex and thus will not be able to balance across conditions on that characteristic. We anticipate comparable distribution of infant sex across study conditions, but will include it as a covariate in analyses of birth and infant health outcomes if it differs significantly across study conditions.

**Treatment Conditions**

**Best Practices Alone.** The 2008 Clinical Practice Guidelines for smoking cessation recommends that pregnant smokers should be provided with the 5As (Fiore et al., 2008). To ensure that referring obstetric practices in the proposed recruitment area are acquainted with the 5As, our staff will conduct office-based training sessions with all referring practices prior to the start of study recruitment and at least once annually throughout the course of the study using training procedures developed previously by our research team and utilized in our prior studies. Practitioners will be trained to implement the following steps: (1) Ask about smoking status starting at first prenatal care visit; (2) Advise those who endorse smoking about the potential harm of smoking to mother and fetus and recommend quitting; (3) Assess the willingness of smokers to make a quit attempt during pregnancy; (4) Assist those willing to make a quit attempt by helping to establish a quit plan, by referring them to the Vermont pregnancy-

specific quit line described below and offering assistance with making the initial contact from the office, and by providing each woman with a copy of the pregnancy-tailored self-help guide "Need Help Putting Out That Cigarette?", distributed by the American College of Obstetricians and Gynecologists; (5) Arrange for follow-up contacts on smoking at each subsequent prenatal care visit. They will refer women to the Vermont pregnancy-specific quitline, operated by Free & Clear, which provides eight proactive telephone counseling calls during the antepartum period, with one prior to a quit date, two within the first week of quitting, and the final antepartum call just before the woman's delivery date. Two additional counseling calls are made during the postpartum period. Calls average about 10 min in length. The quitline makes five attempts to reach the woman within a 3-day period for each scheduled telephone counseling session. We will obtain permission from women to request from Free & Clear the number of telephone counseling sessions completed by each woman during the course of the study.

**Best Practices + Financial Incentives.** Women assigned to this condition will receive the same 5As intervention from providers plus the incentives intervention described above that will be delivered by project staff. Briefly, women report to our smoking-cessation clinic or have a research assistant meet them at a location convenient for them according to a predetermined schedule. At these visits, the women can earn points recorded on vouchers contingent on biochemically-verified abstinence from recent smoking. Abstinence will be assessed for five consecutive days in week 1, decreasing to twice weekly in week 2 where it remains for the next 7 weeks, then decreasing to once weekly for 4 weeks, and then to every other week until delivery. During the postpartum period, abstinence monitoring will be weekly for 4 weeks and then every other week through 12 weeks postpartum at which point the voucher program will be discontinued. The monetary value of vouchers will be kept as they were in our prior trials for women who report smoking < 10 cigs/day at study intake assessment, with the initial negative test specimen worth 5 points at a value of $1.25 per point ($6.25). Each consecutive negative test specimen increments the number of points earned by 1 such that the 2$^{nd}$ consecutive

negative specimen is worth 6 points ($7.50), the 3rd negative specimen 7 points ($8.75), the 4th specimen 8 points ($10.00), etc. Voucher value continues to escalate upward based on consecutive negative test results until it plateaus at a maximal value of $45. A reset contingency is used wherein a positive test or failure to submit a specimen for a scheduled test resets the number of points earned back to the initial 5 points. This reset component of the schedule protects against relapse once an initial period of abstinence has been achieved (Roll & Higgins, 2000). Two consecutive negative tests following a reset returns the number of points earned back to the value that they were at prior to the positive test result. In the postpartum period, voucher value is set at a flat $45/negative test (36 points) independent of how much abstinence was achieved antepartum. A positive test result or failure to submit a scheduled specimen lowers the voucher value to 5 points ($6.25), but two consecutive negative tests returns voucher value back to $45 in the postpartum period. Total possible earnings for a woman who participated in the voucher program for 32 weeks antepartum (duration varies depending on where in the pregnancy a woman enters prenatal care) and 12-weeks postpartum and sustained abstinence throughout is $1,225 ($865 antepartum & $360 postpartum). For women who report smoking > 10 cigs/day at the study intake assessment the schedule described above will be identical except that voucher value will be increased 2-fold at each step such that maximal total earnings = $2,450 ($1,730 antepartum & $720 postpartum). Because vouchers are only paid out when women are abstinent, we project mean payouts of $613 and $1,226 across 9 months or approximately $2.27/day and $4.54 /day across the lower and higher voucher values. Women will not be informed of our criteria for determining who receives higher value incentives. We have conducted prior trials with differing voucher values among substance abusers without difficulty by explaining that interventions are individualized just as medications dosages often are (Higgins et al., 2007a). We anticipate being able to do so in the proposed study. Regarding use of pharmacotherapies, our practice is to explain to women the risks and benefits of using them but recommend against their use because they have not yet been shown to be effective among pregnant women and may interfere with the opportunity to earn

vouchers through cross reactivity with urine cotinine testing. We will monitor use of all such products so that their use could be considered as a potential covariate in the data analysis. There has been minimal use in our prior trials (< 1%).

**Never-smokers condition.** Women in this condition will be assessed at the study intake assessment, second prenatal care visit, at 28-weeks gestation, and then 2-, 4-, 8-, 12-, 24-, and 48-weeks postpartum using the battery outlined below. As described further below, they will also participate in the sonographic serial measures of fetal growth at 30 and 34 weeks and receive monthly postpartum calls from staff to monitor infant health and health care utilization. There will be no other contact with them.

**Assessments**

At the first prenatal visit all participants will complete an assessment addressing six areas: (1) Sociodemographics: age, yrs of education, race/ethnicity, marital status, and health insurance status. (2) Medical/pregnancy history: height/weight, self-reported pre-pregnancy weight, weeks pregnant, history of complications in prior pregnancies; unstable medical problems (e.g., preeclampsia) in current pregnancy; and use of medications, alcohol, and caffeine. (3) Smoking history: age started smoking, average number of cigarettes smoked per day now and immediately before this pregnancy, time to first cigarette in the morning, number of previous quit attempts, number of other smokers in the household, nicotine dependence/tolerance (Fagerstrom & Schneider, 1989), and nicotine withdrawal (Hughes & Hatsukami, 1986). Smoking Timeline Follow-back interviews will be conducted (Brown et al., 1998) to characterize daily smoking rates since learning of the current pregnancy. (4) Smoking attitudes: motivation to stop, confidence in ability to stop, intention to quit before the baby is born, intention to remain abstinent after the baby is born, and measures of perceived stress. (5) Biochemical verification of smoking status: breath CO and urine cotinine levels. (6) Mental health/executive function: lifetime history of depression, general psychiatric symptoms (Brief Symptom Inventory, Derogatis, 1993), current depressive symptoms (BDI, Beck & Beck, 1972), discounting of delayed

hypothetical monetary rewards (Johnson & Bickel, 2002). Appropriately modified versions of this battery will be completed again at the second prenatal care visit and 28-weeks gestation, and then 2-, 4-, 8-, 12-, 24-, and 48-weeks postpartum. We will also assess breastfeeding, including initiation, duration, and different levels of breastfeeding (e.g., exclusive, predominate, any). All women will complete the Postpartum Bonding Questionnaire to examine associations between breastfeeding and maternal/infant bonding (Brockington et al., 2001). Breastfeeding is associated with significant improvements in a wide range of maternal and infant health outcomes, but there have been few opportunities to examine experimentally altered rates of breastfeeding due to the absence of ethical methods to manipulate them (Ip et al., 2007). The proposed study may provide an opportunity to do so by altering smoking status, which in turn impacts breastfeeding duration (Higgins et al., 2010b). These assessments will be conducted with all subjects independent of smoking status or treatment condition. Women will receive $50 per assessment independent of smoking status. We also plan to assess health outcomes and health care utilization for use in the cost-effectiveness analysis. Permission will be requested of all women to review maternal and infant health care records through one-year postpartum and to telephone mothers monthly during postpartum to review infant health and health care visits. Project staff will review records by obtaining faxed copies or visiting the offices of local providers/pharmacies at the time of each of the regularly scheduled assessments. We will track the incidence of smoking-related pregnancy complications, delivery complications, and maternal and infant health outcomes during the 1st year postpartum (all illnesses requiring a visit to a healthcare professional). Infant outcomes will include birth outcomes (mean birth weight, % low birth weight deliveries (< 2500 g), mean gestational length, % premature deliveries (< 37 weeks), incidence of NICU admissions and mean length of stay, and health outcomes through one year postpartum (respiratory distress syndrome, upper and lower respiratory infections, otitis media, sudden infant death syndrome, and other infant death). We will track all maternal prenatal and postpartum health care utilization including pharmacy use through one-year postpartum and infant utilization through one-

year postnatal. Greater than 99% of women in our trials deliver at our university teaching hospital and with maternal permission we will have access to all delivery and infant care records related to the delivery. Over the past 10 years 100% of women in our trials have provided permission to review maternal and infant medical records. We have used this system to obtain the birth outcomes data described above and will now extend that timeframe through the 1st year postpartum. We did not anticipate reviewing medical billings in our earlier studies and thus did not request permission. However, we anticipate no difficulty obtaining consent to review the cost data. Our staff has strong working relationships with local primary care clinicians, which will facilitate the logistics of our staff coordinating with them to review records.

**Biochemical Verification of Abstinence**

Breath and urine specimens will be collected at each clinic visit. Breath CO levels will be analyzed using a breath CO Monitor. Readings < 6 ppm will indicate abstinence during week 1. Beginning in week 2, abstinence will be verified using onsite urine cotinine (< 80 ng/ml) analyzed with an Enzyme Multiplied Immunoassay Test (EMIT). Smoking-status classifications based on EMIT urine-cotinine levels using a cutoff of < 80 ng/ml are in > 98% agreement with those made by gas chromatography mass spectroscopy using a cut-point of 12.5 or 25 ng/ml (Higgins et al., 2007b). Urine and breath specimens will be collected at each of the follow-up assessments and analyzed similarly. Specimens collected at the end-of-pregnancy, and 12 & 24-week postpartum assessments will be sent to an outside laboratory for confirmation testing.

**Monitoring Fetal/Infant Health**

**Fetal Growth**. We will compare the growth profiles for each of the fetal parameters measured across study conditions. This includes abdominal circumference, head circumference, femur length, estimated fetal weight and mid-thigh lean body and fat areas. We will also characterize birth weight between conditions employing birth weight percentiles (Bernstein et al., 1994; 1996; Fry, 2002). We have developed ultrasound techniques that are capable of distinguishing and quantifying specific fetal body

compartments with focus on the lean body and fat mass compartments (Bernstein et al., 1991; 1997; 2000). We will use this ultrasound technology to examine participants at 30 and 34 weeks of pregnancy to estimate changes in overall fetal growth and body composition. We will estimate fetal weight according to the method of Hadlock et al (1985) employing head circumference, femur length and abdominal circumference. We will estimate fetal peripheral muscle and fat areas according to the methods we have developed (Bernstein et al., 1991; 1997; 2000) and are now used broadly (Galan, 2001; Padoan, 2004; Larciprete et al., 2003). **Infant Growth.** Infant growth measures will also be obtained at 6 and 12 months. Weight will be obtained through the use of an electronic scale and length measurements will employ a measuring board that employs the tonic neck reflex for accurate assessment of infant length, thereby estimating ponderal index (Rohrer 1921, Walther & Ramaekers, 1982). At 6 and 12 months we will also measure skinfold thickness at 5 sites (triceps, subscapular, flank, anterior thigh and abdominal wall) (Bernstein 1991, 1997) to estimate subcutaneous fat stores. At 12 months only we will conduct an assessment of infant body composition using whole body dual x-ray absorptiometry (DEXA).

**Statistical Methods**

Study conditions will be compared on baseline demographics and other characteristics using analysis of variance for continuous variables and chi-square tests for categorical variables. If a specific characteristic differs significantly across study conditions and is predictive of outcome, it will be considered as a potential covariate in subsequent analyses. Analyses of treatment effects on smoking status will be limited to smokers randomized to the two treatment conditions. We will adhere to an intent-to-treat approach (Armitage, 1983) wherein all women randomized to the study conditions will be included in the analyses independent of early dropout, noncompliance, etc., with the exception of excluding women for abortion/fetal demise as is convention in this research area. Cochran Mantel Haenszel tests (CMH) will be performed for comparisons of the two treatment conditions on point-prevalence smoking abstinence at end-of-pregnancy and 6-months postpartum assessments with

referring clinic as a stratification variable. The Breslow-Day Test will be used to examine the homogeneity of treatment effects across referring clinics. Comparisons of point-prevalence abstinence rates between treatment conditions across all assessments through one-year postpartum will be analyzed using mixed model repeated measures for categorical data based on generalized estimating equations (GEE) utilizing a logistic link function (SAS: PROC GENMOD, SAS Institute, Cary, NC). We will include women from the nonsmoker condition in analyses of fetal growth, birth outcomes, and breastfeeding and other postpartum outcomes. Comparisons of treatment conditions on dichotomous outcomes (e.g. % low birth weight, % preterm, % NICU admissions, % breastfeeding, % medical treatment in first year) will parallel categorical analyses for point prevalence abstinence using PROC GENMOD to adjust for strata (referring clinics) and potential covariate effects. Analysis of covariance will be used to compare study conditions on mean birth weight adjusting for variables known to predict birth weight (i.e., maternal prepregnancy BMI, parity, and sex), mean gestational age at delivery, and frequency measures of medical illnesses. Statistical analyses of fetal growth outcomes (i.e. estimated fetal weight, fetal lean area, fat area, femur length and head circumference) will be based on linear growth models with slope and intercept as random effects (SAS PROC MIXED). This methodology allows for the within-subjects ultrasound assessments not to be at identical timepoints across subjects. Study condition will be considered a fixed factor with fetus nested within study condition. Two-way analyses of covariance will also be used for analyzing effects of study condition and referring clinic on DEXA body composition measures at 12 months. Additional subject level covariates will include maternal pre-pregnancy body mass index, maternal age and fetal gender. Analyses of infant growth will parallel those used to examine fetal growth. Repeated measures analyses of variance will be used to test for differences between study conditions in skinfold thickness obtained during infant 1st year of life and continuous measures of medical illnesses. Significance will be based on alpha = .05 for all analyses.

**Sample Size Justification**

Sample size was determined to have sufficient power to detect differences between study conditions corresponding to our primary hypotheses regarding point prevalence smoking abstinence at late pregnancy and 24weekpostpartum assessments, fetal growth, birth weight, and breastfeeding. Estimates of abstinence were based on our prior trials where 7-day point-prevalence abstinence in the incentives vs. control conditions were 34% vs. 7% at the late-pregnancy assessment and 14% vs. 1% at 24weeks postpartum assessment, respectively (Higgins et al., 2010a). We estimated that the proposed increase in the value of the incentives used with heavier smokers will increase late-pregnancy abstinence rate to approximately 50% in the incentives condition while the best practices alone condition is estimated at <10%. Assuming a decline in abstinence of approximately 20% from late-pregnancy to the 24-week postpartum assessment as we saw in our prior trials, we estimate abstinence rates of approximately 30% vs. < 5% at 24weeks postpartum in the best practices plus incentives vs. best practices alone conditions, respectively. The proposed sample size of 115 per study condition will result in greater than 90% power to detect a difference between the two treatment conditions in abstinence rates of 50% vs. 10% at late-pregnancy or 30% vs. 5% at 24weeks postpartum assessments using a chi-square test. The proposed sample size is also expected to be more than sufficient for examining differences between study conditions in fetal growth, birth weight, and breastfeeding outcomes. The proposed sample size after considering noncompliance in completing scheduled ultrasounds is estimated to have power of 80% for detecting a mean growth difference of 23 g/wk in estimated fetal weight between any two conditions based on our estimated pooled within group SD=49.7. This difference is slightly more than half the difference observed between the incentive and control condition in our 2008 study (Heil et al, 2008) and represents a conservative expected difference. With respect to mean birth weight, power is estimated to be 80% to detect a difference of approximately 200 g between any two study conditions assuming a pooled SD=550, which aligns well with treatment effects in our study combining results across prior trials (Higgins et al., 2010a) where

mean birth weights were 3295.6 + 588 g vs. 3093.6 + 603 g in the incentives and control conditions, respectively and with our estimate of a mean birth weight of 3595.6 + 404 g in the nonsmoker condition. For this estimate of the mean birth weight that might be expected in the nonsmoker condition, we examined birth weights in a sample (n = 88) of women followed in our clinic who were smokers at the time that they learned of the current pregnancy but quit prior to entering prenatal care (i.e., spontaneous quitters) and were continuously abstinent through the remainder of antepartum. We are estimating breastfeeding rates of 50% and 30% in the incentives condition and 17% and 13% in the best practices alone condition at 12 and 24 weeks postpartum, based on our prior study results (Higgins et al., 2010b) and our planned use of higher value vouchers with heavier smokers in the proposed study. Again using the same group of spontaneous quitters but restricting it to women who remained abstinent through 24-weeks postpartum (n=32), the estimated percent breastfeeding at 12- and 24-weeks postpartum was 70% and 48%. Using chi-square tests, we will have over 80% power to detect differences in rates between any two of the three study conditions at the two assessments. Power calculations were done using a two-sided significance level of .05.

**Economic Evaluation**

**Cost analysis.** We will conduct an economic evaluation from the societal perspective including both cost-effectiveness and cost-benefit analyses (Drummond et al., 2005). The outcome measures in this trial were described above, with antepartum abstinence being primary and the related outcomes of longer-term abstinence, birth outcomes, and health and health care utilization in the 1st year postpartum important as well. Each of these outcomes can be viewed from the perspective of incremental cost effectiveness (e.g., the incremental cost to produce an additional abstinent mother at final antepartum assessment). We hypothesize that the best practices plus incentives intervention will be cost-effective (i.e., dominant) as compared to the best practices alone condition. To determine the cost of each intervention, we will employ the Brief Drug Abuse Treatment Cost Analysis Program (Brief DATCAP; French et al., 2004; French, 2010), which has been widely used in the area of

substance abuse, including projects utilizing incentives (Knealing et al., 2008). The direct and indirect economic cost of treatment will be derived by allocating fixed costs based upon the proportion of time or space utilized by the programs (e.g., treatment facility costs), as well as costs that vary by patient engagement and smoking status (e.g., drug tests, quitline staff time, incentives). The total cost per treatment episode will be individual specific and will include the opportunity cost of the patient's time while in treatment (Salomé et al., 2003; French 2005). The time period of the cost analysis will span from intake to discontinuation or completion of the program. However, since the duration of treatment will vary according to where in the pregnancy a woman enters the study, the economic cost per person per week will also be calculated. The cost of all research-specific resources consumed will be excluded from the evaluation. All costs and benefits will be expressed in a common dollar year without the need for discounting. Estimated treatment costs will be combined with the maternal and infant health outcomes outlined above to conduct the economic evaluation. Cost-effectiveness analysis (CEA). CEA will be conducted wherein the average (mean) difference in treatment costs across the two interventions will be divided by the average (mean) difference in each outcome to derive incremental cost-effectiveness ratios (ICERs). Statistical significance of these ICERs will be determined probabilistically by employing nonparametric bootstrapped standard errors (Drummond et al. 2005). Priority will be given to comparing ratios on key birth outcome measures and NICU admissions. Additionally, a special form of CEA, cost-utility analysis (CUA), will be performed. Based upon smoking status from the quit date through one year postpartum, the number of quality-adjusted life years (QALYs) gained by the mother—as measured by the proportion of time spent in 'smoking' and/or 'nonsmoking' status—will be derived using QALY weights recommended in the extant literature (e.g., Cromwell et al., 1997; Flack et al., 2007). Women still abstinent at 1year postpartum will be treated as long-term quitters. QALYs gained by the infant will be calculated using QALY weights recommended in the literature (Taylor et al., 2009). The incremental cost per QALY gained

between the two modalities will be calculated and compared for mothers and infants separately and also summed across mother-infant dyads.

**Cost-benefit analysis (CBA).** CBA can often be especially useful by allowing consideration of multiple, often very different, outcomes. CBA yields two specific evaluation metrics, which are both placed in monetary terms, the benefit-cost ratio and the net benefit, that can be compared across health programs and economic sectors. We will conduct a partial CBA from a societal perspective for the intake through 12month postpartum period. Total health care costs for the mother and infant will be measured using the 'allowed' amounts extracted from administrative insurance claims data collected from health care providers. Adding smoking cessation treatment costs to health care costs will yield the total economic cost of care for a mother/infant dyad for the specified time period. Given randomization, the mean difference across the treatment arms (the average net benefit) will be attributed to intervention effectiveness. Cost benefit ratios also will be calculated and compared across the two treatment conditions for statistically significant differences. Sensitivity analysis. A multiway sensitivity analysis will assess the levels to which our incremental cost effectiveness ratios (ICERs) are robust to changes in component assumptions and costs. For example, while a theoretical 100% quit rate may never reach the low cost of treating the group of nonsmokers in our third condition, we can explore the maximum threshold of incentive required to maximize health benefits with respect to their costs one year postpartum. More within a realistic target, a 50% quit rate, for example, may be cost effective under all exploratory ranges of incentive compensation. The sensitivity analysis will therefore explore changes to assumptions over a broad range.

## PROTECTION OF HUMAN SUBJECTS

### 1. RISKS TO THE SUBJECTS

#### a. Human Subjects Involvement, Characteristics, and Design

Participants will be 345 women seeking prenatal care at participating clinics who are insured by Medicaid. 230 women who endorse being smokers at the time that they learned of the current pregnancy will be informed that they might be eligible for a study on cigarette smoking cessation and birth outcomes while 115 women who endorse being nonsmokers will be informed that they might be eligible for a study on birth outcomes. Both will be offered the opportunity to participate in further screening to determine study eligibility.

For inclusion in the smoking cessation component, women must report being smokers at the time that they learned of the current pregnancy, report smoking in the 7 days prior to the first prenatal care visit and have that confirmed by urine toxicology testing, be 18 years of age or older, be < 25 weeks pregnant, reside in the county in which the clinic is located and immediately surrounding areas, speak English, plan on remaining in the geographical area through the pregnancy and 12-months postpartum, and provide written informed consent to participate. Failure to meet the aforementioned criteria, incarceration, untreated psychosis, current treatment with buprenorphine/methadone for opioid dependence, and refusal to participate will be reasons for exclusion.

For inclusion in the nonsmoker component of the study, women must meet the same inclusion and exclusion criteria listed above with the exception of smoking status where they must report being nonsmokers at the time they learned of the current pregnancy, report no smoking in past 6 months, not even a puff, test negative in a urine-cotinine test for current smoking, and report smoking < 100 cigarettes in their lifetime. Nonsmokers will also be matched to women in the smoker conditions on the following characteristics that may influence treatment outcome (educational attainment,

prepregnancy BMI, parity, chronological age, comorbidities (i.e., diabetes, hypertension), and use of cocaine/opioids and thus could be excluded from study participation based on not aligning with our need to keep the conditions comparable on these characteristics. No participants will be excluded based on race or ethnicity. All study participants will complete informed consent. Smokers who consent to study participation will be randomly assigned to one of two treatment conditions: (1) Best practices for smoking cessation during pregnancy involving the 5 As and referral to pregnancy-specific telephone quitline counseling and self-help cessation materials or (2) Best practices for smoking cessation during pregnancy plus financial Incentives delivered contingent on smoking abstinence. Nonsmokers who consent to study participation will complete the same assessments as the smokers, but none of the smoking-cessation aspects of the study.

**b. Sources of Materials**

The research materials to be obtained include interviews, questionnaires, urine and breath specimens to verify smoking status, and medical records to assess birth and maternal and infant health outcomes through one-year postpartum.

**c. Potential Risks**

(a) A potential risk to all subjects in the proposed studies is that an unauthorized person would obtain access to the information contained in their study files. (b) There is the risk that some subjects may misuse vouchers or the money provided for completing the baseline and follow-up assessments. (c) Women in the financial-incentives condition could be enticed to use over the counter smoking cessation pharmacotherapies in order to obtain incentives, which have not been approved for use with pregnant women.

**2. ADEQUACY OF PROTECTION AGAINST RISKS**

**a. Recruitment and Informed Consent**

All participants will provide written informed consent after having a face-to-face discussion of the research with PI, Co-I or research staff designated and trained to represent the PI/Co-I in this

function. That discussion is conducted in a private setting and permits the prospective participants ample opportunity to raise questions and seek clarifications regarding the research. Later that day, the participant will take a consent form quiz to ensure she understands the critical elements of what she agreed to do (e.g. randomized to experimental or control condition, study is voluntary and can withdraw at any time). Incorrect answers will be carefully reviewed with the participant and the quiz will be readministered until all questions are answered correctly.

We operate in full compliance with HIPAA regulations. All participants in the present study will receive a HIPAA authorization form upon entry into treatment and are fully informed regarding their rights with respect to the release of personal health information. We will comply with the new regulations for protection of pregnant women in research (effective December 13, 2001). Further, as mandated by NIH, all personnel funded by this project will complete the NIH required course on Human Subjects Research Training.

**b. Protection Against Risk**

We take the following actions to protect against the potential risks noted above: (a) All study files will be stored in locked filing cabinets. All study participants receive a participant identification code that is used in place of their name in all study data files. The key that connects participant names with identification codes is kept in a locked file and stored separately from the data files. (b) Study computers will be password protected and encrypted. (c) All voucher purchases must be approved in advance by project staff who retain veto power. If in the judgment of project staff there is a risk that the money obtained by completing the assessments might be misused, vouchers will be substituted for cash. Misuse of vouchers has not been a problem in our prior trials with this population. (d) Regarding pharmacotherapies, we inform women about the risks/benefits of over-the-counter pharmacotherapies, inform them that the use of nicotine replacement therapies will limit their ability to earn incentives, and make a recommendation that smoking cessation pharmacotherapies not be used. We have had no problems during the prior trials related to women using pharmacotherapies for smoking cessation.

## 3. POTENTIAL BENEFITS OF THE PROPOSED RESEARCH TO THE SUBJECTS AND OTHERS

Among the smokers, we believe that the aforementioned risks are reasonable in relation to the anticipated benefits to the mother and fetus/neonate of treatment for smoking during pregnancy. There is a reasonable likelihood that women assigned to the Best Practices alone condition will not achieve outcomes as good as those assigned to the Best practices plus financial-Incentives condition. Nevertheless, all women will receive treatment that meets Best Practices as outlined in the 2008 Clinical Practice Guidelines on Treating Tobacco (Fiore et al., 2008). To the extent that either intervention promotes smoking cessation, there is likely to be benefits to both mother and fetus/infant in terms of improved growth and birth outcomes. Any improvements in birth outcomes should also provide benefits to society in terms of lowered medical costs for infant care and improved child outcomes.

Among the nonsmokers, we feel that the risks are justified by the potential to contribute new knowledge with the potential to enhance understanding of the adverse effects of smoking and provide insights into how much more might be invested into improving smoking-cessation interventions without exceeding cost-effectiveness. Although this study is considered high-risk by definition (i.e., pregnant population), the potential benefits are substantial in terms of our scientific understanding of the effectiveness of treating smoking cessation among pregnant smokers and for increasing knowledge regarding the impact of smoking cessation on birth outcomes and maternal and infant health outcomes. Overall, the risk/benefit ratio appears highly favorable.

## 4. IMPORTANCE OF THE KNOWLEDGE TO BE GAINED

Smoking during pregnancy is the leading preventable cause of poor pregnancy outcomes in the U.S. Despite 72 controlled trials involving more than 25,000 women, quit rates achieved with existing interventions are low (often < 15%). In addition, no intervention has reported significant main effects

of treatment on birth outcomes for more than 25 years. The proposed study will continue research on the efficacy of a novel smoking-cessation intervention, voucher-based financial incentives, which has demonstrated promising effects on smoking abstinence rates and fetal/infant outcomes in at least four prior efficacy trials. The proposed trial will thoroughly contrast the effectiveness, especially the cost-effectiveness, of adding financial incentives to current Best Practices compared to offering Best Practices alone in terms of increasing antepartum and postpartum smoking abstinence and improving birth outcomes, breastfeeding, and other maternal and infant health outcomes during the 1st year of life. The proposed study has the potential to be pivotal to the development, testing, and eventual dissemination of this incentives-based treatment approach and will contribute new and important scientific knowledge about how to effectively treat smoking during pregnancy and postpartum and the maternal, infant health, and economic benefits of doing so.

## 5. DATA AND SAFETY MONITORING PLAN

Our overall monitoring plan consists of ongoing, close monitoring of data and safety issues by the PI, Co-Investigators, and other project staff and prompt reporting of any adverse events (AEs) or serious adverse events (SAEs) to the institutional review board at the appropriate site and/or NIH, as suggested by Notice OD00038. We provide more detail below regarding particular areas recommended by Notice OD00038.

**Patient eligibility and status**. All recruitment will be managed by trained research staff under the supervision of the PI using specialized forms and procedures. All information collected will be reviewed by the research staff, PI, or designated representatives, who will determine participant eligibility, contact them about scheduling and completing an intake assessment where appropriate. Eligible women will provide written informed consent. The status of all active participants will be reviewed weekly at staff meetings between the PI, Co-Investigators and trained support staff. Rigorous data management/quality assurance. Study data will come from participant screening and intake

sessions, periodic assessments, urine and breath specimen collections, and medical and pharmacy records.

Study data collection will be primarily with paper questionnaires that will be manually double-entered into computers for analysis. Similar to prior and ongoing studies, we will create Excel databases for entry and coding of all data collected. All data will be independently coded by trained research staff. The two coded data sets at each site will be compared against each other for agreement and discrepancies will be resolved and corrected using source materials at each site. Once each month, current compared data sets will be delivered electronically to the University of Vermont Bioinformatics Facility where they will again be reviewed for accuracy. Any apparent errors will be resolved and corrected under supervision of the biostatistician and using source materials. The biostatistician and PI will discuss any problems at weekly data meetings. Auditing procedures. Review of any problems related to quality of data collection, transmission or analyses and of any AEs and SAEs that occurred during the past week will occur at weekly research staff meetings. Interim analyses of data will be conducted when half the subjects have been entered or at other times based on the discretion of the PI and biostatistician.

**Reporting mechanisms of AEs and SAEs to the UVM IRB and Funding Agency**. In the proposed study, we will use the FDA's definition of AEs and SAEs. AEs and SAEs will be assessed at each subject visit by a trained staff member and copies of all reports noting AEs and SAEs will be kept in a central file as well as in the individual subject's chart. AEs will be discussed at the weekly research staff meetings. Any SAE will be brought to the attention of the PI or a Co-Investigator as soon as possible and not longer than 24 hours. Any AE or SAE that is both unexpected and related to study participation will be reported to the IRB within 7 days of the event. That IRB will make a determination as to whether additional reporting requirements are needed. IRB actions will be reported to the funding agency by the PI no less than annually and more frequently as recommended by the local IRB. Any SAEs will be summarized in the yearly Progress Reports to the funding agency,

including a review of frequency and severity. All SAEs will be followed through ongoing consultation with the physician caring for the patient until they resolve, result in death, or stabilize and are not expected to improve.

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