Document Coversheet

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UNIVERSITY OF KENTUCKY STUDY PROTOCOL

Behavioral and Enhanced Perinatal Intervention for Cessation (B-EPIC): Reducing Tobacco use among Opioid Addicted Women

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Project Protocol

Objective:

This proposal addresses a highly significant topic, tobacco and opioid addiction among pregnant women, at a time in which opioid addiction is considered a rising national epidemic.[1] Each year, 225,000 infants in the United States are exposed prenatally to illicit drugs. Women with substance use disorders, particularly those with opioid dependence (per DSM-4), are highly vulnerable to cigarette smoking during the perinatal period. Pregnant opioid dependent patients seeking medication-assisted treatment (MAT) have high rates of smoking, ranging from 88% to 95%. Smoking during pregnancy is an independent risk factor (outside of illicit drug use) for several adverse outcomes including ectopic pregnancy, premature birth, orofacial clefts,[2] and sudden infant death syndrome. Illicit opioid use magnifies these risks; among women who use opioids during pregnancy, there is a 6-fold greater risk for intrauterine growth restriction, third trimester vaginal bleeding, preterm delivery, and a majority also will experience neonatal abstinence syndrome (NAS).[3] Prenatal tobacco use significantly increases the severity and duration of NAS, yet is not commonly treated among opioid dependent pregnant women receiving MAT.[4] On average, the healthcare cost per discharged infant with NAS ranges from $39,400 to $53,400; and 77.6% is paid for by Medicaid.[5] MAT has been shown to decrease the severity of NAS[6] compared to no treatment; yet, most opioid dependent women in MAT still continue to smoke cigarettes throughout pregnancy, clearly suggesting that there is a significant need for a comprehensive, evidence-based tobacco treatment intervention. To date, there is no specific pharmacologic or non-pharmacologic tobacco-treatment standard for opioid dependent pregnant women in MAT. More research is needed to develop and test tailored tobacco treatment interventions for pregnant, opioid dependent women.

The purpose of this pilot services effectiveness research trial is to test feasibility and efficacy of a **B**ehavioral and **E**nhanced **P**erinatal **I**ntervention for **C**essation (B-EPIC) of tobacco use in an established MAT clinic. B-EPIC includes four core components: 1) Individualized tobacco treatment plus supplemental counseling, 2) Biomarker validation and feedback, 3) Focus and adoption of healthy behavior, and 4) Pharmacotherapy as needed. The B-EPIC is designed to reduce tobacco-associated morbidity (e.g., preterm birth, NAS) and healthcare expenditures in pregnant women who are tobacco users receiving buprenorphine for opioid dependence. This two-group randomized and controlled clinical trial (n =100) will provide critical preliminary data to test larger-scale trials. As most B-EPIC services are billable services via public and private insurers; there is high likelihood for sustainability.

Background Information:

In the United States (US), opioid use has tripled since the 1990s, with the Centers for Disease Control and Prevention (CDC) now referring to opioid addiction as a national epidemic.[1] Although a higher percentage of men abuse drugs compared to women, the gender gap has lessened. Women who use illicit opioids are a particularly vulnerable population. Women with substance use disorders often have mood (29.7%) and anxiety disorders (26.2%). Rates of sexual or physical abuse among women in substance use disorder treatment facilities range from 55-99%, and 34.4% of individuals with post-traumatic stress disorder also had a substance use disorder. In addition, illicit opioid use among women is highest among women of childbearing age.[7]

Each year, 225,000 infants in the US are exposed prenatally to illicit drugs.[8] Women who abuse opioids during pregnancy have a 6-fold greater risk for intrauterine growth restriction, third trimester vaginal bleeding, preterm delivery, and stillbirth.[3] The use of intravenous opioids raises the risk of infectious diseases (e.g., HIV, hepatitis C

and endocarditis), further complicating pregnancy.[9] Each year, 50,000 infants are treated for neonatal abstinence syndrome (NAS).[10] On average, the healthcare cost per NAS discharge ranges from $39,400 to $53,400, and 77.6% of these costs are paid for by Medicaid.[5]

Medication-assisted-treatment (MAT) with methadone remains the standard of care; however, given difficulties with accessing licensed methadone opioid treatment programs (e.g., some states have only one), many rural (and non-rural) women do not access methadone treatment. Buprenorphine can be prescribed in outpatient physician office, which increases access to and decreases the stigma of care. It also has similar efficacy and improved NAS outcomes compared to methadone; thus, it is increasingly accepted and utilized for the outpatient treatment of opioid dependence in pregnancy.[11,12]

Pregnant women engaged in MAT have high rates of smoking, ranging from 88-95%.[13] Smoking during pregnancy increases the risk of multiple adverse outcomes including ectopic pregnancy, premature birth, orofacial clefts,[2] and sudden infant death syndrome,[14] and the risk continues beyond pregnancy. Children exposed to secondhand smoke (SHS) have an increased risk for asthma and other respiratory disorders,[15] as well as attention deficit hyperactivity disorder[16] and poor neurocognitive performance.[17] Children born to mothers who smoke during pregnancy have a higher risk of nicotine dependence in adulthood than their peers.[18] Further, there is growing evidence that treating tobacco use concurrently with substance use disorder treatment may lead to a greater likelihood of abstinence from alcohol or other drugs.[19-21]

Smoking during pregnancy also has adverse economic consequences for families and the health care system. Maternal smoking increases the risk of admission to a NICU by as much as 20% in some studies, while also increasing overall hospital length of stay for the newborn infant, resulting in significant smoking-attributable hospital costs during the episode of delivery.[22,23] Over the longer term, infants born to mothers who smoked during pregnancy are more likely to be readmitted to the hospital during their first year of life,[24] more likely to experience asthma requiring medication use, and are more likely to have emergency room utilization.[23]

The American College of Obstetrics and Gynecologists recommends the 5A's approach for smoking cessation during pregnancy.[25,26] The integration of a 5A's based tobacco treatment intervention into an MAT clinic for pregnant and parenting women led to a significant reduction in cigarettes per day (49% among pregnant and 32% among non-pregnant clients). However, a very small percentage of the participants stopped smoking, indicating the need for a more intense, tailored intervention for this population. To date, there is no specific treatment standard for pregnant women addicted to opioids. Few tobacco treatment interventions have been tested for pregnant women in MAT[27-29] One study showed promise utilizing a 12 vs. 6 week intervention that included contingency-behavioral incentives; however long-term abstinence was not measured. Further, effects of contingency incentives often cease after the intervention period ends. There is a need to shift clinical practice for pregnant women who are opioid dependent to include focused intervention on tobacco. We are integrating a pilot proof of concept novel tobacco intervention into an existing MAT program. The majority of addiction in pregnancy treatment programs are located within urban settings despite rural and non-urban residents being disproportionally affected by tobacco and opioid dependence.[30] We will be the first to provide a tobacco treatment intervention among opioid dependent pregnant women in an MAT clinic serving a large proportion of non-urban women. This significantly increases the generalizability and prospect that the B-EPIC intervention could be replicated in both urban and rural communities.

Based on the breadth and depth of evidence summarized above, the premise of the application is to provide a tobacco treatment standard for pregnant women addicted to opioids. Few tobacco treatment interventions have been tested for pregnant women in MAT; this intervention has the capacity to shift the clinical practice paradigm to give more emphasis on tobacco use. Finally, it is likely that B-EPIC will have significant impact on maternal and infant health outcomes, while also imparting a profound reduction on healthcare utilization.

Specific Aims

Aim 1. To determine the impact of the B-EPIC intervention on maternal tobacco use and stage of change during and after pregnancy compared to the tobacco treatment as usual (TAU) control group among women with opioid dependence receiving MAT.

Hypothesis$_1$: The B-EPIC group will have a greater percentage of perinatal women who quit smoking (determined by urine cotinine), decrease the number of cigarettes (conventional or electronic) smoked per day, and/or increase their readiness to quit smoking than TAU.

Aim 2. To determine the impact of B-EPIC on tobacco-related adverse health outcomes including: gestational age at birth, birthweight; NAS diagnosis and severity; and number of infant ear and respiratory infections during the first 5-6 months.

Hypothesis$_2$: Women in the B-EPIC intervention will have longer gestational periods and their infants will experience less severe NAS (e.g., number of days in the neonatal intensive care unit [NICU], total mg of morphine needed to treat NAS), associated childhood illnesses (e.g., frequency of ear and respiratory infections) and increased number of well-child visits compared to TAU. All post-discharge infant data will be retrieved via national Medical Expenditure Panel Survey (MEPS) data.

Aim 3. To compare health care utilization and costs incurred by pregnant patients that receive the B-EPIC intervention versus TAU, with estimates of the incremental cost-effectiveness of the B-EPIC intervention. Outcomes will include medical record data, such as length in days of maternal hospitalization, and infant outcomes (number of days in NICU, and number of sick infant outpatient or emergency department (ED) visits).

Hypothesis$_3$: Infants of participants in B-EPIC will have lower NICU use, shorter lengths of stay and fewer readmissions, and ED/ill-child outpatient visits than the TAU group, resulting in a beneficial cost-effectiveness ratio.

Study Procedures

One hundred pregnant women undergoing medically-assisted treatment (MAT) with buprenorphine for opioid dependence will be recruited and randomized to B-EPIC (*n*=50) or TAU (*n*=50). UK Departments of OBGYN/Maternal Fetal Medicine, College of Nursing, and UK Center on Drug and Alcohol Research will manage the program (letters of support provided from Co-Is in each of these departments).

Table 2. Estimated retention at each perinatal period

	2nd Trimester (18-24 weeks)	3rd Trimester (30-36 weeks)	Postpartum (1-2 months)	Postpartum (5-6 months)
Usual Care	50	45	39	28
B-EPIC	50	45	39	28
Total	**100**	**90**	**78**	**56**

Inclusion criteria: 1) current diagnosis of opioid dependence with participation in the buprenorphine treatment program; 2) less than 32 weeks gestation; 3) age 18-49 years old; 4) diagnosis of current tobacco use disorder; and 5) read or write in English. **Exclusion criteria:** Women are excluded if they have current prisoner status, current severe mental illness (e.g., bipolar disorder with current mania, current suicidal ideation), or alcohol or sedative/hypnotic dependence that requires medical intervention.

Recruitment, Screening and Informed Consent: Institutional Review Board (IRB) approval will be obtained from the University of Kentucky for this study. The screening, recruitment and retention plan is anchored by our previous work among pregnant and postpartum women who smoke. All study personnel will have completed human subjects training - and good clinical practice (GCP) research training. There will be two methods of recruitment: 1) study flyers will be posted in highly visible areas in the UKHC MAT clinics for pregnant/postpartum women and 2) the research nurse will provide an overview of the B-EPIC study in the buprenorphine treatment clinic for pregnant women. At conclusion of the overview, all women will be given a flyer in which they can either check that they are interested in screening for the study, verbally let the research nurse know they are interested in screening, and also be given the study recruitment phone number. Volunteers interested in the study will be screened for eligibility by research staff and those meeting initial eligibility screening criteria will be invited to come in for an in-person screening whereby informed consent will be completed before any study procedures are initiated (see Human Subjects).

Randomization: After informed consent and screening are completed, participants meeting study inclusion/exclusion criteria will be randomized (1:1) to the B-EPIC group (tobacco intervention) or TAU tobacco treatment (control group). All will continue to receive opioid dependence treatment with buprenorphine, regardless of treatment assignment. Randomization will be stratified by age (30+ vs less than 30). We will create a separate randomization schedule for each age stratum using the PLAN procedure in SAS (SAS Institute, Inc.); each schedule will include 17 blocks of 6 participants, with half per block randomized to each of the two treatment groups. Recruitment in this fashion will ensure an approximately equal number of subjects in each group throughout the enrollment period in both age strata, and we will continue recruitment until we have enrolled 100 subjects.

Study Procedures. Participants will be asked to provide urine samples and complete a survey at four times throughout the study (2nd and 3rd trimester, and 1-2 months, 5-6 months after delivery). There will be minimum of 8 weeks between individual data collection time periods. First, a survey available via iPad (paper/pen by request) will be administered by the research staff. The survey will take approximately 20 minutes to complete and will assess current and past use of tobacco products, demographic and psychosocial variables, stage of change, and personal characteristics; skip patterns will be used if indicated to minimize respondent burden. See Table 4. The survey will be stored on RedCap, a secure web-based data management system managed through the UK Clinical and Translational Research Center. The research nurse will then collect prenatal biomarkers (urine for cotinine and drug testing). Dr. Ashford (PI) will train all study personnel collecting prenatal biomarkers consistent with procedures refined in previous studies. Participants will be informed their urine will be tested for cotinine (metabolite of nicotine) and other illicit drugs to confirm tobacco and/or illicit substance use at each data collection point and informed of their results in compliance with American Congress of Obstetricians and Gynecologists (ACOG) clinical standards. Participants will be informed their survey and biomarkers results will remain confidential. Confidentiality will be maintained through the use of non-identifying subject numbers; all study data will be saved daily on a secure server in a password-protected folder.

Follow up data collection: Healthcare outcome data will be collected from the mother's and infant's electronic medical record and national MEPS data. Maternal data obtained includes: prenatal history, medications and complications, gestational age at birth, birthweight, delivery method and complications, hospital readmissions, medical care adherence/attendance, readmission, emergency room visits and number of positive urine drug testing results. Infant data obtained from the maternal medical record or national MEPS data includes: sex and birth weight, NICU admission, length of NICU stay, NAS scores, treatment offered for NAS/total mg dose in morphine equivalents of such treatment, infant outpatient visits, including, well-child, sick visits and emergency department. Our team has successfully established methods to increase retention through the perinatal period by encouraging open and engaging communication. Various communication methods include: regularly scheduled (monthly) contact, telephone calls, post cards, emails, and text messaging. Preferred methods of communication will used (as indicated by the participant).

Compensation: Participants are compensated for study completion in the form of gift cards ($20-$40 value). Gift cards are given in-person at prenatal and postpartum appointments. To bolster retention in the postpartum period we have increased the gift card value from $20 to $40. Participants will receive an additional $20 gift card if three of four data collection points are completed. Refer to Table 3.

Usual Care (TAU): Women enrolled in the control group are informed of the risks of tobacco use and benefits of quitting using the ACOG 5'A's approach (see Box 1) by their healthcare provider. This standard takes approximately 5-15 minutes, and is offered at each prenatal and postpartum appointment.

BOX 1. ACOG's 5 A's Treatment as Usual

1. **ASK** the patient about smoking status at the 1st prenatal visit and follow-up with her at subsequent visits.
2. **ADVISE** the patient who smokes to stop by providing advice to quit with information about the risks of continued smoking to the woman, fetus, and newborn.
3. **ASSESS** the patient's willingness to attempt to quit smoking at the time. Quitting advice, assessment, and motivational assistance should be offered at subsequent visits.
4. **ADVISE** the patient who smokes to stop by providing advice to quit with information about the risks of continued smoking to the woman, fetus, and newborn.
5. **ASSESS** the patient's willingness to attempt to quit smoking at the time. Quitting advice, assessment, and motivational assistance should be offered at subsequent visits.

B-EPIC Intervention. Women enrolled in the intervention group will receive TAU plus B-EPIC, which includes four core components: 1) Individualized tobacco treatment plus supplemental counseling, 2) Biomarker validation and feedback, 3) Change in maternal thought process and adoption of healthy behavior (e.g. exercise, based on PI framework), and 4) Pharmacotherapy as needed (see Table 3 for a summary of the study design). The initial assessment for this intervention takes 60 minutes, with follow-up sessions typically lasting 15-20 minutes. All sessions occur prior to or after pre-scheduled perinatal appointments. The intervention will be led by a certified tobacco treatment specialist (CTTS) (see Box 2 for CTTS core competencies).

Box 2. Certified Tobacco Treatment Specialists Core Competencies
1. Tobacco dependence knowledge
2. Counseling and motivational interviewing skills
3. Assessment skills
4. Individualized treatment planning
5. Pharmacotherapy knowledge
6. Relapse prevention
7. Competence in working with diverse population subgroups
8. Referral resources for additional support

CTTS Training: An existing nurse in the intervention site will undergo training to become a Certified Tobacco Treatment Specialist (CTTS) through completion of an accredited certification program. A CTTS is a professional who possesses the skills, knowledge and training to provide effective, evidence-based interventions for tobacco dependence across a range of intensities. CTTS's are trained in core competencies for the delivery of tobacco dependence treatment consistent with established evidence. For example, the CCTS will follow-up contact with participants to strengthen brief MI interventions. Assessment, motivational counseling, treatment planning for both cessation and relapse, which are tailored to the unique needs of tobacco users, are core skills used in the delivery of CTTS services. Further, women are empowered to avoid secondhand smoke exposure often resulting in adoption of a smokefree home (PI framework). These services can be provided to individuals and groups, in person, via telephone or using other platforms, such as online. Two healthcare providers (primary and backup) will be trained from the intervention site. In case of staff turnover, an alternative healthcare provider may require CTTS training at a later date to ensure no interruption of CTTS services.

Table 3. Summary of Study Design

Timepoints	B-EPIC -Taking Action	Biomarkers	Survey	Incentives
Baseline **2nd trimester** (18-24 weeks)	• Individualized tobacco treatment (every month-minimum) plus supplemental counseling • Biomarker validation and feedback • Focus and adoption of health behavior and change in maternal thought process (e.g. exercise) based on PI framework • Pharmacotherapy as needed.	• Urinary Cotinine • iCup Drug & Quantitative Analysis	• Prenatal History • Demographics • Adverse Childhood Events (ACE) • Outcomes Measures Survey (SOMs). Refer to Table 4	$20 gift card
3rd trimester (30-36 weeks)		• Urinary Cotinine • iCup Drug & Quantitative	• Prenatal History • SOM	$20 gift card
Postpartum (1-2 months)		• Urinary Cotinine • iCup Drug & Quantitative	• Labor and Birth History • Newborn History • SOM	$40 gift card
Postpartum (5-6 months)		• Urinary Cotinine • iCup Drug & Quantitative	• Maternal and Infant Outcomes • SOM	$40 gift card*

*If 3 of 4 timepoints are completed, participants receive an additional $20.

Measures

Biological Measures. Urine cotinine assay. Smoking cessation will be defined by a urine cotinine assay <100 ng/mL. Nonsmokers will be defined by urine cotinine $\leq$ 99 ng/mL, and conventional smokers will be defined by urine cotinine $\geq$ 100 ng/mL.

Urine Screen for Drugs-of-Abuse. The iCup Drug Screen (BioScan Screening Systems, Inc., Smyrna, TN) will be used to validate illicit drug use. The iCup employs enzyme-linked immune assays (ELIZA) to detect the presence or absence of the following drugs/drug classes: buprenorphine, morphine/opiates, methadone, oxycodone, benzodiazepines, amphetamines, methamphetamine, cocaine, and THC.

Survey Measures. Refer to Table 4 for validation studies key outcome measures.
Tobacco Measures: cigarette, e-cig and dual use. All participants will be cigarette smokers. The measurement of cigarette use (i.e., self-report of number of cigarettes smoked per day, e-cig usage, etc.,) is relatively straightforward; the measurement of e-cig use has previously presented challenges.

Measures of cigarette and e-cig dependence. Foulds et al., (2014) developed a valid measure of e-cig dependence (PSEDI), as well as a very similar measure for cigarette smokers. Thus, we plan to use this measure of dependence in conjunction with the established Fagerstrom Test of Nicotine Dependence.

Measures of non-tobacco substance use. Pregnant women in this study are all opioid dependent receiving buprenorphine. Their urine will be tested at the four assessment time-points for non-tobacco substance use.

Measures of SHS exposure and psychosocial symptoms. SHS exposure is a known barrier to persistent perinatal smoking and relapse. We will use the Edinburgh Postnatal Depression Scale (EDPS), the gold standard for measuring depressive symptoms during and after pregnancy. Maternal anxiety and perceived stress will be measured using the validated tools, (GAD, PSS respectively) to determine number of adverse childhood events (abuse and neglect) and intimate partner violence, the Adverse Childhood Events (ACE) and Hurt, Insult, Threaten and Scream (HITS) validated tools will also be used.

Measures of birth and infant outcomes are summarized in Table 4 and will be collected from the maternal and infant medical records and national MEPS data up to 6 months after delivery.

Covariates. Covariates will include demographic variables (age in years, education level, marital status, race/ethnicity), tobacco use and cessation history (e.g., average number of cigarettes smoked per day, severity of nicotine dependence, readiness to quit smoking), SHS exposure (smokers in the home), psychosocial measures (depression, anxiety, stress), use of other prescription medications (number), substance use severity (as measured by composite scores in the ASI-Lite), number of recent days of illicit substance use (using ASI for alcohol and other illicit drug use specifically illicit opioids, cocaine, marijuana/THC, benzodiazepines, and methamphetamine), and urine drug test results (positive/negative for marijuana, non-prescribed opioids, benzodiazepines, cocaine, methamphetamine). Covariates will be measured at baseline and at each data collection time-point (with the exception of demographic variables, which are not expected to change) Given the pilot nature of this study and the number of control variables, ability to detect differences in groups may not be possible; however, these data will provide critical information about what baseline demographic, psychosocial and substance use characteristics may be most associated with outcomes.

Aim 3 Measures: Using methods described by Drummond and Gold we will assess the reasonableness of the B-EPIC intervention's costs in relation to clinical outcomes achieved and examine the potential for program costs to be offset by reductions in health care utilization. Three types of economic measures will be collected during the

intervention and follow-up periods. First, measures of direct intervention costs will be constructed from logs and records detailing staff time, equipment, facilities, and supplies used in the routine, ongoing operation of the intervention. These costs will be tracked on a continuous basis throughout the intervention period. Steps will be taken to discern costs associated with the research from those actually generated by the intervention, and to distinguish program start-up costs from ongoing maintenance costs. Second, measures of medical indirect costs and lifestyle indirect costs will be constructed using participant-reported measures of health care utilization and tobacco product utilization during each follow-up period along with measures of utilization from the medical record. Third, estimates of productivity-loss costs will be constructed using participant-reported measures of time lost from work, school, or usual activities due to illness, medical care, infant caregiving, and participation in intervention activities or other tobacco cessation programs (including the state tobacco quitline). Costs associated with medical care utilization will not be measured directly but rather will be estimated using national MEPS data on medical care costs associated with the utilization measures assessed in this study (e.g., hospital readmission, emergency department use).

These economic measures will allow for assessments of intervention cost-effectiveness from several different perspectives, including health care system, and society at large. Cost measures will be examined in relationship to improvements in proximal health outcomes to determine the within-trial, incremental costs and cost-effectiveness of the intervention relative to usual care. Within-trial measures of the cost per unit change in health outcome (e.g. preterm, low birth weight) will be constructed for this purpose.

Table 4: Summary of Outcomes Measures (SOMs)

Variable (Name)	Measure
Susceptibility to use	Items adapted from 4 item questionnaire for susceptibility to initiate smoking.
Switching/dual use	A series of yes/no items to discern dual use and switching behavior.
Fagerstrom Test for Nicotine (Cigarette) Dependence	The Fagerstrom Test for Nicotine Dependence (FTND) is a 6-item scale that measure s dependence on nicotine.
Electronic Cigarette Dependence Index	The Electronic Cigarette Dependence Index is a 10-item scale that measures dependence to electronic cigarettes.
Perceptions of conventional tobacco and e-cig use	
Proportion of women/ pregnant or postpartum women using e-cigs	Item adapted from questionnaire used to examine normative perceptions of smoking among teen girls. (Example: 'How many women/pregnant or postpartum women do you think use e-cigs?')
SHS and e-cigarette vapor exposure	
Home, Family & Peer Tobacco Use	Home SHS exposure will be assessed by number of smokers in home To assess their family members' and peers' tobacco (and e-cig) use, the participants will be asked to identify (from a list provided) which individuals in their lives use tobacco.
Exposure to SHS smoke and e-cig vapor	12-item scale on exposure to SHS to assess environmental impact. We will adapt this scale to apply to e-cig vapor.
Other substance use	
Substance Use Severity and recent (Last 30 days use) from Addiction Severity Index (ASI)-Lite	Composite scores of drug and alcohol use severity and five other domains of function that are affected by substance use: medical, family, social, legal, and employment problem severity are collected. Also, number of days of drug use in the last 30 days will be assessed for all major classes of substances (e.g., alcohol, cocaine, benzodiazepines…).
Psychosocial, Lifestyle and Safety Measures	
Stages of Change	The short form for the Classification of Stages of Change for Smoking Cessation is a 3 item assessment to indicate.

Variable (Name)	Measure
Readiness to Quit (smoking cessation	A "ladder scale" with 10 options to indicate an individual's readiness to quit tobacco use
Edinburgh Postnatal Depression Scale (EPDS)	A 10-item scale examines clinical depressive symptoms in pregnant and postpartum women. Higher scores indicate more depressive symptoms. Tool has been consistently validated in pregnant and postpartum women.
Anxiety	Generalized *Anxiety* Disorder 7 (*GAD-7*) is a 7-item, self-reported *survey* for screening and severity measuring of generalized *anxiety*
Perceived Stress Scale (PSS)	A 4-item scale validated to assess prenatal stress
Adverse Childhood Events (ACE)	A 10-item self-report measure developed for the ACE study to identify childhood experiences of abuse and neglect.
Hurt, Insult, Threaten and Scream (HITS)	A 4-item scale providers use to assess risk for Intimate Partner Violence (IPV)
Birth and Infant Outcomes (medical record and Kentucky Medicaid Claims Data)	
Gestational Age at Birth: Preterm Birth	Age in weeks on delivery day, and based on first trimester or earliest ultrasound (ACOG). Preterm birth defined as gestational age < 37 weeks.
Birth Weight: Low Birth Weight	First infant weight on day of delivery (grams). Low birth weight defined as < 2500 grams on day of delivery.
Neonatal Abstinence Syndrome	19-item scoring system for NAS, modified Finnegan Scale.
Well-child and Sick Visits, Hospital Admission-Readmission, Length of Stay	The International Statistical Classification of Diseases and Related Health Problems (usually abbreviated as ICD) is a diagnostic code such as 388.30 for tinnitus, unspecified.
Biological Abstinent Measures	
Urine Cotinine	Cotinine <100 ng/mL will confirm abstinence for active tobacco use
Urine Screen for Drugs of Abuse	Negative urine screen for illicit substances (iCup). If positive for anything other than buprenorphine, then quantitative laboratory analysis.

*Age, Race/Ethnicity/Income/Education/Partner Status will also be measured

Statistical Analysis Plan

One hundred pregnant women undergoing medically-assisted treatment (MAT) with buprenorphine for opioid dependence will be recruited and randomized to B-EPIC (*n*=50) or TAU (*n*=50).

Data Analysis (to determine the impact of the B-EPIC intervention on smoking indicators as well as birth and infant outcomes; Aims 1-2). Data analyses will be done using SAS 9.4, with an alpha level of .05; analyses for these two aims will be done by Dr. Rayens. Descriptive analysis, including means and standard deviations or frequency distributions, will be used to summarize all study variables. Baseline comparisons of covariates between the intervention group and the control, and between those who complete the study and those who drop out will be done using t-sample t-tests, Mann-Whitney U tests, or chi-square tests of association. Primary outcomes to be compared between treatment groups will include tobacco indicators, such as smoking and illicit drug use status (abstinence via urine cotinine, iCup results), smoking frequency and readiness to quit (cigarettes per day and stages of change), and maternal-child measures (gestational age of birth, birthweight, NAS, NAS severity, early childhood respiratory and ear infections). The collected variables will include not only these primary outcomes and covariates, but also feasibility indicators, such as average number of sessions completed and ratings of intervention by participants randomized to the intervention group. We will also make group comparisons between other variables that may affect maternal-child outcomes, including SHS exposure, infant feeding status at discharge (breastfeeding vs. formula), and number of people in the home. Those factors with group differences (including demographic factors measured at baseline) will be used as covariates in the corresponding analysis of group comparisons of maternal-child outcomes over time. The primary analysis strategy for the first

two study aims will be two-factor (group x time) repeated measures mixed models; these will be estimated using the MIXED procedure or group comparisons of continuous outcomes over time, including cigarette use and tobacco dependence. Generalized estimating equation (GEE), analyses with an exchangeable correlation structure will be used to assess for significant differences between groups and across time for categorical and dichotomous outcomes (e.g., preterm birth, NAS) using the SAS GENMOD procedure. The main effects of group and time and the interaction between them will be included in each model, and covariates will be added to control for group differences. As appropriate, post-hoc pairwise comparisons will be done using Fisher's least significant difference procedure for mixed models and using contrast statements for GEE models.

Handling Missing Data*.* Based on our prior longitudinal studies with pregnant and postpartum women, we anticipate retention to be at least 60% (9-12% attrition from 2nd-3rd trimester through1-2 months postpartum; additional 30% attrition to 5-6 month postpartum), as show in Table 2. The power estimates outlined below are expected to be conservative for several reasons: 1) attrition in the current UKHC MAT program is 12%; 2) we will use escalating and completion incentives to encourage completion; and 3) increased options for follow-up communication (email, text), using each participant's preferred communication method. Maternal and infant outcome data will be extracted from the UKHC medical record and national MEPS, reducing participant burden. Nonetheless, missing data will occur in this vulnerable population and we acknowledge this in the analysis, given that our analysis strategies allow for inclusion of participants who are missing one or more assessments. We will use the intention to treat convention (those randomized to the B-EPIC group will be retained in this group in the analysis whether or not they complete the entirety of the intervention). For the tobacco use indicators, we will examine group differences assuming the last observation carried forward (LOCF; e.g., if a participant is an active smoker at one time-point, we will assume this status at future time-point(s), if she drops out). We will conduct initial analyses using the maximum likelihood approach, as it emphasizes the use of all available data. The use of random effects modeling techniques, including repeated measures mixed modeling, allows for missing data by adjusting the estimation process to account for bias resulting from data missing at random. In addition, multiple imputation will be used as an alternative procedure for handling missing data. Multiple imputation produces results similar to maximum likelihood when used under identical conditions. The strategy of observing differences in group comparisons under these two methods of dealing with missing data is suggested by Hedeker et al. as a way to determine the robustness of the results under these different assumptions. This approach will provide a sensitivity analysis of the group comparisons.

Power Considerations. With approximately 50 per group and an alpha level of .05, the power of the two-sample t-test to detect a baseline group difference in a continuous covariate will be at least 84% if the ratio of the difference in means to the standard deviation is at least 0.6. This is slightly larger than a medium effect size. With approximately 50 per group and a .05 level of significance, the power of the chi-square test of association to detect an odds ratio as small as 3.5 will be at least 81%. One way to obtain an odds ratio of this magnitude would be if the prevalence of a given binary covariate at baseline were 60% in one group and 30% in the other. With at least 30 mother/baby dyads completing the study per group and an alpha level of .05, the power of the repeated measures analysis of variance F test to detect a significant main for group will be 79%, assuming a medium effect size, while the power of the F tests to detect a significant main effect of time or group by time interaction will be at least 95%, under these conditions. In the context of repeated measures modeling, a medium effect size is one such that the ratio of the standard deviation of the group means to the standard deviation of the observations within the populations is at least 0.25. Even if this ratio is smaller than a medium

effect (i.e., 0.20), the power of the repeated measures mixed model will be at least 60% to detect a group effect and 87% to detect a time or interaction effect. While an algorithm for estimating the power associated with a generic GEE model has not been developed, this strategy is analogous to a repeated measures application of logistic modeling. With at least 60 mother/baby dyads completing the study and an alpha level of .05, the power of logistic regression to detect an odds ratio of 2.5 or larger will be at least 68%. While this level of power is not optimal, inclusion of 4 time-points in the GEE models will increase the power of this analysis technique relative to a logistic model for a fixed point in time; this phenomenon is consistent with the comparison of the expected power of a two-sample t-test relative to expected power of a repeated measures comparison of two groups over 4 time-points, namely power for the later exceeds the former under the same conditions. Given the paucity of research regarding tobacco cessation in this at-risk population, it is unknown whether a medium (or slightly smaller) effect size is appropriate for continuous outcomes, such as cigarettes per day. However, in a preliminary study of this population by our group (EMPOWR, described above), we found that 14% of pregnant women decreased their cigarette consumption between intake (typically during the second trimester) and the third trimester. This is notable since each participant chose a health goal to work on (including reducing stress, reducing alcohol/drug use, reducing smoking, or weight management), so not all would have focused on decreasing cigarette consumption. While smoking cessation is the ultimate goal of this intervention, prior research has demonstrated that cutting cigarette consumption below 8 cigarettes per day is a risk reduction strategy for preventing low birthweight, so we will consider outcomes of both successful cessation as well as reduction in consumption for this exploratory project. In addition, a prior study (using a different cessation intervention but with a similar sample size) has demonstrated that while pregnant women addicted to opioids were not able to quit smoking at a higher rate than those not exposed to the intervention, there was a significant increase in readiness to quit, as assessed via stage of change, in the intervention group relative to the controls. We are assessing changes in stage of change over time between the groups for this reason. For all of the inferential tests used in this study, the primary emphasis of these group comparisons will be to estimate effect sizes for the impact of the intervention, which will allow us to estimate power for future (larger) studies. We expect to be able to demonstrate group differences with this exploratory study, given the relatively modest effect sizes required to have a reasonable level of power to detect differences in outcomes between groups. As outlined above, the estimated effect sizes for the longitudinal analyses are expected to be conservative, given that they are based on the minimum expected sample size at the completion of the study; however, since the repeated measures modeling allows for the inclusion of participants who drop out prior to completion, the effective sizes for these group comparisons over time are actually underestimated.

Data Analyses (Aim 3): The economic analysis will use estimates of intervention efficacy from the pilot trial together with estimates of intervention costs and expected cost-savings to project the aggregate economic value of the intervention from several important perspectives, including a health system/payor perspective and a societal perspective. Analysis for this aim will be conducted by Dr. Mays. Results from this analysis will allow the intervention to be compared based on costs required to achieve a standard set of outcomes, including a 1 unit decrease in the preterm risk, a 1 unit decrease in low birth weight risk. Results will allow projections to be made of the costs required to implement the intervention on a broad scale such as at the level of a community, state, or health plan. The results of this exploratory economic analysis will also provide preliminary data that will be used to estimate the statistical power associated with cost-effectiveness ratios for the purpose of planning a larger future study.

Standard methods of economic evaluation will be used to assess the within-trial, incremental cost-effectiveness of the intervention relative to the control environment. We will first assess costs from the health system perspective by aggregating the costs associated with intervention implementation and medical care utilization. These cost estimates will be used together with measures of clinical outcomes to project the average reimbursement levels that would be required for providers and/or payors to break even financially in delivering the active intervention included in the trial. We will assess costs from the societal perspective by adding in any indirect medical costs, lifestyle costs, and productivity costs or cost-savings incurred by participants. The within-trial, incremental cost effectiveness ratio will be computed as the ratio of (1) intervention costs net of all medical and productivity-loss costs averted and (2) the difference in clinical outcomes observed between the intervention and control groups. Separate estimates will be generated for each outcome measure (e.g. preterm, low birth weight). Additionally, a cost-benefit summary measure will be computed for the intervention as the total medical and productivity-loss costs averted by the intervention net of the intervention costs. All estimates of costs and cost savings will be transformed to a net present value using an annual discount rate.

Potential Risks of Participation

The potential risks for participants in this program include: (1) potential discomfort discussing tobacco-related issues or answering questions related to the topics in the survey; (2) loss of confidentiality of data; (3) risks inherent in everyday life (for example, experiencing an injury while traveling to the clinic).

All study procedures will be conducted by trained team members who are employees of the University associated prenatal clinics, or of the University Medical Center and are under supervision of the study PIs, Co-Is, or designated OBGYN clinic personnel. Collection of urine and EACO will be coordinated whenever possible with the subjects' normal or routine collection visits. All team Key Personnel have completed the Human Subjects Protection training for clinical research.

Expected benefits of participation: Subjects who quit smoking may benefit from the change in behavior as smoking during pregnancy has been linked to various adverse maternal and infant outcomes including low birth weight and preterm birth. Otherwise, subjects will not directly benefit by the study but will receive at least standard of care treatment as usual with their regular visits. This is a minimal risk study, with the possibility of patients feeling uncomfortable answering survey questions pertaining to tobacco and opioid use, and the possibility of a loss of confidentiality of data.

Protection against risk: Team members will make every effort to protect against loss of confidentiality of data. All research team members who take part in data collection, data analysis or data storage will be certified in human subject protections through the Collaborative Institutional Training Initiative program (CITI). All data will be stored in a locked research area associated with the UK College of Nursing, or in a secure area of the respective clinic, or on a password protected computer or tablet with encryption. All participant information will be identified by study number only.

The PI and other key research personnel will review the study protocol quarterly and additionally as deemed necessary; reviewing progress reports from the study coordinator; monitoring adverse events and adverse event reporting to the IRB; monitoring interventions for subjects as deemed necessary; monitoring subject recruitment; and monitoring subject termination/withdraw from the study. Annual progress reports are required to the Sponsor, and annual Continuation Reviews by the IRBs.

All source documents for potential study subjects including medical histories, demographic data, consent forms, treatment notes, and study data will be stored in a locked cabinet in each respective clinic during the active phase of the study. Once completed, study documents and materials will be stored in a locked cabinet behind the locked door of the Project Coordinator's office. Only the Principal Investigator, Study Coordinator and Data Analysis members will have access to all data and patient identifiers if the study code needs to be broken in the case of an adverse event or at the end of the study. All participant information will be identified by study number only. Data and electronic records will be kept for at least six years post-study closure, after which time they will be destroyed in accordance with UK Policy A13-050.

The sponsors (NIDA) as well as the Institutional Review Board and regulatory authorities could be granted direct access to original medical and research records for verification of clinical trial procedures and/or data. If this is required, it will be done under conditions that will protect privacy to the fullest extent possible consistent with laws relating to public disclosure of information and the law-enforcement responsibilities of the agency.

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KEY INFORMATION FOR Behavioral and Enhanced Perinatal Intervention for Cessation (B-EPIC): Reducing Tobacco use among Opioid Addicted Women

You are being invited to take part in a research study to help us understand how our program (B-EPIC) can help pregnant and postpartum women receiving Medication Assisted Treatment (MAT) for opioid dependence to stop smoking cigarettes.

WHAT IS THE PURPOSE, PROCEDURES, AND DURATION OF THIS STUDY?

By doing this study, we hope to learn about the impact of the B-EPIC intervention on your tobacco use as well as birth and infant outcomes. Your participation in this research will last up to one year.

WHAT ARE REASONS YOU MIGHT CHOOSE TO VOLUNTEER FOR THIS STUDY?

You might want to volunteer for this study to receive support for stopping smoking during pregnancy. Decreased smoking is linked to better outcomes for both mother and baby. Otherwise, you might join to help us learn more about whether our program is effective for helping women stop smoking during pregnancy.

WHAT ARE REASONS YOU MIGHT CHOOSE NOT TO VOLUNTEER FOR THIS STUDY?

You might not want to volunteer if you will be uncomfortable discussing your tobacco or opioid use. You might choose not to participate if you are worried about loss of confidentiality of your data. However, we will take every precaution to prevent loss of confidentiality of your data.

DO YOU HAVE TO TAKE PART IN THE STUDY?

If you decide to take part in the study, it should be because you really want to volunteer. You will not lose any services, benefits or rights you would normally have if you choose not to volunteer.

WHAT IF YOU HAVE QUESTIONS, SUGGESTIONS OR CONCERNS?

The person in charge of this study is Kristin Ashford, PhD, WHNP, FAAN (Principal Investigator, PI) of the University of Kentucky, College of Nursing. If you have questions, suggestions, or concerns regarding this study or you want to withdraw from the study her contact information is: 859-257-9333 or kristin.ashford1@uky.edu.

If you have any questions, suggestions or concerns about your rights as a volunteer in this research, contact staff in the University of Kentucky (UK) Office of Research Integrity (ORI) between the business hours of 8am and 5pm EST, Monday-Friday at 859-257-9428 or toll free at 1-866-400-9428.

DETAILED CONSENT:

ARE THERE REASONS WHY YOU WOULD NOT QUALIFY FOR THIS STUDY?

You would not qualify for this study if you are:

- Under the age of 18, or over the age of 49
- More than 32 weeks gestation in your pregnancy
- Not currently participating in the UKHC PATHways or Beyond Birth programs
- Not a current smoker
- Cannot read or write in English
- Are currently incarcerated

WHERE IS THE STUDY GOING TO TAKE PLACE AND HOW LONG WILL IT LAST?

The research procedures will be conducted at the University of Kentucky PATHways clinic and Beyond Birth clinic, and will include two groups of volunteers. One group will receive usual care services (TAU) provided for pregnant tobacco users, which includes a 5-step intervention approach for tobacco cessation as recommended by the American Congress of Obstetrics and Gynecologists (ACOG) which takes approximately 5-15 minutes, and is offered at each prenatal and postpartum appointment, regardless of whether or not you participate in this study. The five steps of the ACOG recommendation are: 1. Ask about tobacco use, 2. Advise to quit, 3. Assess willingness to make a quit attempt, 4. Assist in quit attempt, and 5. Arrange follow-up. Your provider may also talk to you and/or offer nicotine replacement therapy. A second group of participants will receive the same 5-step tobacco cessation services (approximately 5-15 minutes), as offered by the clinic, plus additional counseling (B-EPIC) and may also be offered nicotine replacement therapy. This counseling will include an initial assessment by a certified tobacco treatment specialist (CTTS) lasting approximately 60 minutes, with follow-up sessions typically lasting 15-20 minutes. Regardless of group assignment, all enrolled volunteers will attend three or four study visits prior to or after pre-scheduled perinatal appointments, complete the 20 minute survey and provide a urine sample and Expired Air Carbon Monoxide (EACO). In total, you can expect to spend between 20-60 minutes each session of the program, based on your randomly assigned group.

WHAT WILL YOU BE ASKED TO DO?

Once you have agreed to volunteer for this study, a computer will randomly place you in one of two possible groups of participants receiving tobacco cessation services. This process is called randomization. There is a 50% chance the computer will place you in the tobacco treatment as usual (TAU) group, and a 50% chance you will be placed in the B-EPIC group.

Participants will provide urine samples, and EACO and complete a survey at three or four time points throughout the study (4 time points include: enrollment up to 31.6 weeks, third trimester 28-36.6 weeks, postpartum 2-8.6 weeks and postpartum 20-28.6 weeks; 3 time points include: enrollment up to 31.6 weeks, third trimester 28-36.6 weeks, postpartum 2-8.6 weeks). There will be minimum of 8 weeks between individual data collection time periods. First, a survey available via iPad (or paper/pen if you prefer) will be administered by our research staff. The survey will take approximately 20 minutes to complete and will assess current and past use of tobacco products, demographic and psychosocial variables, stage of change, and personal characteristics. See Table 1. In addition to the surveys, you will receive the 5-step tobacco cessation services monthly throughout your pregnancy provided by your healthcare provider, which is usually 5-15 minutes in length and is provided regardless of your participation in this study. Additionally, if you are among the B-EPIC participant group, you will also receive individualized tobacco cessation counseling with a Certified Tobacco Treatment Specialist (CTTS) at your scheduled study visits. After completion of the survey, EACO, urine screen and tobacco cessation treatment at each of the two visits during your pregnancy, you will receive a $20 gift card. After completion of the survey, EACO, urine screen and tobacco cessation treatment at each of the two postpartum study visits, you will receive a $40 gift card. If you complete all four of your study visits (2 during pregnancy and 2 postpartum), you will receive an additional $20 gift card for a potential total of $140. If you complete three of your study visits (2 during pregnancy and 1 postpartum), you will receive an additional $20 gift card for a potential of $100.

Table 1. Summary of Study Visits

Time points	B-EPIC -Taking Action	Treatment as Usual	Biomarkers	Survey	Incentives
Baseline (up to 32 weeks)	• Individualized tobacco treatment (every month-minimum) plus supplemental counseling • Biomarker validation and feedback • Focus and adoption of health behavior and change in maternal thought process (e.g. exercise) based on PI framework • Pharmacotherapy as needed.	• 5-step ACOG tobacco cessation treatment • Pharmacotherapy as needed	• Urinary Cotinine *iCup Drug & Quantitative Analysis • EACO	• Prenatal History • Demographics • Adverse Childhood Events (ACE) • Outcomes Measures Survey (SOMs). Refer to Table 4	$20 gift card
3rd trimester (28-36.6 weeks)			• Urinary Cotinine *iCup Drug & Quantitative • EACO	• Prenatal History • SOM	$20 gift card
After Delivery of Baby (2-8.6 weeks)			• Urinary Cotinine *iCup Drug & Quantitative • EACO	• Labor and Birth History • Newborn History • SOM	$40 gift card
After Delivery of Baby (20-28.6 weeks)			• Urinary Cotinine *iCup Drug & Quantitative • EACO	• Maternal and Infant Outcomes • SOM	$40 gift card
If complete 3 or 4 study visits					Additional $20 gift card

- iCUP screen is included within the participants existing treatment program and will be managed by the medical provider. For purposes of this study, results from iCUP will be obtained via retrospective chart review only.

Finally, at the conclusion of our study, you may be asked to participate in a focus group to discuss your opinion about the program. The focus group will be voice recorded, professionally transcribed by a UK employee, and analyzed using computer software. Voice recordings will be safely deleted in accordance with the University of Kentucky procedures for record destruction, once they have been checked against the transcripts for accuracy.

WHAT ARE THE POSSIBLE RISKS AND DISCOMFORTS?

The potential risks of participating in this program include: (1) you may feel uncomfortable discussing tobacco-related or opioid-related issues or answering questions related to the topics in the survey; (2) loss of confidentiality of data; (3) risks inherent in everyday life (for example, experiencing an injury while traveling to the clinic).

There is always a chance that any medical treatment can harm you. The research treatments/procedures in this study are no different. In addition to risks described in this consent, you may experience a previously unknown risk or side effect.

WILL YOU BENEFIT FROM TAKING PART IN THIS STUDY?

We do not know if you will get any benefit from taking part in this study. Participation in this study may help some women stop smoking, which would reduce the risk of many health problems. Your willingness to take part may help us design a smoking cessation program that may be used in a larger population.

WHAT WILL IT COST YOU TO PARTICIPATE?

Whenever possible, your study appointment will be coordinated with your prenatal (before delivery) or postpartum (after delivery) appointments in the clinic. You are responsible for travel and parking costs associated with visiting the clinic. There is no cost to participate in this study other than the time spent participating in program-related activities and potential transportation costs related to your clinic visits.

WHO WILL SEE THE INFORMATION THAT YOU GIVE?

When we write about or share the results from the study, we will write about the combined information. We will keep your name and other identifying information private. We will make every effort to prevent anyone who is not on the research team from knowing that you gave us information, or what that information is. We will use a code number and not your name on the survey. We will keep all participant records in a locked cabinet in our research office and/or the College of Nursing.

You should know that there are some circumstances in which we may have to show your information to other people. For example, the law may require us to show your information to a court to tell authorities if you report information about a child being abused or if you pose a danger to yourself or someone else.

We will conduct surveys using REDCap, which is a secure, web-based program to capture and store data at the University of Kentucky. Please be aware, while we make every effort to safeguard your data once received on servers via REDCap, given the nature of online surveys, as with anything involving the Internet, we can never guarantee the confidentiality of the data while still en route to the server.

Officials of the National Institutes of Health, the National Institute on Drug Abuse (NIDA) (the funding agency of this study), and the University of Kentucky may look at or copy pertinent portions of records that identify you.

With a few exceptions, study payments are considered taxable income and reportable to the IRS. A Form 1099 will be sent to you if your total payments are $600 or more in a calendar year.

Certificates of Confidentiality (CoC):

This research is covered by a Certificate of Confidentiality from the National Institutes of Health. The researchers with this Certificate may not disclose or use information, documents, or biospecimens that may identify you in any federal, state, or local civil, criminal, administrative, legislative, or other action, suit, or proceeding, or be used as evidence, for example, if there is a court subpoena, unless you have consented for this use. Information, documents, or biospecimens protected by this Certificate cannot be disclosed to anyone else who is not connected with the research except, if there is a federal, state, or local law that requires disclosure (such as to report child abuse or communicable diseases but not for federal, state, or local civil, criminal, administrative, legislative, or other proceedings, see below); if you have consented to the disclosure, including for your medical treatment; or if it is used for other scientific research, as allowed by federal regulations protecting research subjects.

The Certificate cannot be used to refuse a request for information from personnel of the United States federal or

state government agency sponsoring the project that is needed for auditing or program evaluation by NIDA which is funding this project. You should understand that a Certificate of Confidentiality does not prevent you from voluntarily releasing information about yourself or your involvement in this research. If you want your research information released to an insurer, medical care provider, or any other person not connected with the research, you must provide consent to allow the researchers to release it.

The Certificate of Confidentiality will not be used to prevent disclosure as required by federal, state, or local law of such as child abuse and neglect, or harm to self or others.

CAN YOU CHOOSE TO WITHDRAW FROM THE STUDY EARLY?

If you decide to volunteer for this study, you have the right to decide at any time that you no longer want to continue. Your choice to withdraw early from the study, will have no impact on the medical care you receive in your prenatal clinic. However, early withdrawal from the study will terminate your opportunity to earn the gift cards for completing the required sessions. The data collected to the point of withdrawal will be retained. Additionally, the study investigators may need to remove you form the study if:

- you are not able to follow the directions
- they find that your participation in the study is more risk than benefit to you, or
- the agency paying for the study chooses to stop the study early for a number of scientific reasons.

WHAT HAPPENS IF YOU GET HURT OR SICK DURING THE STUDY?

If you believe you are hurt or if you believe you have become sick because of something that is due to the study, you should immediately contact your healthcare provider. In the case of emergencies, call 911 or go directly to the Emergency Room. Next, you should call the study investigator, Kristin Ashford, PhD, 859-257-9333.

It is important for you to understand that the University of Kentucky does not have funds set aside to pay for the cost of any care or treatment that might be necessary because you get hurt or sick while taking part in this program. Also, the University of Kentucky does not have funds to pay for any wages you may lose if you are harmed by this study.

The medical costs related to your care and treatment because of research-related harm will be your responsibility. You do not give up your legal rights by signing this form.

WILL YOU RECEIVE ANY REWARDS FOR TAKING PART IN THIS STUDY?

Walmart Gift Card: At four times during the study (twice during pregnancy and twice after delivery) or three times (twice during pregnancy and once after delivery), you will be asked to complete an online survey (administered via a password protected iPad), provide urine, EACO, and complete tobacco treatment. After completing these requirements at each of the two study visits during your pregnancy, you will receive a $20 Walmart gift card. After completing the study requirements at each of the two visits after your delivery, you will receive a $40 Walmart gift card. If you complete all four study visits, you will receive an additional $20 Walmart gift card. The total potential amount of gift cards for completing all study time points is $140. If you complete three of your study visits (2 during pregnancy and 1 postpartum), you will receive an additional $20 gift card for a potential of $100.

WHAT IF NEW INFORMATION IS LEARNED DURING THE STUDY THAT MIGHT AFFECT YOUR DECISION TO PARTICIPATE?

You will be informed if the investigators learn new information that could change your mind about staying in the study. You may be asked to sign a new informed consent form if the information is provided to you after you have joined the study.

WILL YOU BE GIVEN INDIVIDUAL RESULTS FROM THE RESEARCH TESTS?

You will be given the results of your NicAlert urine test. This test provides a number 0-6 that confirms your smoking status. You will also be provided your EACO levels. You will breathe into this small hand-held monitor and will be able to immediately see your EACO levels and the equivalent level for your baby. EACO levels tell us about the amount of oxygen available in your body. For this study, results from other tests

obtained from your healthcare provider, for example the iCup test to screen for other drugs, will be collected from your chart after the birth of your baby. These results will only be used for data analysis.

WHAT ELSE DO YOU NEED TO KNOW?

If you volunteer to take part in this study, you will be one of about 100 women to do so through the University of Kentucky.

The National Institute on Drug Abuse (NIDA) is providing financial support and/or material for this study.

A description of this clinical trial will be available on ClinicalTrials.gov as required by U.S. Law. This website will not include information that can identify you. At most, the website will include a summary of the results. You can search this website at any time.

THE USE OF YOUR PROTECTED HEALTH INFORMATION OR SPECIMEN(S):

Identifiable information such as your name, medical record number, or date of birth may be removed from the information or samples collected in this study. After removal, the information or samples may be used for future research or shared with other researchers without your additional informed consent.

In addition to the main study, you are being asked to allow us to keep and use your information and/or specimens for future research that involves smoking among women of childbearing age. See Appendix A.

FUTURE USE/OPTIONAL SUB-STUDY:

- ☐ Yes, I choose to participate in the optional registry sub-study. ___ Initials
- ☐ No, I choose not to participate in the optional registry sub-study. ___ Initials

AUTHORIZATION TO USE OR DISCLOSE YOUR IDENTIFIABLE HEALTH INFORMATION

The privacy law, HIPAA (Health Insurance Portability and Accountability Act), requires researchers to protect your health information. The following sections of the form describe how researchers may use your health information.

Your health information that may be accessed, used and/or released includes:

- Healthcare outcome data will be collected from the mother's and infant's electronic medical record and national MEPS data.
- Maternal data obtained includes: prenatal history, medications and complications, gestational age at birth, birthweight, delivery method and complications, length of stay, hospital readmissions, medical care adherence/attendance, readmission, emergency room visits and number of positive urine drug testing results.
- Infant data obtained from the maternal medical record or national MEPS data includes: sex and birth weight, NICU admission, length of NICU stay, NAS scores, treatment offered for NAS/total mg dose in morphine equivalents of such treatment, infant outpatient visits, including, well-child, sick visits and emergency department.

Researchers may use and share your health information with:

- The University of Kentucky's Institutional Review Board/Office of Research Integrity;
- Law enforcement agencies when required by law;
- University of Kentucky representatives;
- UK Hospital
- National Institute of Health and National Institute on Drug Abuse
- Your primary physician will be contacted if the researcher, in the course of the project, learns of a medical condition that needs immediate attention.

The researchers agree to only share your health information with the people listed in this document.

Should your health information be released to anyone that is not regulated by the privacy law, your health information may be shared with others without your permission; however, the use of your health information would still be regulated by applicable federal and state laws.

You may not be allowed to participate in the research study if you do not sign this form. If you decide not to sign this form, it will not affect your:

- Current or future healthcare at the University of Kentucky;
- Current or future payments to the University of Kentucky;
- Ability to enroll in any health plans (if applicable); or
- Eligibility for benefits (if applicable).

After signing the form, you can change your mind and NOT let the researcher(s) collect or release your health information (revoke the Authorization). If you revoke the authorization:

- You will send a written letter to Kristin Ashford, PhD to inform her of your decision at:
  Kristin Ashford, PHD
  University of Kentucky College of Nursing
  750 Rose Street, CON #447
  Lexington, KY 40536-0232
- Researchers may use and release your health information **already** collected for this research study.
- Your protected health information may still be used and released should you have a bad reaction (adverse event).

The use and sharing of your information has no time limit.

If you have not already received a copy of the Privacy Notice, you may request one. If you have any questions about your privacy rights, you should contact the University of Kentucky's Privacy Officer between the business hours of 8am and 5pm EST, Monday-Friday at (859) 323-1184.

Study Related Communication

You give permission for a member of the research staff to use text or verbal telephone messages to communicate with you while you are participating in this study. **You understand the messages will include study related information, but not include Protected Health Information (PHI). Text messaging should NOT be used in emergency situations and will NOT be checked outside of normal research study hours from 8am-4pm, M-F.**

You understand that communication via text may not be secure and there is some level of risk that information transmitted via text message could be read or otherwise accessed by a third party. There is no assurance of confidentiality when communicating via text messaging, and the use of text messages carries a risk of inadvertent disclosure through the mistyping of text/contact names or numbers.

You understand that additional charges and fees may be applied by my mobile device service carrier. You understand that you are responsible for any fees that may occur as a result of this communication.

(Please mark one and initial.)

☐ Yes ☐ No _____ (Initials)

INFORMED CONSENT SIGNATURE PAGE

You are a participant or are authorized to act on behalf of the participant. This consent includes the following:

- **Key Information Page**
- **Detailed Consent**
- **Appendix A: Subject information to be stored for future use**

You will receive a copy of this consent form after it has been signed.

_____ _____
Signature of research subject **Date**

_____
Printed name of research subject

_____ _____
Printed name of [authorized] person obtaining informed consent/HIPAA authorization Date

_____
Signature of Principal Investigator or Sub/Co-Investigator

Revised: 06/12/18; 11/29/18; 05/07/19, 11/14/19; 10/08/20

Appendix A: Subject information to be stored for future research

WHAT IS A REGISTRY AND WHAT IS THE PURPOSE OF THE REGISTRY?

The purpose of the registry is to collect and store contact and/or health information for research purposes. The information you provide for this study will be stored for future research studies to learn more about smoking among pregnant women. The registry provides a ready supply of information, so investigators do not have to look for participants for each new study.

The registry will enroll approximately 100 participants from the B-EPIC study.

WHERE WILL INFORMATION BE STORED AND FOR HOW LONG?

The information will be stored in the University of Kentucky's secure research database, Redcap, indefinitely.

WHAT WILL THE REGISTRY/DATABASE COLLECT AND STORE FOR RESEARCH?

As explained in the informed consent, Healthcare outcome data will be collected from the mother's and infant's electronic medical record and national MEPS data. Additionally, Maternal data obtained includes: prenatal history, medications and complications, gestational age at birth, birthweight, delivery method and complications, length of stay, hospital readmissions, medical care adherence/attendance, readmission, emergency room visits and number of positive urine drug testing results.

Infant data obtained from the maternal medical record or national MEPS data includes: sex and birth weight, NICU admission, length of NICU stay, NAS scores, treatment offered for NAS/total mg dose in morphine equivalents of such treatment, infant outpatient visits, including, well-child, sick visits and emergency department.

You will complete surveys at each study time point as described in the informed consent. The questions will ask about your health, medical condition, medical history, and quality of life. You can skip any question that you do not want to answer. *You may be contacted annually to update information.*

We also would like to have permission to look at your medical records from time to time. We would collect general information related to your health such as test results, treatments, and doctor's notes. Medical records may also include psychiatric, genetic, HIV/AIDS, alcohol/substance abuse information. The confidentiality section below provides details about how we will keep your information private.

WILL YOU BE CONTACTED ABOUT OTHER RESEARCH STUDIES?

Neither the registry nor investigators who access information from the registry will contact you about other research studies.

HOW WILL THE REGISTRY INFORMATION BE SHARED WITH OTHER INVESTIGATORS?

Your information may be shared with University of Kentucky (UK) investigators and investigators outside of UK. Investigators may contact the registry to request permission to use information for their studies. An oversight committee will review the investigator's qualifications and proposed research. The committee will also determine if any additional review or approval is necessary.

If plan includes sharing de-identified sample/information:

The registry will remove all information that could identify you such as your name, address, medical record number, etc., before sharing with investigators.

The registry will not share information that could identify you without your permission.

Large-Scale Data Sharing:

Investigators can do studies that are more powerful when they share with each other data or information they get from studying human samples. Information from analysis of your samples and your medical information may

be put into scientific databases available on the Internet, along with information from other research participants. Your name and other information that could identify you will not be included. Therefore, no one would know just from looking at the data that the information came from you.

Privacy and Social/Psychological:

There is a risk that someone could get access to the information stored in the registry. In spite of the security measures and safeguards we will use, we cannot guarantee that your identity will never become known.

Unknown:

There may be risks that at this time are unknown. As technology advances, there may be new ways of linking information back to you that we cannot foresee now.

HOW IS YOUR PRIVACY AND CONFIDENTIALITY PROTECTED?

The registry will take careful steps to keep your information confidential. All iPads and laptops used in this study are password protected. The Research database used for this study is called REDCap, which is a secure, web-based program to capture and store data at the University of Kentucky. Please be aware, while we make every effort to safeguard your data once received on protected servers via REDCap, as with anything involving the Internet, we can never guarantee the confidentiality of the data while still en route to the server.

We will remove information such as your name or other direct identifiers from your medical information. We will label your information with a code. The coded information will be stored in the REDCap password-protected database. Only select registry staff will have access to the list that links the code to you. The registry staff members sign an agreement to keep your identity a secret to the extent allowed by law. In very unusual cases, registry staff may be required to release your identifiable medical and research information in response to an order from a court of law.

Officials of the National Institutes of Health and the University of Kentucky may look at or copy pertinent portions of records that identify you.

DOES TAKING PART IN THE REGISTRY COST ANYTHING?

There will be no additional costs or charges to you for taking part in the registry.

ARE THERE OTHER CHOICES IF YOU DO NOT WANT TO PARTICIPATE IN THE REGISTRY?

If you do not want to take part in the registry, there are no other choices except not to take part. Your decision will not affect your enrollment in the B-EPIC study, or current or future medical care.

WHAT IF YOU CHOOSE NOT TO PARTICIPATE OR CHANGE YOUR MIND AND WANT TO WITHDRAW FROM TAKING PART IN THE REGISTRY?

Taking part in the registry is voluntary. Choosing not to take part will not affect your care or cause you to lose benefits to which you are entitled. You may withdraw your permission to continue taking part in the registry at any time. To do so, you must send a written withdraw request to the registry at:
Kristin Ashford, PHD
University of Kentucky College of Nursing
750 Rose Street, CON #447
Lexington, KY 40536-0232

The registry will destroy any remaining information that has been stored. In addition, it may be possible for the registry to destroy the code that links you with your medical information. However, the information that has already been shared with other investigators or placed in shared databases cannot be withdrawn.