PROTOCOL AND STATISTICAL ANALYSIS PLAN

Study Title: **Tobacco Use in Pregnancy Intervention for Cessation (ToPIC)**

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Study Protocol:

Study Design: The effectiveness-implementation hybrid design[1] of this proposal enables the simultaneous evaluation of both effectiveness outcome measures as well as of the process of implementation. We propose a type 2 hybrid trial to test both the effectiveness of the clinical intervention (the 5A's delivered via a CTTS) while simultaneously gathering multi-level contextual data regarding potential barriers and facilitators to clinical implementation. Effectiveness questions will be explored using a two-armed cluster randomized controlled design. Implementation questions include: (1) what are the facilitators/barriers to delivering tobacco treatment to pregnant women using existing healthcare provider in the clinic settings; (2) how likely is intervention delivered as prescribed (fidelity); (3) what implementation strategies might maximize the facilitators and overcome barriers to implementation; and (4) what potential modifications could be made to maximize implementation? This pilot project will gather quantitative and qualitative data for a mixed-method, multi- stakeholder process evaluation of intervention training and delivery among 12 clinic staff and providers involved in the project. Furthermore, our use of Medicaid claims data will enhance understanding of the strengths and limitations of these data for future evaluations.

Aim 1 - Effectiveness evaluation: As part of routine standard of care, all pregnant Medicaid patients who receive first trimester screening through the intervention or Tobacco Treatment as Usual (TTAU) clinic will also be asked about their tobacco use consistent with the ACOG recommended questionnaire (the standard of care for TTAU is the ACOG recommended questionnaire in Box 1. ACOG 5A's).[2] All women who report tobacco use would be considered eligible to participate to receive ToPIC or TTAU. Participants in the intervention and TTAU clinics will be informed their urine will be tested for cotinine to confirm tobacco use at each data collection point and be informed of their results in compliance with ACOG clinical standards. Inclusion criteria are: 1. Pregnant and age 18-44; 2. Tobacco user (self-reported) 3. Can read and write in English; and 4. Medicaid subscriber.

BOX 1. ACOG's 5A's[2]

1. **ASK** the patient about smoking status at the 1st prenatal visit and follow-up with her at subsequent visits.
   - A. I have never smoked or I have smoked fewer than 100 cigarettes in my lifetime
   - B. I stopped smoking before I found out I was pregnant and I am not smoking now
   - C. I stopped smoking after I found out I was pregnant, but I am not smoking now
   - D. I smoke now, but I cut down on the number of cigarettes I smoke since I found out I was pregnant
   - E. I smoke regularly now, about the same as before I found out I was pregnant
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. **ASSIST** the patient willing to make an attempt using counseling and pharmacotherapy to help her quit.
5. **ARRANGE** the follow-up contact, in person or by telephone, preferably within the first week after the quit date.

Usual Care (TTAU): Eligible women randomized to the control group will be informed of the risks of tobacco use and benefits of quitting using the ACOG 5A's approach by their healthcare provider.[2] This standard takes approximately 5-15 minutes, and is offered at each prenatal and postpartum appointment. The research nurse or key personnel will invite participants to complete the tobacco use questionnaires (TUQ), urine cotinine validation, and Expired Air Carbon Monoxide (EACO) analysis to assess ongoing tobacco use at the designated time points; participants will receive a monetary gift card as compensation for their time, at the denominations listed below in Table 1.

The Intervention (ToPIC): Eligible women randomized to the intervention will receive TTAU plus ToPIC administered by the CTTS. At least once monthly, at routinely scheduled prenatal visits or through telephone, the CTTS will provide cessation counseling (see components of a typical counseling session in Box 2). The CTTS will invite participants to complete TUQs, urine cotinine validation and EACO analysis to assess ongoing tobacco use at the designated time points; participants will receive a monetary gift card as compensation for their time. See summary of study procedures in Table 1.

Table 1. Summary of Study Procedures

Time points	ToPIC participants	TTAU participants	Outcome	Compensation
Pregnant Patient Participants:				
Baseline <20 weeks gestation	• Urine cotinine • EACO • ACOG tobacco use screen	• Urine cotinine • EACO • ACOG tobacco use	Eligibility screen for tobacco	$10
Monthly through end of pregnancy at regularly scheduled prenatal visits	• CTTS tobacco treatment education support, including • Individualized treatment plan (baseline) • 5As • Motivational Interviewing • Navigation to resources	• 5As, as per usual		
28-34 weeks gestation	• Urine cotinine • EACO • TUQ	• Urine cotinine • EACO • TUQ	Tobacco cessation or reduction	$10
Postpartum 2-8 weeks after delivery	• Urine cotinine • EACO • TUQ	• Urine cotinine • EACO • TUQ	Tobacco cessation or reduction	$20
Postpartum 12-18 weeks after delivery	• Urine cotinine • EACO • TUQ	• Urine cotinine • EACO • TUQ	Tobacco cessation or reduction	$20

BOX 2. Typical Counseling Session with a CTTS for Pregnant Women

- Assessment of tobacco use and tobacco use history using an evidence-based tool
- Motivational and practical counseling based on assessment of readiness, including providing education on the maternal and fetal health impacts of smoking
- Provide strong advice to quit as soon as possible
- Exploration of the pros and cons of tobacco use/quitting (decisional balance) and triggers/cues to smoke, including partner smoking and potential engagement in treatment
- Collaboratively developing a tailored treatment plan, which may include but is not limited to incentives, and trigger management strategies, such as stress management or partner support
- Setting a quit date with close follow up
- Discussion relapse prevention strategies during the perinatal and postpartum periods

Our target sample size is 60 participants in each the intervention and control group, for a total of 120 pregnant participants for this pilot project. Additionally, 12 clinic staff and providers will provide quantitative and qualitative data for a mixed-method, multi-stakeholder process evaluation of intervention training and delivery. Due to our limitation of only two participating clinics, we acknowledge that it will not be possible to fully distinguish the effects of the intervention from differences between the two clinic populations. A future larger study of this intervention will include a true group randomized trial, with multiple clinics per treatment, so that the effect of nesting of patients within clinics within treatment will be estimable. In light of this limitation, we will use sample demographic characteristics as covariates in the repeated measures mixed modeling; we acknowledge that the group effects are still likely to be somewhat inflated in this analysis, given the expected artificially small errors due to correlations among patients who visit the same clinic and who may see the same provider. Although we will have limited power, the results from this pilot proof-of-concept study will provide preliminary data to support a highly competitive NIH Health Care Systems Research Pragmatic Trial application.

Statistical Analysis Plan

Analysis and estimated power: **Primary outcome:** The primary outcome is smoking cessation in the third trimester, defined as urine cotinine level of <100 ng/mL. **Secondary outcomes** include: self-reported number of cigarettes smoked/day, smoking cessation after delivery, infant birth weight, gestational age at delivery, health care utilization outside of scheduled normal prenatal and infant well-child visits. Two-factor mixed models with group by time interactions will be employed to analyze longitudinal continuous data collected over the course of the trial. Significant main and interaction effects will be explored further using Tukey post-hoc tests. Generalized estimating equation (GEE) modeling will be used to test for significant differences between groups and across time for categorical and dichotomous outcomes; these models will also consider possible group by time interactions. Post-hoc analysis of significant main or interaction effects in the GEE models will be accomplished using contrasts. Demographic and personal factors (e.g., maternal age, gestational age at enrollment) may be included as covariates if linked to outcomes in bivariate analysis. We **hypothesize** that compared with the TTAU group, the ToPIC group will have higher tobacco cessation rates, fewer infants born preterm, and fewer ill child health care visits. While we will assess group differences over time

in this way, the emphasis on the analysis will be the detection of average differences between the groups, so that we may use this to estimate effect sizes for a larger study in the future. With 60 participants per group and an alpha level of .05, the power of the repeated measures mixed model F test will have at least 90% power to detect a medium effect in the context of group differences, time differences, or a group by time interaction. A medium effect is 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.[3] While an effect size driven algorithm for estimating the power associated with GEE models has not been developed, logistic regression is considered as a similar technique. With 120 participants and an alpha level of .05, the power of logistic regression to detect an odds ratio as small as 2.3 will be at least 91%. One way to attain an odds ratio of this magnitude would be if the percent of participants in each group with a particular outcome were 50% versus 30%. The power associated with the corresponding GEE model (and extension of logistic regression to the longitudinal application) is expected to be at least as large, given the additional time points included. Power estimates were obtained using nQuery Advisor, v. 6.02 (Elashoff, J. 1995-2005. nQuery Advisor, Statistical Solutions. Saugus, MA).

References

1. Curran GM, Bauer M, Mittman B, Pyne JM, Stetler C. Effectiveness-implementation hybrid designs: combining elements of clinical effectiveness and implementation research to enhance public health impact. *Med Care.* Mar 2012;50(3):217-226.
2. ACOG committee opinion. Number 316, October 2005. Smoking cessation during pregnancy. *Obstetrics And Gynecology.* 2005;106(4):883-888.
3. Cohen J. *Statistical power analysis for the behavioral sciences.* Hillsdale, N.J.: L. Erlbaum Associates; 1988.