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# BMJ Open

## Study Protocol: Validating Screening Tools for Illicit and Prescription Drug Use in Pregnancy Using Hair and Urine Sample Testing

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# 1 Study Protocol: Validating Screening Tools for Illicit and Prescription Drug Use in

## 2 Pregnancy Using Hair and Urine Sample Testing

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## 14 List of Abbreviations

15 NIDA - National Institute on Drug Abuse

16 ASSIST – Alcohol, Smoking, and Substance Involvement Screening Test

17 SURP-P - Substance Use Risk Profile-Pregnancy

18 EMR – Electronic Medical Records

19 NICU - Neonatal Intensive Care Unit

20 WHO – World Health Organization

21 HIPAA - Health Insurance Portability and Accountability Act

## Abstract for Protocol

**Introduction:** Prescription drug use in the United States (U.S.) has increased by more than 60% in the last 3 decades. Prevalence of prescription drug use among pregnant women is currently estimated around 50%. Prevalence of illicit drug use in the U.S. is 14.6% among pregnant adolescents, 8.6% among pregnant young adults, and 3.2% among pregnant adults. The first step in identifying problematic drug use during pregnancy is screening; however, no specific substance use screener has been universally recommended for use with pregnant women to identify illicit or prescription drug use. This study compares and validates three existing substance use screeners for pregnancy - 4 P's Plus, NIDA Quick Screen/ASSIST, and the Substance Use Risk Profile-Pregnancy (SURP-P) scale.

**Methods and Analysis:** This is a cross-sectional study designed to evaluate the sensitivity, specificity and usability of existing substance use screeners. Recruitment occurs at two obstetric clinics in Baltimore, Maryland (USA). We are recruiting 500 participants to complete a demographics questionnaire, NIDA Quick Screen/ASSIST, 4 P's Plus, and SURP-P (ordered randomly) during their regularly scheduled prenatal appointment, then again one week later by telephone. Participants consent to multi-drug urine testing, hair drug testing, and allowing access to prescription drug and birth outcome data from electronic medical records (EMR). For each screener, reliability and validity will be assessed. Test-retest reliability analysis will be conducted by examining the results of repeated screener administrations within one week of original screener administrations for consistency via correlation analysis. Furthermore, we will assess if there are differences in the validity of each screener by age, race, and trimester.

**Ethics and Dissemination:** This study is approved by the Institutional Review Board (IRB) of the University of Maryland (HP-00072042), Baltimore; and Battelle Memorial Institute (0619-100106433). All participants are required to give their informed consent prior to any study procedure.

**Keywords:** substance use, pregnancy, screening, biochemical verification, NIDA Quick Screen/ASSIST, SURP-P, 4P's Plus

## Strengths and limitations of this study

- We will conduct hair and urine analysis to assess for biochemically verified long-term and short-term drug use in large sample of 500 pregnant women.
- The study has the potential to provide validated comparisons of all three pregnancy drug use screeners currently acknowledged by the World Health Organization (WHO), and thus provide a universally acceptable evidence-based screener for drug use in pregnancy.
- The study utilizes electronic medical records (EMR) to capture prescribed drugs and birth outcome data of enrolled participants to assess for associations between drug use in pregnancy and adverse birth outcomes
- This study will rely on a convenience sample from two urban clinics rather than a national sample.

## 66 Introduction

67 Abuse of prescription and illicit drugs in pregnancy is a growing cause of maternal and neonatal  
68 morbidity and mortality in the United States (U.S.). According to data from the 2012 and 2013 U.S.  
69 National Survey on Drug Use and Health (NSDUH), the rate of current illicit drug use (including non-  
70 medical use of prescription drugs) in pregnant adolescents and women was 14.6% among adolescents  
71 ages 15 to 17, 8.6% among young adults (18 to 25), and 3.2% among adults (26 to 44)[1]. The  
72 consequences of this problem include spontaneous abortions, stillbirths, low birth weight, prematurity,  
73 neonatal abstinence syndrome and congenital malformations[2].

74 Given the relatively high frequency of provider-patient contact during the prenatal period, obstetric care  
75 providers have the unique opportunity to identify substance abuse in pregnancy. Furthermore, for  
76 pregnant women from socioeconomically disadvantaged groups, obstetricians often serve as primary care  
77 physicians and typically are the only contact these women have with the healthcare system[3]. Prenatal  
78 screening for drug use is an important way to identify drug abuse in pregnancy, as strongly recommended  
79 by the American Congress of Obstetricians and Gynecologists (ACOG)[4]. But, while validated alcohol  
80 and tobacco screeners have been recommended by the United States Preventive Services Task Force  
81 (USPSTF), there is currently no universally recommended validated screening tool for identifying illicit  
82 drug use in pregnancy.

83 Currently three separate, validated tools exist that screen for use of more than one substance among  
84 pregnant women: The Alcohol, Smoking, and Substance Involvement Screening Test (ASSIST); the 4 P's  
85 Plus; and the Substance Use Risk Profile – Pregnancy (SURP-P).[5-8] The ASSIST has been validated  
86 across several populations, but it has not yet been formally validated with pregnant women[5]. A  
87 modified ASSIST, with items on tobacco and alcohol use removed, was incorporated by NIDA to their  
88 Quick Screen as a follow-up to the 4-question pre-screener, this is referred to as the NIDA Quick  
89 Screen/ASSIST. The 4 P's Plus was designed to identify drug use in pregnancy and has been validated

1  
2  
3 90 with pregnant women[7]. The 4P's Plus is brief but is associated with a licensing fee which may be a  
4  
5 91 hindrance to widespread use. The SURP-P is a validated scale composed of three questions that can  
6  
7 92 differentiate between populations of pregnant women at low-risk or high-risk for substance use[8]. The  
8  
9 93 SURP-P is a simple and flexible tool for identifying possible substance use in pregnancy; however, a  
10  
11 94 further screen is required for identifying those who would require treatment.  
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13

14 95 To bridge this gap and identify the most universally valid and reliable screening tool for drug abuse in  
15  
16 96 pregnancy, this study aims to compare and validate three existing substance use screeners - 4 P's Plus,  
17  
18 97 NIDA Quick Screen/ASSIST, and the Substance Use Risk Profile-Pregnancy (SURP-P) scale - among a  
19  
20 98 cross section of 500 pregnant women presenting to two obstetrics clinics in Baltimore, Maryland (US).  
21  
22 99 The overarching goal of this effort is to determine which screening tool is most effective in identifying  
23  
24 100 prescription drug abuse and illicit drug use among pregnant women and acceptable among patients and  
25  
26 101 clinicians so that evidence-based guidance may be offered.  
27  
28  
29

## 30 102 **Methods/Design**

### 31 103 **Specific Aims**

32  
33 104 Specific Aims of this study are to: a) conduct validity analyses to determine sensitivity, specificity,  
34  
35 105 usability (test-retest reliability), and how each scale compares to the others and to the gold standard of  
36  
37 106 urine and hair drug testing in identifying prescription and illicit drug use; b) determine the impact of  
38  
39 107 clinic population variables (age, race, trimester of pregnancy) on validity of the three substance use  
40  
41 108 screeners; and c) assess birth outcomes (birth weight, gestational age, head circumference, and Neonatal  
42  
43 109 Intensive Care Unit (NICU) admissions) associated with the most widely used prescription drug and  
44  
45 110 multi-drug exposure.  
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### 51 111 **Study Design**

52  
53 112 This study is a cross-sectional study that evaluates the sensitivity, specificity and usability of existing  
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55 113 substance use screeners. We chose this study design following an extensive search of the literature, an  
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3 114 overall assessment of feasibility and consultation with stakeholders (e.g., clinicians, pregnant women and  
4  
5 115 substance use researchers). We believe that a cross-sectional study such as ours is appropriate for the  
6  
7 116 evaluation of the accuracy and reliability of these screeners. We were also aided by the knowledge that  
8  
9 117 the prevalence of substance use in pregnancy is high[1]. This implies that we are likely to obtain good  
10  
11 118 sensitivity and specificity estimates, with narrow confidence intervals, in a cross-sectional design which is  
12  
13 119 favorable in terms of cost and feasibility.

### 16 120 Setting

18 121 The study is being implemented at two urban obstetric clinics which serve diverse populations of  
19  
20 122 pregnant women. The study plans to recruit 500 participants to complete a demographics questionnaire,  
21  
22 123 followed by a randomized order of the NIDA Quick Screen/NIDA-modified ASSIST, 4 P's Plus, and  
23  
24 124 SURP-P. Participants are recruited during their regularly scheduled prenatal appointment, then contacted  
25  
26 125 again one week later by telephone to re-administer the screeners. Participants consent to multi-drug urine  
27  
28 126 testing, hair drug testing, and access to prescription drug and birth outcome data from electronic medical  
29  
30 127 records (EMR).

34 128 Recruitment Sites. We are recruiting participants from two obstetric outpatient clinics. Currently all  
35  
36 129 obstetric patients are screened for use of drugs, alcohol and tobacco at their first prenatal visit by medical  
37  
38 130 staff. Additionally, all new obstetric patients receive an in-depth evaluation by a social worker which  
39  
40 131 includes a more detailed assessment of both substance use and mental health disorder history.

43 132 In the first clinic, which is the larger of the two clinics, most patients (97%) are publicly insured with  
44  
45 133 medical assistance and are over the age of 20 (80%). This clinic's population is primarily African-  
46  
47 134 American and low-income, all of whom undergo urine toxicological screening for substance use  
48  
49 135 identification. Based on preliminary data obtained from the clinic, about 950 individual obstetric patients  
50  
51 136 are cared for at this clinic annually. In the second (smaller) clinic, approximately 500 pregnant women are  
52  
53 137 cared for annually. Most patients (87%) have commercial insurance and 13% have either medical  
54  
55 138 assistance or Medicare. Most are over the age of 20 years (90%). Due to varying insurance coverage for



1  
2  
3 139 urine toxicology screens, patients in this office do not universally undergo urine toxicology screening but  
4  
5 140 all are screened for drug use using various interview techniques by their obstetric care providers at their  
6  
7 141 first prenatal visit. Based on historical data, we expect about 500 individual obstetric patients to be cared  
8  
9 142 for in this clinic across all trimesters of pregnancy in the one year of study recruitment.

11  
12 143 Across both study sites, our source population covers a diverse set of participants and captures pregnant  
13  
14 144 women across all socioeconomic categories, insurance types, ethnicities and drug use patterns. This  
15  
16 145 ensures that our study results are generalizable to most populations of pregnant women.

### 18 19 146 Study Population

20  
21 147 In the first clinic, of the estimated 950 individual obstetric patients cared for at this clinic annually, we  
22  
23 148 anticipated approaching 403 (50%), and expected 322 (80%) or more to agree to participate in this study.

24  
25  
26 149 In the second clinic, of the approximately 500 pregnant women cared for annually, we expect at least 450  
27  
28 150 (90%) to meet eligibility criteria. We anticipate approaching 225 pregnant women (50%) and expect 180  
29  
30 151 (80%) or more to agree to participate in this study.

31  
32  
33 152 Expected participation percentages are based on a similar grant-funded study that recruited pregnant  
34  
35 153 smokers from the same population and required consent for urine testing (cotinine) and birth data  
36  
37 154 abstraction from EMR.

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39  
40 155 Participant eligibility criteria include the following: a) currently pregnant (pre-determined by clinic staff);  
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42  
43 156 b) age 18 or older; c) able to speak and understand English sufficiently to provide informed consent; and  
44  
45  
46 157 d) natural hair length at least 3 cm to allow for substance use testing.

47  
48 158 If eligibility criteria are met, research staff then obtain informed consent and medical releases for urine  
49  
50 159 collection, hair drug testing, and prescription drug and birth outcome data abstraction from the EMR.

## 160 Ethical Approval

161 This study is approved by the Institutional Review Boards (IRB) of the University of Maryland,  
162 Baltimore; and Battelle Memorial Institute. All participants are required to give their informed consent  
163 prior to any study procedure. All research staff complete ethics training annually.

## 164 Study Procedures

### 165 *Approach*

166 All patients entering the clinics for prenatal appointments are approached by research staff at check-in  
167 and asked to read a brief description of the study to determine their interest in participating (excluding  
168 those previously approached). Research staff keep track of which patients have been approached already  
169 to avoid repetitive recruitment efforts. The study description includes a section requesting basic  
170 demographic information (if they would allow its use for anonymous, grouped analysis) and at the bottom  
171 asks potential participants to note their interest and return to clinic staff. There are checkboxes for “not  
172 interested” (with additional space beneath for noting reasons for lack of interest) and “interested in  
173 learning more.” Patients who are not interested in the study are not to be contacted further; however, the  
174 basic demographic information provided is used for comparative analyses with study participants to  
175 assess for selection bias. If a patient expresses interest, the research staff approaches her as she waits for  
176 her prenatal appointment either on the same day or at a future prenatal appointment.

### 177 *Recruitment*

178 At the enrollment visit, the staff escorts potential participants from the waiting area to a private room,  
179 further describes the study and determines whether potential participants meet all eligibility criteria. If  
180 eligibility criteria are met, the staff obtains informed consent and HIPAA (Health Insurance Portability  
181 and Accountability Act) authorization (for urine collection, hair drug testing, and prescription drug and  
182 birth outcome data abstraction from the EMR). Women who refuse to participate are thanked for their  
183 time and no further contact is made. The research visit takes 20-30 minutes. Enrolled participants are  
184 compensated for their time using a reloadable gift card for their time. The typical patient wait time to see

185 medical staff at each clinic is 30 minutes to 1 hour, so data collection does not typically interfere with  
 186 medical visits. See Figure 1 for study procedures.

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### 189 *Self-Report Measures*

190 Participants complete a demographics questionnaire. Afterwards, the NIDA Quick Screen/NIDA-  
 191 modified Alcohol, Smoking, and Substance Involvement Screening Test (ASSIST), 4 P's Plus, and  
 192 Substance Use Risk Profile-Pregnancy (SURP-P) surveys are administered on a Wi-Fi enabled iPad Pro  
 193 through SurveyMonkey (i.e., online survey software). These surveys are assigned to participants in a  
 194 random sequence; this randomization service is provided by SurveyMonkey. The questions are read aloud  
 195 by the interviewer and entered directly into SurveyMonkey so that electronic submission is instantaneous  
 196 and data can be obtained by the research team at any time.

197 Table 1: Study Instruments

Instrument	Description/Construct	Use in Study
Demographic Questionnaire	20-item questionnaire that collects demographic and general information such as age, marital status, education, employment status, ethnicity and reproductive history	Enrollment
NIDA Quick Screen/ ASSIST	9-item combined NIDA Quick Screen and modified-ASSIST to screen for tobacco, alcohol and illicit drugs	Enrollment, 1-week follow up
4P's Plus	4-item screener for alcohol and general substance use	Enrollment, 1-week follow up
SURP-P	3-item screener for alcohol and substances	Enrollment, 1-week follow up

198

199 *Biochemical Measures*

200 Participants are asked to consent that urine collected for their prenatal appointment that day is  
 201 also tested for various drugs by research staff (Table 2). If sufficient urine is unavailable for testing,  
 202 participants are given bottled water and asked to provide another sample prior to leaving the clinic.  
 203 Participants must also consent to hair testing, which involves the cutting of approximately 100 strands of  
 204 hair from the crown of the head (or other body hair if head hair is unavailable). Samples are then shipped  
 205 to an external laboratory same-day for drug testing utilizing mass spectrometry.

206 Table 2: Drug detection windows and cutoffs for urine and hair testing

	Drug class	Detection	Confirmation
<b>U</b>	Cocaine COC	2-4 Days	300 ng/mL
	Marijuana THC	15-30 Days	50 ng/mL
	Opiates OPI	2-4 Days	2000 ng/mL
<b>R</b>	Amphetamines AMP	2-4 Days	1000 ng/mL
	Methamphetamines AMP	3-5 Days	1000 ng/mL
<b>I</b>	Phencyclidine PCP	7-14 Days	25 ng/mL
	Benzodiazepines BZO	3-7 Days	300 ng/mL
	Barbiturates BAR	4-7 Days	300 ng/mL
<b>N</b>	Methadone MTD	3-5 Days	300 ng/mL
	Tricyclic Antidepressants TCA		1,000 ng/mL
<b>E</b>	Oxycodone	2-4 Days	100 ng/mL
	Propoxyphene	1-2 Days	300 ng/mL
	Buprenorphine BUP (Suboxone, Subutex)	2-3 Days	10 ng/mL
<b>H A I R</b>	Marijuana THC	Up to 90 days	
	Amphetamines AMP	Up to 90 days	
	Cocaine COC	Up to 90 days	
	Opiates OPI	Up to 90 days	
	Phencyclidine PCP	Up to 90 days	

207  
 208 All women who screen positive on either biological multi-drug test or any one of the screeners  
 209 are contacted immediately (for urine and screener results) or within 72 hours (for hair results) to detail the  
 210 results of her test, encourage the participant to talk with her physician about her substance use, and offer  
 211 her referrals to community resources for treatment that mirror what is currently given to patients by

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3 212 medical staff in each clinic. They are encouraged to speak with the on-site clinic social worker who can  
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5 213 provide further support.  
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#### 8 214 *Birth Outcome Measures*

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10 215 Birth outcome data, including miscarriage, stillbirth, birth weight, gestational age, head circumference,  
11  
12 216 and NICU admissions, as well as a list of drugs prescribed during pregnancy and their dosage are  
13  
14 217 collected by research staff via the EMR and entered into SurveyMonkey.  
15  
16

#### 17 218 *Participant Follow-Up*

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19 219 After completion of this research visit, participants are contacted once more by telephone one week after  
20  
21 220 completing the surveys to complete the three screeners again to assess test-retest reliability. The average  
22  
23 221 time commitment for the call is about 10-15 minutes, and upon completion \$25 is loaded onto the  
24  
25 222 reloadable gift card provided the week prior.  
26  
27

#### 28 223 *Pilot Study*

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30 224 To examine the recruitment process and determine acceptability from the target population of substance-  
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32 225 using pregnant women prior to the start of the study, we conducted a one-month pilot study. Each step of  
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34 226 the recruitment process was reviewed to determine where improvements could be made.  
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36

37 227 We recruited 21 participants from each site for a total of 42 participants (Table 3). Mean age (sd)  
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39 228 of participants was 30.1 years (5.64). By race, 11 participants (26.2%) were White, 25 (59.5%) were  
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41 229 Black/African American, 4 (9.5%) were Asian, 1 (2.4%) was Hispanic and 1 (2.4%) was Other. About  
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43 230 24.4% tested positive for illicit drugs on urine testing, 22% tested positive on hair sample testing. Seven  
44  
45 231 (7) participants (16.7%) were lost to follow up.  
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236 *Table 3 Pilot Study Participant Characteristics*

Characteristics, N = 42	Clinical Site		
	<i>Clinic 1</i>	<i>Clinic 2</i>	<i>Both Sites</i>
<b>Number of participants</b>	21	21	42
<b>Participant age in years, mean (SD)</b>	27.10 (5.09)	33.05 (4.54)	30.07 (5.64)
<b>Ethnicity n (%)</b>			
African American/Black	18 (85.7)	7 (33.3)	25 (59.5)
Asian	0 (0.0)	4 (19.0)	4 (9.5)
Caucasian/White	2 (9.5)	9 (42.9)	11 (26.2)
Hispanic, Latino or Chicano	0 (0.0)	1 (4.8)	1 (2.4)
Some other group	1 (4.8)	0 (0.0)	1 (2.4)
<b>Trimester n (%)</b>			
1 <sup>st</sup>	2 (9.5)	2 (9.5)	4 (9.5)
2 <sup>nd</sup>	6 (28.6)	6 (28.6)	12 (28.6)
3 <sup>rd</sup>	13 (61.9)	13 (61.9)	26 (61.9)
<b>Urine Results n (%)</b>			
Negative for all substances	15 (71.4)	16 (80.0)	31 (75.6)
Positive for at least 1 substance	6 (28.6)	4 (20.0)	10 (24.4)
<b>Hair Results n (%)</b>			
Negative for all substances	12 (60.0)	18 (85.7)	30 (73.2)
Positive for at least one substance	7 (35.0)	2 (9.5)	9 (22.0)
Invalid	1 (5.0)	1 (4.8)	2 (4.9)
<b>Study Disposition n (%)</b>			
Study completes	19 (90.48)	16 (76.2)	35 (83.3)

Lost to follow-up	2 (9.52)	5 (23.8)	7 (16.7)
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237

238 Results from the pilot study confirmed the feasibility of this study. Eligibility criteria did not  
 239 appear too restrictive, given the eligibility rate of 78% (although slightly lower than anticipated) (Figure  
 240 2). Overall, there was good comprehension of surveys, a low refusal rate for hair sampling (1 refusal/95  
 241 approached, 1.1%), and high study enrollment (Figure 2). The recruitment process took an average of 40  
 242 minutes.

### 243 *Power and Sample Size*

244 The sample size of 500 participants was chosen based on power analyses for the primary study questions.  
 245 Based on a one-sample binomial approach, with a sample size of 500 participants, we can be 95%  
 246 confident that the false negative rate in the population is under 10% (assuming no more than 35  
 247 individuals test positive in the biologic drug tests without a positive survey screener result). Similarly, we  
 248 can be 95% confident that the false negative rate in the population is under 5% (assuming no more than  
 249 15 individuals test positive in the urine drug test without a positive survey screen result in the study).  
 250 According to McNemar's Test, if at least 15% of the study participants have disagreement between any  
 251 pair of survey results, 500 is a sufficient sample size to determine significant disagreement.

252 After a preliminary sample size of 500 was chosen, a power analysis was conducted to determine the  
 253 detectable differences in age, race, and trimester with a sample size of 500. The power of the test of  
 254 proportions was calculated based on the difference in the proportion of false negatives in each age group,  
 255 race, and trimester of pregnancy. Assuming recruitment of an equal number of women aged 18 to 25  
 256 years and women 26 and older, and that their respective positive screener results are 20% and 10%, then  
 257 the power to detect that difference is 0.88. If the respective screener results are 15% and 20%, then the  
 258 power is much lower (0.31). If we further assume that recruitment of 23% White women and 77% non-  
 259 White women and that white women have a false negative rate of 5% and non-White women have a false  
 260 negative rate of 15%, then the power is high (0.87). Similarly, if we assume recruitment of an equal

1  
2  
3 261 number of women in each of the three trimesters of pregnancy and that women in one trimester have a  
4  
5 262 false negative rate of 20% while women in another trimester have a false negative rate of 35%, then the  
6  
7 263 power is high (0.87).  
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## 10 264 [Analysis](#)

11  
12 265 For each screener, reliability and validity (convergent/discriminant validity) will be assessed, including  
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14 266 calculating correlation coefficients between each pair of screeners and between each screener and the  
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16 267 appropriate biologic drug tests. Test-retest reliability analysis will be conducted by examining the results  
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18 268 of repeated screener administrations within one week of original screener administrations for consistency  
19  
20 269 via correlation analysis. The sensitivity and specificity of each instrument will be calculated, presented,  
21  
22 270 and interpreted. Each survey instrument will be compared to the gold standard (hair and urine sample  
23  
24 271 drug testing) by comparing the false negative rates to a predetermined limit of acceptability. If the upper  
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26 272 one-sided 95% binomial confidence interval around the false negative rate in the sample is less than that  
27  
28 273 limit, then the survey instrument is considered acceptable. The 4P's Plus and SURP-P survey screeners  
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30 274 will be compared to both urine and hair testing in the assessment of their sensitivity and specificity in  
31  
32 275 relation to short and long-term drug use, respectively. The NIDA Quick Screen/NIDA-Modified ASSIST  
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34 276 screener will be compared to urine testing, while particular questions from the screener regarding long-  
35  
36 277 term drug use will be compared to hair testing.  
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40 278 Furthermore, we will assess if there are differences in the validity of each screener by age, race, and  
41  
42 279 trimester. The false negative rate for each screener will be presented by age, race, and trimester. A two-  
43  
44 280 sided test of proportions will be conducted to test for significant differences in false negative rates  
45  
46 281 between age, race, and trimester for each screener. Chi-square tests (or Fisher's exact tests if subgroup  
47  
48 282 sizes are small) may be conducted to determine whether the distribution of responses on each survey  
49  
50 283 instrument is similar for age, race, and trimester. To examine differences in screener validity by age, race,  
51  
52 284 and trimester, logistic regression models will be fitted to the data. To separately analyze differences in  
53  
54 285 probability of false positive results and false negative results on each survey, data will be stratified by  
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3 286 screener and screener result (positive or negative) for a total of six models. In each model, the dependent  
4  
5 287 variable will be coded 1 for invalid screener result (false negative or false positive) and 0 for valid  
6  
7 288 screener result (true negative or true positive). Independent variables for age, race, and trimester will be  
8  
9 289 added to the models to test whether they have a significant effect on the probability of an invalid screener  
10  
11 290 result. Two-way interaction terms will be included in the model if they are found to be significant effects.  
12  
13 291 In order to stratify results by trimester, if trimester or any two-way interaction term including trimester is  
14  
15 292 a significant effect in the models for any of the screeners, probabilities of false positive/ false negative  
16  
17 293 result will be presented separately by each trimester.  
18  
19  
20  
21 294 Finally, the prevalence of prescription and illicit drug use will be calculated based on hair test results and  
22  
23 295 self-report. Prevalence of multi-drug exposure will also be calculated. An ANOVA model will be fitted to  
24  
25 296 the data with a fixed effect for drug use (negative, positive, positive for multi-drug exposure) to test for  
26  
27 297 significant differences in birthweight, gestational age, and head circumference based on participant hair  
28  
29 298 drug tests result. Significant differences will be noted and discussed. The relative risk of NICU  
30  
31 299 admission, stillbirth, and miscarriage will be examined. A risk ratio will be calculated and will quantify  
32  
33 300 the percentage difference in these three variables between those with positive hair drug tests versus  
34  
35 301 negative drug test. The risk ratio takes on values between zero and infinity. A risk ratio of one means that  
36  
37 302 there is no difference in NICU admissions, stillbirth, or miscarriage between the participants' biologic  
38  
39 303 drug tests results. A risk ratio very small (close to zero) or very large means a large difference between  
40  
41 304 NICU admissions, stillbirth, or miscarriage based on the hair drug tests results. Approximate 95%  
42  
43 305 confidence intervals for the relative risk will be calculated. The same relative risk ratios and 95%  
44  
45 306 confidence intervals will be calculated for a positive biologic drug tests for multi-drug exposure versus  
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47 307 positive for a single-drug exposure. Further, relative risk ratios will be computed with 95% confidence  
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49 308 intervals stratified by trimester.  
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## 309 Discussion

310 Our ongoing research has five aspects of significance. First, the importance of screening pregnant women  
311 and the public health impact of the current research is tied directly to the negative health consequences  
312 associated with illicit and prescription drug use during pregnancy. Second, it utilizes both urine and hair  
313 testing to enable us to examine past 90-day substance use history with precision. Hair analysis provides  
314 nearly twice the number of positives due to its longer detection window, but often cannot capture very  
315 recent use. Urine analysis supplements hair analysis to allow for the most comprehensive validation of  
316 screeners possible. Third, the study compares all three screeners acknowledged by the World Health  
317 Organization (WHO) to screen for multiple substances to each other and to the biological screeners (gold  
318 standard). This is the first study to conduct a direct, head-to-head comparison of multiple screening tools  
319 for prescription and illicit drug use among pregnant women, while also utilizing biologic measures as a  
320 gold standard against which to compare. Fourth, the study utilizes electronic medical records (EMR) to  
321 capture prescribed drugs and birth outcome data of enrolled participants. The ability to access a  
322 participant's prescription drug orders enables better tracking and distinction between prescription drug  
323 use and abuse, while birth outcome data allows for determination of associations between specific drug  
324 use and birth outcomes. Fifth, the study has the potential to shift clinical practice towards universal  
325 standardized substance use screening.

326 The primary innovation of this project is that it may provide a final evidence-based  
327 recommendation for the tool(s) best suited for screening for illicit and prescription drugs among a diverse  
328 sample of pregnant women. The provision of this evidence-based guidance to clinicians is a concrete  
329 application of findings that is rare in public health research.

330 Substance use during pregnancy, and specifically prescription and illicit drug use, are high  
331 priority topics for the Centers for Disease Control and Prevention (CDC), WHO, The American Congress  
332 of Obstetricians and Gynecologists (ACOG), Substance Abuse and Mental Health Services

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3 333 Administration (SAMHSA), National Institute on Drug Abuse (NIDA), and the National Institutes of  
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5 334 Health (NIH). Universal screening has the potential to greatly enhance maternal and infant health  
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7 335 outcomes and reduce healthcare costs. Specifically, the current research supports the following Healthy  
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9 336 People 2020 public health goals and objectives which include reducing maternal illness and complications  
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11 337 due to pregnancy; increasing the proportion of pregnant women who receive adequate prenatal care;  
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13 338 increasing abstinence from alcohol, cigarettes, and illicit drugs among pregnant women; and increasing  
14  
15 339 the proportion of women delivering a live birth who received preconception care services and practiced  
16  
17 340 key recommended preconception health behaviors.

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21 341 This research addresses an important problem by identifying a valid substance use screening  
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23 342 instrument for illicit and prescription drugs among pregnant women that is accurate, brief, and acceptable  
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25 343 to both patients and health care providers in a primary care setting. Identifying and validating one  
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27 344 instrument that functions the closest to the “gold standard” of biologic testing (i.e., urine and hair) and  
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29 345 disseminating this information widely will increase the likelihood that primary care clinics nationwide  
30  
31 346 may adopt a quick and easy screener universally. We may find that one instrument does not stand out but  
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33 347 that each has its distinct advantages and disadvantages; in this case, the performance of each measure will  
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35 348 be detailed with recommendations for which screener may work the best with a given population.

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14 363 **Declarations**15 364 *Ethics approval and consent to participate*

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17 365 This study is approved by the Institutional Review Boards (IRB) of the University of Maryland (HP-  
18 366 00072042), Baltimore; and Battelle Memorial Institute (0619-100106433). All participants are required to  
19 367 give their informed consent prior to any study procedure.

20  
21 368 *Availability of data and materials*

22  
23 369 The data that support the findings of this study are available on request from the corresponding author  
24 370 [VHCC]. The data are not publicly available due to them containing information that could compromise  
25 371 research participant privacy/consent.

26  
27 372 *Competing interests*

28  
29 373 The authors declare that there are no competing interests.

30  
31 374 *Authors' contributions*

32  
33 375 VCC conceived the study. VCC, EO, EP, KT, BK and KM participated in the drafting of the manuscript and  
34 376 each approved the final draft

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42 380 The content is solely the responsibility of the authors and does not represent the official views of the

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44 381 National Institutes of Health.

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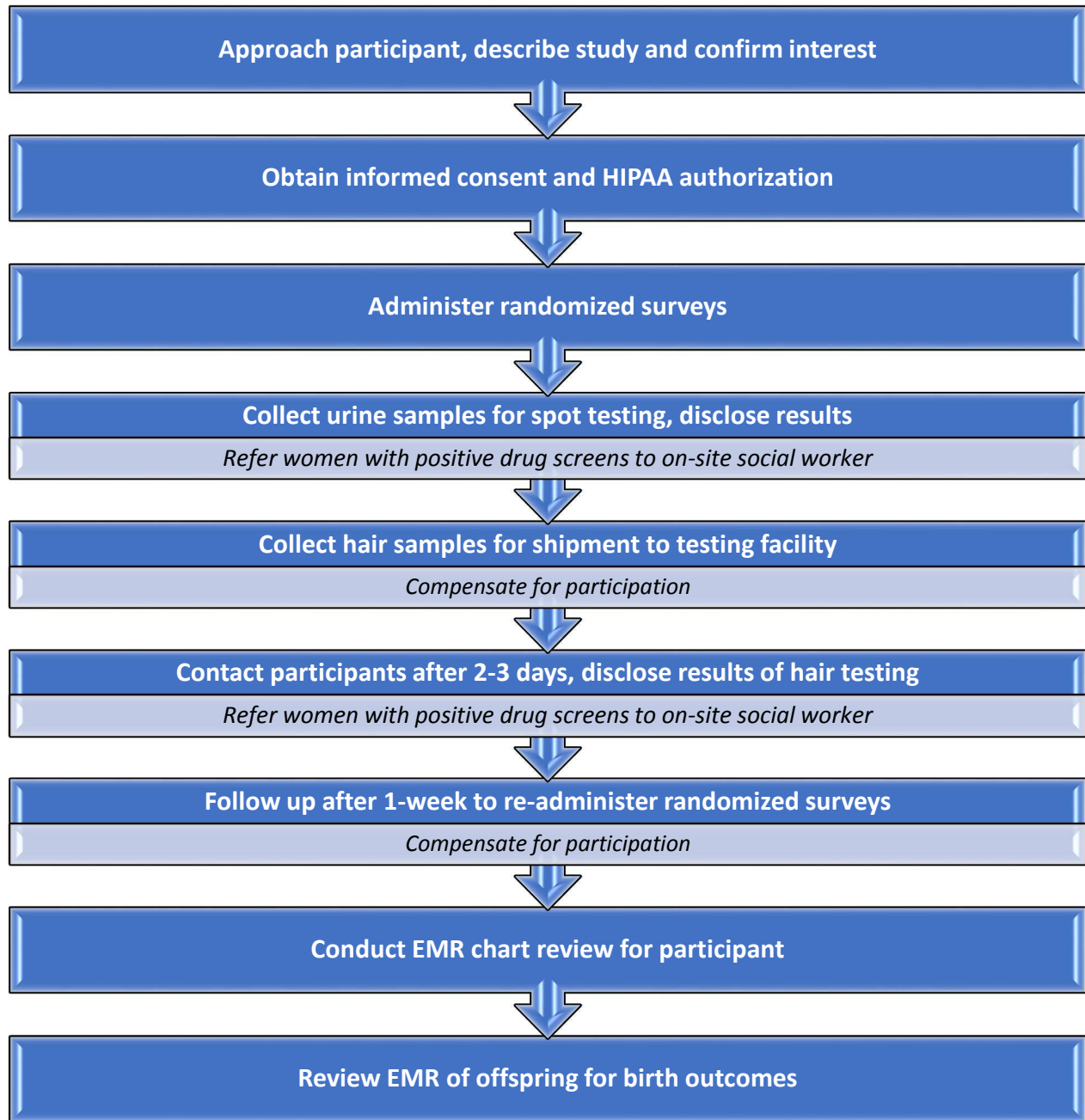
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1 **FIGURE 1: Study procedures**

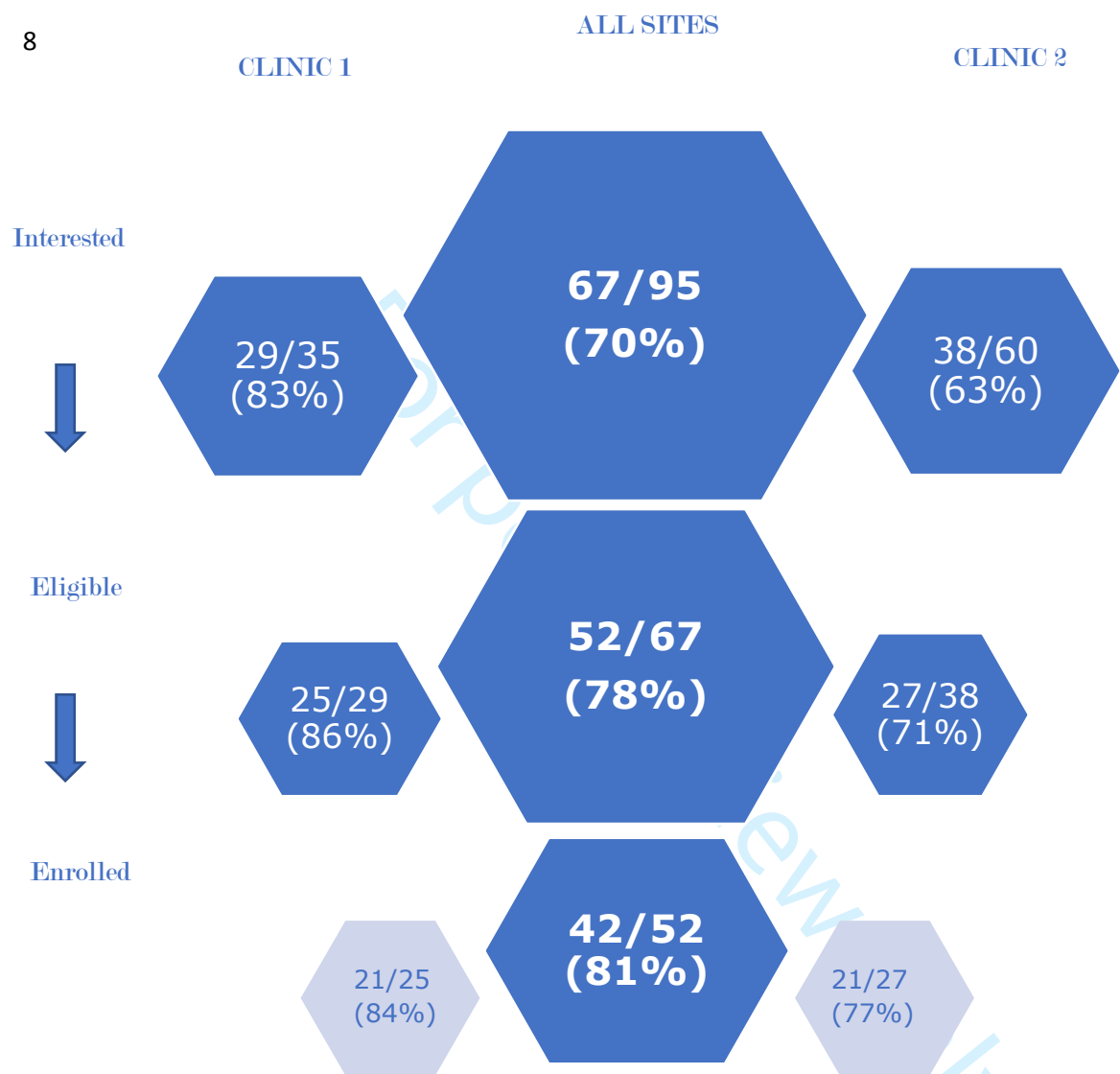


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3 **Figure 1: Study procedures**

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6 **FIGURE 2: Pilot study participation**



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10 **Figure 2: Pilot study participation**

# BMJ Open

## Comparison and Validation of Screening Tools for Substance Use in Pregnancy: A Cross-Sectional Study conducted in Maryland Prenatal Clinics

Journal:	<i>BMJ Open</i>
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<b>Primary Subject Heading</b>:	Public health
Secondary Subject Heading:	Addiction, Public health
Keywords:	pregnancy, biochemical verification, NIDA Quick Screen/ASSIST, SURP-P, 4P's Plus, substance use screening

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# 1 Comparison and Validation of Screening Tools for Substance Use in Pregnancy: A

## 2 Cross-Sectional Study conducted in Maryland Prenatal Clinics

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## 14 List of Abbreviations

15 NIDA - National Institute on Drug Abuse

16 ASSIST – Alcohol, Smoking, and Substance Involvement Screening Test

17 SURP-P - Substance Use Risk Profile-Pregnancy

18 EMR – Electronic Medical Records

19 NICU - Neonatal Intensive Care Unit

20 WHO – World Health Organization

21 HIPAA - Health Insurance Portability and Accountability Act

## 22 Abstract for Protocol

23 **Introduction:** Prescription drug use in the United States (U.S.) has increased by more than 60% in the  
24 last 3 decades. Prevalence of prescription drug use among pregnant women is currently estimated around  
25 50%. Prevalence of illicit drug use in the U.S. is 14.6% among pregnant adolescents, 8.6% among  
26 pregnant young adults, and 3.2% among pregnant adults. The first step in identifying problematic drug  
27 use during pregnancy is screening; however, no specific substance use screener has been universally  
28 recommended for use with pregnant women to identify illicit or prescription drug use. This study  
29 compares and validates three existing substance use screeners for pregnancy - 4 P's Plus, NIDA Quick  
30 Screen/ASSIST, and the Substance Use Risk Profile-Pregnancy (SURP-P) scale.

31 **Methods and Analysis:** This is a cross-sectional study designed to evaluate the sensitivity, specificity  
32 and usability of existing substance use screeners. Recruitment occurs at two obstetric clinics in Baltimore,  
33 Maryland (USA). We are recruiting 500 participants to complete a demographics questionnaire, NIDA  
34 Quick Screen/ASSIST, 4 P's Plus, and SURP-P (ordered randomly) during their regularly scheduled  
35 prenatal appointment, then again one week later by telephone. Participants consent to multi-drug urine  
36 testing, hair drug testing, and allowing access to prescription drug and birth outcome data from electronic  
37 medical records (EMR). For each screener, reliability and validity will be assessed. Test-retest reliability  
38 analysis will be conducted by examining the results of repeated screener administrations within one week  
39 of original screener administrations for consistency via correlation analysis. Furthermore, we will assess  
40 if there are differences in the validity of each screener by age, race, and trimester.

41 **Ethics and Dissemination:** This study is approved by the Institutional Review Board (IRB) of the  
42 University of Maryland (HP-00072042), Baltimore; and Battelle Memorial Institute (0619-100106433).  
43 All participants are required to give their informed consent prior to any study procedure.

44 **Keywords:** substance use, pregnancy, screening, biochemical verification, NIDA Quick Screen/ASSIST,  
45 SURP-P, 4P's Plus

## Strengths and limitations of this study

- This study will provide insight into the substance use screener(s) that works best to identify illicit drug use and prescription drug misuse during pregnancy, utilizing hair and urine analysis for biochemical verification of long-term and short-term substance use in a convenience sample of 500 pregnant women.
- The study will provide evidence of screener usefulness and acceptability in prenatal clinic settings that could inform United States Preventive Services Task Force (USPSTF) recommendations for substance use screening during pregnancy.
- The study utilizes electronic medical records (EMR) to capture prescribed drugs and birth outcome data of enrolled participants to assess for associations between substance use in pregnancy and adverse birth outcomes.
- A limitation of this study is the reliance on a convenience sample from two urban clinics rather than a national sample.
- Findings from this study will not be generalizable to pregnant adolescents who were not included in our study sample.

## 67 Introduction

68 Abuse of prescription and illicit drugs in pregnancy is a growing cause of maternal and neonatal  
69 morbidity and mortality in the United States (U.S.). According to data from the 2012 and 2013 U.S.  
70 National Survey on Drug Use and Health (NSDUH), the rate of current illicit drug use (including non-  
71 medical use of prescription drugs) in pregnant adolescents and women was 14.6% among adolescents  
72 ages 15 to 17, 8.6% among young adults (18 to 25), and 3.2% among adults (26 to 44)<sup>1</sup>. The  
73 consequences of this problem include spontaneous abortions, stillbirths, low birth weight, prematurity,  
74 neonatal abstinence syndrome and congenital malformations<sup>2</sup>.

75 Given the relatively high frequency of provider-patient contact during the prenatal period, obstetric care  
76 providers have the unique opportunity to identify substance abuse in pregnancy. Furthermore, for  
77 pregnant women from socioeconomically disadvantaged groups, obstetricians often serve as primary care  
78 physicians and typically are the only contact these women have with the healthcare system<sup>3</sup>. Prenatal  
79 screening for drug use is an important way to identify drug abuse in pregnancy, as strongly recommended  
80 by the American Congress of Obstetricians and Gynecologists (ACOG)<sup>4</sup>. But, while validated alcohol and  
81 tobacco screeners have been recommended by the United States Preventive Services Task Force  
82 (USPSTF), there is currently no universally recommended validated screening tool for identifying illicit  
83 drug use in pregnancy.

84 Currently three separate, validated tools exist that screen for use of more than one substance among  
85 pregnant women: The Alcohol, Smoking, and Substance Involvement Screening Test (ASSIST); the 4 P's  
86 Plus; and the Substance Use Risk Profile – Pregnancy (SURP-P).<sup>5-8</sup> The ASSIST has been validated  
87 across several populations, but it has not yet been formally validated with pregnant women<sup>5</sup>. A modified  
88 ASSIST, with items on tobacco and alcohol use removed, was incorporated by NIDA to their Quick  
89 Screen as a follow-up to the 4-question pre-screener, this is referred to as the NIDA Quick  
90 Screen/ASSIST. The 4 P's Plus was designed to identify drug use in pregnancy and has been validated

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3 91 with pregnant women<sup>7</sup>. The 4P's Plus is brief but is associated with a licensing fee which may be a  
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5 92 hindrance to widespread use. The SURP-P is a validated scale composed of three questions that can  
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7 93 differentiate between populations of pregnant women at low-risk or high-risk for substance use<sup>8</sup>. The  
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9 94 SURP-P is a simple and flexible tool for identifying possible substance use in pregnancy; however, a  
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11 95 further screen is required for identifying those who would require treatment.  
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14 96 To bridge this gap and identify the most universally valid and reliable screening tool for drug abuse in  
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16 97 pregnancy, this study aims to compare and validate three existing substance use screeners - 4 P's Plus,  
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18 98 NIDA Quick Screen/ASSIST, and the Substance Use Risk Profile-Pregnancy (SURP-P) scale - among a  
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20 99 cross section of 500 pregnant women presenting to two obstetrics clinics in Baltimore, Maryland (US).  
21  
22 100 The overarching goal of this effort is to determine which screening tool is most effective in identifying  
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24 101 prescription drug abuse and illicit drug use among pregnant women and acceptable among patients and  
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26 102 clinicians so that evidence-based guidance may be offered.  
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## 30 103 **Methods/Design**

### 31 32 33 104 **Specific Aims**

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35 105 Specific Aims of this study are to: a) conduct validity analyses to determine sensitivity, specificity,  
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37 106 usability (test-retest reliability), and how each scale compares to the others and to the gold standard of  
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39 107 urine and hair drug testing in identifying prescription and illicit drug use; b) determine the impact of  
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41 108 clinic population variables (age, race, trimester of pregnancy) on validity of the three substance use  
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43 109 screeners; and c) assess birth outcomes (birth weight, gestational age, head circumference, and Neonatal  
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45 110 Intensive Care Unit (NICU) admissions) associated with the most widely used prescription drug and  
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47 111 multi-drug exposure.  
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### 51 112 **Study Design**

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53 113 This study is a cross-sectional study that evaluates the sensitivity, specificity and usability of existing  
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55 114 substance use screeners. We chose this study design following an extensive search of the literature, an  
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3 115 overall assessment of feasibility and consultation with stakeholders (e.g., clinicians, pregnant women and  
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5 116 substance use researchers). We believe that a cross-sectional study such as ours is appropriate for the  
6  
7 117 evaluation of the accuracy and reliability of these screeners. We were also aided by the knowledge that  
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9 118 the prevalence of substance use in pregnancy is high<sup>1</sup>. This implies that we are likely to obtain good  
10  
11 119 sensitivity and specificity estimates, with narrow confidence intervals, in a cross-sectional design which is  
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13 120 favorable in terms of cost and feasibility.

### 16 121 **Setting**

18 122 The study is being implemented at two urban obstetric clinics which serve diverse populations of  
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20 123 pregnant women. The study plans to recruit 500 participants to complete a demographics questionnaire,  
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22 124 followed by a randomized order of the NIDA Quick Screen/NIDA-modified ASSIST, 4 P's Plus, and  
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24 125 SURP-P. Participants are recruited during their regularly scheduled prenatal appointment, then contacted  
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26 126 again one week later by telephone to re-administer the screeners. Participants consent to multi-drug urine  
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28 127 testing, hair drug testing, and access to prescription drug and birth outcome data from electronic medical  
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30 128 records (EMR).

34 129 Recruitment Sites. We are recruiting participants from two obstetric outpatient clinics from January 2017-  
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36 130 January 2018. Currently all obstetric patients are screened for use of drugs, alcohol and tobacco at their  
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38 131 first prenatal visit by medical staff. Additionally, all new obstetric patients receive an in-depth evaluation  
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40 132 by a social worker which includes a more detailed assessment of both substance use and mental health  
41  
42 133 disorder history.

45 134 In the first clinic, which is the larger of the two clinics, most patients (97%) are publicly insured with  
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47 135 medical assistance and are over the age of 20 (80%). This clinic's population is primarily African-  
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49 136 American and low-income, all of whom undergo urine toxicological screening for substance use  
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51 137 identification. Based on preliminary data obtained from the clinic, about 950 individual obstetric patients  
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53 138 are cared for at this clinic annually. In the second (smaller) clinic, approximately 500 pregnant women are  
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55 139 cared for annually. Most patients (87%) have commercial insurance and 13% have either medical

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3 140 assistance or Medicare. Most are over the age of 20 years (90%). Due to varying insurance coverage for  
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5 141 urine toxicology screens, patients in this office do not universally undergo urine toxicology screening but  
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7 142 all are screened for drug use using various interview techniques by their obstetric care providers at their  
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9 143 first prenatal visit. Based on historical data, we expect about 500 individual obstetric patients to be cared  
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11 144 for in this clinic across all trimesters of pregnancy in the one year of study recruitment.

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14 145 Across both study sites, our source population covers a diverse set of participants and captures pregnant  
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16 146 women across all socioeconomic categories, insurance types, ethnicities and drug use patterns. This  
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18 147 ensures that our study results are generalizable to most populations of pregnant women.

### 21 148 **Study Population**

22  
23 149 In the first clinic, of the estimated 950 individual obstetric patients cared for at this clinic annually, we  
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25 150 anticipated approaching 403 (50%), and expected 322 (80%) or more to agree to participate in this study.

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28 151 In the second clinic, of the approximately 500 pregnant women cared for annually, we expect at least 450  
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30 152 (90%) to meet eligibility criteria. We anticipate approaching 225 pregnant women (50%) and expect 180  
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32 153 (80%) or more to agree to participate in this study.

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35 154 Expected participation percentages are based on a similar grant-funded study that recruited pregnant  
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37 155 smokers from the same population and required consent for urine testing (cotinine) and birth data  
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39 156 abstraction from EMR.

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42 157 Participant eligibility criteria include the following: a) currently pregnant (pre-determined by clinic staff);  
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45 158 b) age 18 or older; c) able to speak and understand English sufficiently to provide informed consent; and  
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48 159 d) natural hair length at least 3 cm to allow for substance use testing.

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51 160 If eligibility criteria are met, research staff then obtain informed consent and medical releases for urine  
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53 161 collection, hair drug testing, and prescription drug and birth outcome data abstraction from the EMR.

## 162 Ethics and Dissemination

163 This study is approved by the Institutional Review Boards (IRB) of the University of Maryland,  
164 Baltimore (HP-00072042); and Battelle Memorial Institute (0619-100106433). All participants are  
165 required to give their informed consent prior to any study procedure. All research staff complete ethics  
166 training via the Collaborative Institutional Training Initiative (CITI) annually.

## 167 Study Procedures

### 168 *Approach*

169 All patients entering the clinics for prenatal appointments are approached by research staff at check-in  
170 and asked to read a brief description of the study to determine their interest in participating (excluding  
171 those previously approached). Research staff keep track of which patients have been approached already  
172 to avoid repetitive recruitment efforts. The study description includes a section requesting basic  
173 demographic information (if they would allow its use for anonymous, grouped analysis) and at the bottom  
174 asks potential participants to note their interest and return to clinic staff. There are checkboxes for “not  
175 interested” (with additional space beneath for noting reasons for lack of interest) and “interested in  
176 learning more.” Patients who are not interested in the study are not to be contacted further; however, the  
177 basic demographic information provided is used for comparative analyses with study participants to  
178 assess for selection bias. If a patient expresses interest, the research staff approaches her as she waits for  
179 her prenatal appointment either on the same day or at a future prenatal appointment.

### 180 *Recruitment*

181 At the enrollment visit, the staff escorts potential participants from the waiting area to a private room,  
182 further describes the study and determines whether potential participants meet all eligibility criteria. If  
183 eligibility criteria are met, the staff obtains informed consent and HIPAA (Health Insurance Portability  
184 and Accountability Act) authorization (for urine collection, hair drug testing, and prescription drug and  
185 birth outcome data abstraction from the EMR). Women who refuse to participate are thanked for their  
186 time and no further contact is made. The research visit takes 20-30 minutes. Enrolled participants are



187 compensated for their time using a reloadable gift card for their time. The typical patient wait time to see  
 188 medical staff at each clinic is 30 minutes to 1 hour, so data collection does not typically interfere with  
 189 medical visits. See Figure 1 for study procedures.

### 190 *Self-Report Measures*

191 Participants complete a demographics questionnaire. Afterwards, the NIDA Quick Screen/NIDA-  
 192 modified Alcohol, Smoking, and Substance Involvement Screening Test (ASSIST), 4 P's Plus, and  
 193 Substance Use Risk Profile-Pregnancy (SURP-P) surveys are administered on a Wi-Fi enabled iPad Pro  
 194 through SurveyMonkey (i.e., online survey software) See Table 1 for description of surveys and the  
 195 timing of administration during the study. These surveys are assigned to participants in a random  
 196 sequence; this randomization service is provided by SurveyMonkey. The questions are read aloud by the  
 197 interviewer and entered directly into SurveyMonkey so that electronic submission is instantaneous, and  
 198 data can be obtained by the research team at any time.

199 Table 1: Study Instruments

Instrument	Description/Construct	Use in Study
Demographic Questionnaire	20-item questionnaire that collects demographic and general information such as age, marital status, education, employment status, ethnicity and reproductive history	Enrollment
NIDA Quick Screen/ ASSIST	9-item combined NIDA Quick Screen and modified-ASSIST to screen for tobacco, alcohol and illicit drugs	Enrollment, 1-week follow up
4P's Plus	4-item screener for alcohol and general substance use	Enrollment, 1-week follow up
SURP-P	3-item screener for alcohol and substances	Enrollment, 1-week follow up

200

201 *Biochemical Measures*

202 Participants are asked to consent that urine collected for their prenatal appointment that day is  
 203 also tested for various drugs by research staff (Table 2). If sufficient urine is unavailable for testing,  
 204 participants are given bottled water and asked to provide another sample prior to leaving the clinic.  
 205 Participants must also consent to hair testing, which involves the cutting of approximately 100 strands of  
 206 hair from the crown of the head (or other body hair if head hair is unavailable). Samples are then shipped  
 207 to an external laboratory same-day for drug testing utilizing mass spectrometry.

208 Table 2: Drug detection windows and cutoffs for urine and hair testing

	Drug class	Detection	Confirmation
<b>U</b>	Cocaine COC	2-4 Days	300 ng/mL
	Marijuana THC	15-30 Days	50 ng/mL
	Opiates OPI	2-4 Days	2000 ng/mL
<b>R</b>	Amphetamines AMP	2-4 Days	1000 ng/mL
	Methamphetamines AMP	3-5 Days	1000 ng/mL
<b>I</b>	Phencyclidine PCP	7-14 Days	25 ng/mL
	Benzodiazepines BZO	3-7 Days	300 ng/mL
	Barbiturates BAR	4-7 Days	300 ng/mL
<b>N</b>	Methadone MTD	3-5 Days	300 ng/mL
	Tricyclic Antidepressants TCA		1,000 ng/mL
<b>E</b>	Oxycodone	2-4 Days	100 ng/mL
	Propoxyphene	1-2 Days	300 ng/mL
	Buprenorphine BUP (Suboxone, Subutex)	2-3 Days	10 ng/mL
<b>H A I R</b>	Marijuana THC	Up to 90 days	
	Amphetamines AMP	Up to 90 days	
	Cocaine COC	Up to 90 days	
	Opiates OPI	Up to 90 days	
	Phencyclidine PCP	Up to 90 days	

209  
 210 All women who screen positive on either biological multi-drug test or any one of the screeners  
 211 are contacted immediately (for urine and screener results) or within 72 hours (for hair results) to detail the  
 212 results of her test, encourage the participant to talk with her physician about her substance use, and offer  
 213 her referrals to community resources for treatment that mirror what is currently given to patients by

214 medical staff in each clinic. They are encouraged to speak with the on-site clinic social worker who can  
215 provide further support.

### 216 *Birth Outcome Measures*

217 Birth outcome data, including miscarriage, stillbirth, birth weight, gestational age, head circumference,  
218 and NICU admissions, as well as a list of drugs prescribed during pregnancy and their dosage are  
219 collected by research staff via the EMR and entered into SurveyMonkey.

### 220 *Participant Follow-Up*

221 After completion of this research visit, participants are contacted once more by telephone one week after  
222 completing the surveys to complete the three screeners again to assess test-retest reliability. The average  
223 time commitment for the call is about 10-15 minutes, and upon completion \$25 is loaded onto the  
224 reloadable gift card provided the week prior.

### 225 *Pilot Study*

226 To examine the recruitment process and determine acceptability from the target population of substance-  
227 using pregnant women prior to the start of the study, we conducted a one-month pilot study. Each step of  
228 the recruitment process was reviewed to determine where improvements could be made.

229 We recruited 21 participants from each site for a total of 42 participants (Table 3). Mean age (sd)  
230 of participants was 30.1 years (5.64). By race, 11 participants (26.2%) were White, 25 (59.5%) were  
231 Black/African American, 4 (9.5%) were Asian, 1 (2.4%) was Hispanic and 1 (2.4%) was Other. About  
232 24.4% tested positive for illicit drugs on urine testing, 22% tested positive on hair sample testing. Seven  
233 (7) participants (16.7%) were lost to follow up.

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239 *Table 3 Pilot Study Participant Characteristics*

Characteristics, N = 42	Clinical Site		
	<i>Clinic 1</i>	<i>Clinic 2</i>	<i>Both Sites</i>
<b>Number of participants</b>	21	21	42
<b>Participant age in years, mean (SD)</b>	27.10 (5.09)	33.05 (4.54)	30.07 (5.64)
<b>Ethnicity n (%)</b>			
African American/Black	18 (85.7)	7 (33.3)	25 (59.5)
Asian	0 (0.0)	4 (19.0)	4 (9.5)
Caucasian/White	2 (9.5)	9 (42.9)	11 (26.2)
Hispanic, Latino or Chicano	0 (0.0)	1 (4.8)	1 (2.4)
Some other group	1 (4.8)	0 (0.0)	1 (2.4)
<b>Trimester n (%)</b>			
1 <sup>st</sup>	2 (9.5)	2 (9.5)	4 (9.5)
2 <sup>nd</sup>	6 (28.6)	6 (28.6)	12 (28.6)
3 <sup>rd</sup>	13 (61.9)	13 (61.9)	26 (61.9)
<b>Urine Results n (%)</b>			
Negative for all substances	15 (71.4)	16 (80.0)	31 (75.6)
Positive for at least 1 substance	6 (28.6)	4 (20.0)	10 (24.4)
<b>Hair Results n (%)</b>			
Negative for all substances	12 (60.0)	18 (85.7)	30 (73.2)
Positive for at least one substance	7 (35.0)	2 (9.5)	9 (22.0)
Invalid	1 (5.0)	1 (4.8)	2 (4.9)
<b>Study Disposition n (%)</b>			

Study completes	19 (90.48)	16 (76.2)	35 (83.3)
Lost to follow-up	2 (9.52)	5 (23.8)	7 (16.7)

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241 Results from the pilot study confirmed the feasibility of this study. Eligibility criteria did not  
 242 appear too restrictive, given the eligibility rate of 78% (although slightly lower than anticipated) (Figure  
 243 2). Overall, there was good comprehension of surveys, a low refusal rate for hair sampling (1 refusal/95  
 244 approached, 1.1%), and high study enrollment (Figure 2). The recruitment process took an average of 40  
 245 minutes.

#### 246 *Power and Sample Size*

247 The sample size of 500 participants was chosen based on power analyses for the primary study questions.  
 248 Based on a one-sample binomial approach, with a sample size of 500 participants, we can be 95%  
 249 confident that the false negative rate in the population is under 10% (assuming no more than 35  
 250 individuals test positive in the biologic drug tests without a positive survey screener result). Similarly, we  
 251 can be 95% confident that the false negative rate in the population is under 5% (assuming no more than  
 252 15 individuals test positive in the urine drug test without a positive survey screen result in the study).  
 253 According to McNemar's Test, if at least 15% of the study participants have disagreement between any  
 254 pair of survey results, 500 is a sufficient sample size to determine significant disagreement.

255 After a preliminary sample size of 500 was chosen, a power analysis was conducted to determine the  
 256 detectable differences in age, race, and trimester with a sample size of 500. The power of the test of  
 257 proportions was calculated based on the difference in the proportion of false negatives in each age group,  
 258 race, and trimester of pregnancy. Assuming recruitment of an equal number of women aged 18 to 25  
 259 years and women 26 and older, and that their respective positive screener results are 20% and 10%, then  
 260 the power to detect that difference is 0.88. If the respective screener results are 15% and 20%, then the  
 261 power is much lower (0.31). If we further assume that recruitment of 23% White women and 77% non-  
 262 White women and that white women have a false negative rate of 5% and non-White women have a false

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3 263 negative rate of 15%, then the power is high (0.87). Similarly, if we assume recruitment of an equal  
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5 264 number of women in each of the three trimesters of pregnancy and that women in one trimester have a  
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7 265 false negative rate of 20% while women in another trimester have a false negative rate of 35%, then the  
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9 266 power is high (0.87).  
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## 11 12 267 Analysis 13

14 268 For each screener, reliability and validity (convergent/discriminant validity) will be assessed, including  
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16 269 calculating correlation coefficients between each pair of screeners and between each screener and the  
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18 270 appropriate biologic drug tests. Test-retest reliability analysis will be conducted by examining the results  
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20 271 of repeated screener administrations within one week of original screener administrations for consistency  
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22 272 via correlation analysis. The sensitivity and specificity of each instrument will be calculated, presented,  
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24 273 and interpreted. Each survey instrument will be compared to the gold standard (hair and urine sample  
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26 274 drug testing) by comparing the false negative rates to a predetermined limit of acceptability. If the upper  
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28 275 one-sided 95% binomial confidence interval around the false negative rate in the sample is less than that  
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30 276 limit, then the survey instrument is considered acceptable. The 4P's Plus and SURP-P survey screeners  
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32 277 will be compared to both urine and hair testing in the assessment of their sensitivity and specificity in  
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34 278 relation to short and long-term drug use, respectively. The NIDA Quick Screen/NIDA-Modified ASSIST  
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36 279 screener will be compared to urine testing, while particular questions from the screener regarding long-  
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38 280 term drug use will be compared to hair testing.  
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42 281 Furthermore, we will assess if there are differences in the validity of each screener by age, race, and  
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44 282 trimester. The false negative rate for each screener will be presented by age, race, and trimester. A two-  
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46 283 sided test of proportions will be conducted to test for significant differences in false negative rates  
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48 284 between age, race, and trimester for each screener. Chi-square tests (or Fisher's exact tests if subgroup  
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50 285 sizes are small) may be conducted to determine whether the distribution of responses on each survey  
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52 286 instrument is similar for age, race, and trimester. To examine differences in screener validity by age, race,  
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54 287 and trimester, logistic regression models will be fitted to the data. To separately analyze differences in  
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3 288 probability of false positive results and false negative results on each survey, data will be stratified by  
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5 289 screener and screener result (positive or negative) for a total of six models. In each model, the dependent  
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7 290 variable will be coded 1 for invalid screener result (false negative or false positive) and 0 for valid  
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9 291 screener result (true negative or true positive). Independent variables for age, race, and trimester will be  
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11 292 added to the models to test whether they have a significant effect on the probability of an invalid screener  
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13 293 result. Two-way interaction terms will be included in the model if they are found to be significant effects.  
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15 294 In order to stratify results by trimester, if trimester or any two-way interaction term including trimester is  
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17 295 a significant effect in the models for any of the screeners, probabilities of false positive/ false negative  
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19 296 result will be presented separately by each trimester.  
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23 297 Finally, the prevalence of prescription and illicit drug use will be calculated based on hair test results and  
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25 298 self-report. Prevalence of multi-drug exposure will also be calculated. An ANOVA model will be fitted to  
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27 299 the data with a fixed effect for drug use (negative, positive, positive for multi-drug exposure) to test for  
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29 300 significant differences in birthweight, gestational age, and head circumference based on participant hair  
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31 301 drug tests result. Significant differences will be noted and discussed. The relative risk of NICU  
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33 302 admission, stillbirth, and miscarriage will be examined. A risk ratio will be calculated and will quantify  
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35 303 the percentage difference in these three variables between those with positive hair drug tests versus  
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37 304 negative drug test. The risk ratio takes on values between zero and infinity. A risk ratio of one means that  
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39 305 there is no difference in NICU admissions, stillbirth, or miscarriage between the participants' biologic  
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41 306 drug tests results. A risk ratio very small (close to zero) or very large means a large difference between  
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43 307 NICU admissions, stillbirth, or miscarriage based on the hair drug tests results. Approximate 95%  
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45 308 confidence intervals for the relative risk will be calculated. The same relative risk ratios and 95%  
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47 309 confidence intervals will be calculated for a positive biologic drug tests for multi-drug exposure versus  
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49 310 positive for a single-drug exposure. Further, relative risk ratios will be computed with 95% confidence  
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51 311 intervals stratified by trimester.  
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## 312 Discussion

313 Our ongoing research has five aspects of significance. First, the importance of screening pregnant women  
314 and the public health impact of the current research is tied directly to the negative health consequences  
315 associated with illicit and prescription drug use during pregnancy. Second, it utilizes both urine and hair  
316 testing to enable us to examine past 90-day substance use history with precision. Hair analysis provides  
317 nearly twice the number of positives due to its longer detection window, but often cannot capture very  
318 recent use. Urine analysis supplements hair analysis to allow for the most comprehensive validation of  
319 screeners possible. Third, the study compares three screeners acknowledged by the World Health  
320 Organization (WHO) to screen for multiple substances to each other and to the biological screeners (gold  
321 standard). This is the first study to conduct a direct, head-to-head comparison of multiple screening tools  
322 for prescription and illicit drug use among pregnant women, while also utilizing biologic measures as a  
323 gold standard against which to compare. Fourth, the study utilizes electronic medical records (EMR) to  
324 capture prescribed drugs and birth outcome data of enrolled participants. The ability to access a  
325 participant's prescription drug orders enables better tracking and distinction between prescription drug  
326 use and abuse, while birth outcome data allows for determination of associations between specific drug  
327 use and birth outcomes. Fifth, the study has the potential to shift clinical practice towards universal  
328 standardized substance use screening.

329 Despite the significant contributions of this work, it is not without limitations. Though the study will  
330 enroll a large sample of pregnant women, it is a convenience sample from two prenatal clinics in an urban  
331 area. We have attempted to increase generalizability by enrolling women from two clinics with different  
332 population characteristics: one clinic serves low-income, Medicaid-eligible, primarily African-American  
333 women and the other serves privately-insured, primarily White women. Second, there is a possibility of  
334 selection bias. Incentive may be more appealing to those who have lower socioeconomic status,  
335 individuals with more time may be those willing to take the study, and pregnant women who use  
336 substances may not want to participate. For the latter point, we have obtained a Certificate of



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3 337 Confidentiality and ensured participants that their data will not be shared with anyone including clinic  
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5 338 staff. Finally, our study is limited to adults. Though our initial protocol included adolescents, the IRB did  
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7 339 not allow for “no-benefit” studies enrolling pregnant adolescents. This is an important area for further  
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9 340 exploration, given that pregnant adolescents report higher substance use rates than pregnant adults in  
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11 341 national surveys.

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14 342 The primary innovation of this project is that it may provide a final evidence-based  
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16 343 recommendation for the tool(s) best suited for screening for illicit and prescription drugs among a diverse  
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18 344 sample of pregnant women. The provision of this evidence-based guidance to clinicians is a concrete  
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20 345 application of findings that is rare in public health research. We recognize that screening is a first step;  
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22 346 also important is the need for a public health focus on treatment of substance use during pregnancy to  
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24 347 enhance the odds of a successful pregnancy outcome. Barriers to treatment that are imperative to address  
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26 348 are the potential legal repercussions of identifying substance use during pregnancy that exist in some  
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28 349 states<sup>9</sup> and unintentional breach of confidentiality.<sup>10</sup> There is a strong need for a re-examination of state  
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30 350 policies so that women are not punished for having a treatment need.

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34 351 Substance use during pregnancy, and specifically prescription and illicit drug use, are high  
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36 352 priority topics for the Centers for Disease Control and Prevention (CDC), WHO, The American Congress  
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38 353 of Obstetricians and Gynecologists (ACOG), Substance Abuse and Mental Health Services  
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40 354 Administration (SAMHSA), National Institute on Drug Abuse (NIDA), and the National Institutes of  
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42 355 Health (NIH). Universal screening has the potential to greatly enhance maternal and infant health  
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44 356 outcomes and reduce healthcare costs. Specifically, the current research supports the following Healthy  
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46 357 People 2020 public health goals and objectives which include reducing maternal illness and complications  
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48 358 due to pregnancy; increasing the proportion of pregnant women who receive adequate prenatal care;  
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50 359 increasing abstinence from alcohol, cigarettes, and illicit drugs among pregnant women; and increasing  
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52 360 the proportion of women delivering a live birth who received preconception care services and practiced  
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54 361 key recommended preconception health behaviors.

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3 362 This research addresses an important problem by identifying a valid substance use screening  
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5 363 instrument for illicit and prescription drugs among pregnant women that is accurate, brief, and acceptable  
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7 364 to both patients and health care providers in a primary care setting. Identifying and validating one  
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9 365 instrument that functions the closest to the “gold standard” of biologic testing (i.e., urine and hair) and  
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11 366 disseminating this information widely will increase the likelihood that primary care clinics nationwide  
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13 367 may adopt a quick and easy screener universally. We may find that one instrument does not stand out but  
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15 368 that each has its distinct advantages and disadvantages; in this case, the performance of each measure will  
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17 369 be detailed with recommendations for which screener may work the best with a given population.  
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## 390 Declarations

### 391 *Ethics approval and consent to participate*

392 This study is approved by the Institutional Review Boards (IRB) of the University of Maryland (HP-  
393 00072042), Baltimore; and Battelle Memorial Institute (0619-100106433). All participants are required to  
394 give their informed consent prior to any study procedure.

### 395 *Availability of data and materials*

396 The data that support the findings of this study are available on request from the corresponding author  
397 [VHCC]. The data are not publicly available due to them containing information that could compromise  
398 research participant privacy/consent.

### 399 *Competing interests*

400 The authors declare that there are no competing interests.

### 401 *Authors' contributions*

402 VCC conceived the study. VCC, EO, EP, KT, BK and KM participated in the drafting of the manuscript and  
403 each approved the final draft

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408 National Institutes of Health.

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3 444 Figure 1: Study procedures  
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3 447 Figure 2: Pilot study participation  
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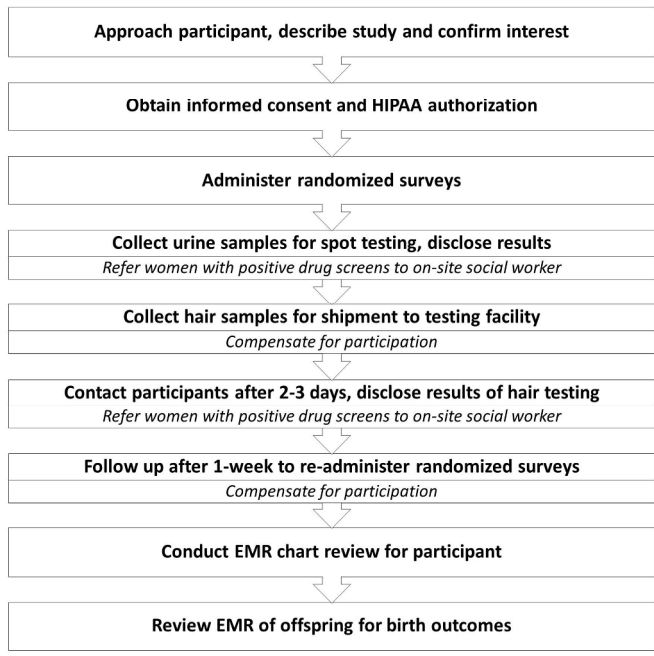


FIGURE 1: Study procedures

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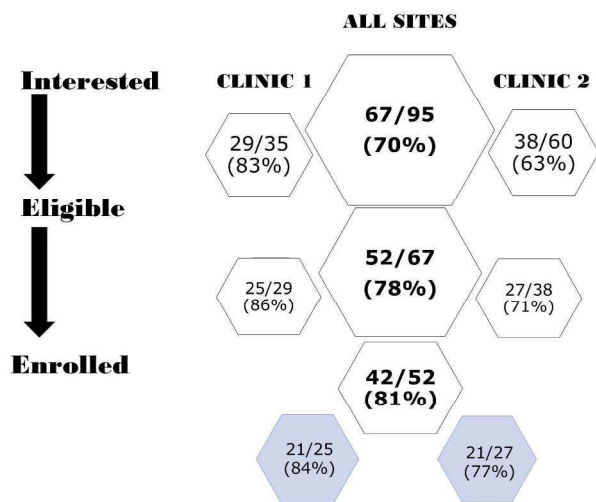


Figure 2: Pilot study participation

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