Document Coversheet

Study Title: Integrated PrEP Interventions for People Who Inject Drugs in Rural Kentucky

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KEY INFORMATION FOR HIV PREVENTION IN RURAL KENTUCKY- AIM 3 PWID

We are asking you to choose whether or not to volunteer for a research study about HIV risk and HIV prevention options, including medicines that can prevent getting HIV. We are asking you because you are a client of the syringe exchange program and we are interested in providing HIV education and access to prevention medicines to people who inject drugs. This page is to give you key information to help you decide whether to participate. We have included detailed information after this page. Ask the research team questions. If you have questions later, the contact information for the research investigator in charge of the study is below.

WHAT IS THE STUDY ABOUT AND HOW LONG WILL IT LAST?

By doing this study, we hope to better understand whether providing HIV prevention medications onsite at the syringe exchange helps people who inject drugs be able to start these medicines. Everyone in the study will receive education about HIV risk and prevention options and will have the opportunity to meet with a nurse practitioner to receive HIV prevention medication. Half of the study participants will also meet with a member of the study team to work on removing any barriers to starting HIV prevention medication. It will be up to chance (like flipping a coin) whether you have one study session or up to five. We will do these sessions here at the Health Department when you are visiting the exchange program. Your participation in this research starts today and continues for 6 months.

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

You might choose to volunteer for this study if you think you would be interested in learning more about medications to prevent HIV or starting a medication to prevent HIV. There is no guarantee that you will get any benefit from taking part in this study, however, you will be given information about HIV prevention. Your willingness to take part may help us improve these services in the community.

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

You might choose not to participate in the study if you do not want to discuss HIV prevention medications or take a medication. You might choose not to participate if you live very far from the health department and would be unable to attend between 1 and 5 appointments. If you take part in this study, there is a small chance that you may feel upset when discussing health concerns or HIV prevention activities. You may refuse to answer any questions that make you uncomfortable. For a complete description of risks, refer to the Detailed Consent.

DO YOU HAVE TO TAKE PART IN THE STUDY?

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

WHAT IF YOU HAVE QUESTIONS, SUGGESTIONS OR CONCERNS?

If you have questions, suggestions, or concerns regarding this study or you want to withdraw from the study contact Hilary L. Surratt, PhD, Principal Investigator, at the University of Kentucky, Department of Behavioral Science, at 859-562-2458.

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

CONSENT TO PARTICIPATE IN A RESEARCH STUDY
HIV PREVENTION IN RURAL KENTUCKY- AIM 3 PWID

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

You should not participate in this study if you are under 18 years of age, have not used the syringe exchange program or injected drugs in the past month, or if you have been diagnosed with HIV.

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

The study will be conducted at the Health Department where you were screened. The first research visit will take about sixty to ninety minutes, and subsequent weekly visits (1 to 5) will take about 45 minutes. After this you will need to come once for a 3-month research follow-up interview and once for a 6-month research follow-up interview, each of which will last about an hour. The total amount of time you will be asked to volunteer for this study is approximately 10 hours over the next six months.

WHAT WILL YOU BE ASKED TO DO?

If you agree to take part in this study, you will be assigned by chance to one of two interventions. You have a 50/50 chance of being assigned to each intervention. Both complete the same research assessments and receive HIV education and preventive medication for HIV. Everyone in the study will have the opportunity to meet with a nurse practitioner to receive HIV prevention medication. The main difference is that one group (called PrEP-Strengths) will be asked to come to 1-4 additional sessions with a study staff member to address any barriers to HIV medication use. Both groups complete 6 months of research follow-up. Both groups are asked to sign an information release so that the study team can review information from medical records at the health department.

Your participation starts right after the informed consent process. You will be asked to answer questions about your health, behavior and drug use by a trained study team member. The interviewer will ask you questions in a private office using a laptop computer. This session will last approximately 1 to 1.5 hours. The interviewer will also ask you to provide contact information so that we can contact you for follow-up interviews and appointments. At the end of this, the interviewer will schedule your first intervention session within one week. Depending on your intervention assignment, you will be asked to attend between 1 and 5 intervention sessions approximately once a week with a study staff member. The sessions will provide information on HIV risk and available prevention options. If you wish to start HIV prevention medication you will be asked to undergo a brief medical screening that involves a finger-stick blood draw. You will be informed on the results of the tests by the study nurse practitioner. After the intervention period, both groups will be asked to complete a 3-month and 6-month follow-up research assessment. We will also collect information from medical records at the health department regarding your visits with the study nurse practitioner.

A smaller group of participants (about thirty) will also be asked to complete an additional survey about recovery and treatment outcomes.

WHAT ARE THE POSSIBLE RISKS AND DISCOMFORTS?

Risk of behavioral assessments: During the research assessments, it is possible that you may feel uncomfortable answering personal questions about your health and drug use history. You may refuse to answer any questions that make you uncomfortable.

Risk of loss of confidentiality: There is the risk that others may see your Protected Health Information (PHI). The following PHI will be collected as part of this project: names (individual), address, telephone number, dates (birth, medical appointments), medical record numbers, psychiatric and physical health history, drug use history, results from physical health assessments, and medication prescription history. We will make every effort to keep private all research records that identify you to the extent allowed by law. However, there is a very small risk that a breach in confidentiality may occur.

Risk of a blood draw: The medical screening will involve a blood draw to check that you are medically appropriate to start HIV prevention medication. The tests involve a finger-stick that only requires a small amount of blood to

test for HIV, HBV, and kidney function. The risk of a blood draw may include minor bruising or bleeding at the site, fainting, pain, soreness, and infection.

Risk of HIV prevention medication: Two oral medications are FDA-approved for prevention of HIV infection, these are not experimental treatments. There is some risk of mild side effects with these medications, including headache, nausea, stomach upset, and a small risk of reduced kidney function; the study nurse practitioner will discuss these with you if you decide to start a medication.

WILL YOU BENEFIT FROM TAKING PART IN THIS STUDY?

There is no guarantee that you will get any benefit from taking part in this study, however, you will be given educational information about HIV prevention that may help you protect yourself. You may benefit from gaining access to HIV prevention medication. Your willingness to take part may help us improve HIV prevention services for people who inject drugs.

IF YOU DON'T WANT TO TAKE PART IN THE STUDY, ARE THERE OTHER CHOICES?

If you do not want to be in the study, there are no other choices except not to take part in the study.

WHAT WILL IT COST YOU TO PARTICIPATE?

Participating in the interviews and education session(s) of this study will not cost you anything. If you decide to start an HIV prevention medication, you and/or your insurance company, Medicare, or Medicaid will be responsible for the costs for the prescription. HIV prevention medications are covered by Medicaid, Medicare and commercial insurance. If Medicaid is your insurer, you will not have a copay. However, if you have another insurance, you may have deductibles and copays. If you have no insurance, study staff will connect you with payment assistance programs to cover the costs of medication and lab testing.

WHO WILL SEE THE INFORMATION THAT YOU GIVE?

We will make every effort to keep confidential all research records that identify you to the extent allowed by law. Your information will be combined with information from other people taking part in the study. When we write about the study to share it with other researchers, we will write about the combined information we have gathered. You will not be personally identified in these materials. We may publish the results of this study; however, we will keep your name and other identifying information private.

We will make every effort to prevent anyone who is not on the research team from knowing that you gave us information, or what that information is. Your records will be kept confidential. Your records will be kept under lock and key and will not be shared with anyone without your written permission. Your name will not appear on any data file or research report.

All documentation that contains protected health information (PHI) is kept apart from research data. Files will not contain your name or identifying information. You will be assigned a unique identifying number if you decide to participate in this study. Some data will be collected using an application called REDCap, which stores data on a secure web server located behind a firewall on UK's network. All other electronic files will be stored on the HIPAA-compliant Center on Drug and Alcohol Research (CDAR) server that is located in the data center of the UK hospital and is behind the firewall. Access to the CDAR server and to the REDCap application is password protected and only assigned staff are granted access. Any laptops used for data collection will be encrypted. The specific files are also password-protected. All personal identifiers are encrypted when the data are uploaded.

All paper documents will be stored in locked cabinets at the Center on Drug and Alcohol Research at 845 Angliana Avenue, Lexington, KY. Paper documents that contain PHI will be stored separately from research data. Offices are locked and building entry is protected by badge access. Key access will be limited to study personnel. We will maintain study informed consent forms and identifying information for six years from the end of the study. De-identified study data will be kept indefinitely.

Certificates of Confidentiality (CoC):

To help us protect your privacy, this research has a Certificate of Confidentiality. The researchers can use this Certificate to refuse to disclose information that may identify you to anyone not connected with this study, or in any legal proceedings. The exceptions to this rule are release of information:

- you have requested us to provide, for instance, to your insurance company or doctor;
- to the sponsor (e.g., National Institutes of Health) or agency auditing the research (e.g., Food and Drug Administration);
- about child or elder abuse, neglect, or intent to kill yourself or others; and
- about you if it involves a reportable disease. If your screening test for HIV or HBV is positive, these results will be confidentially reported to the Kentucky Department for Public Health in Frankfort.

CAN YOUR TAKING PART IN THE STUDY END EARLY?

You can choose to leave the study at any time. You will not be treated differently if you decide to stop taking part in the study. If you started an HIV prevention medication in the study, we will work to help you continue this medication with another provider if you wish. If you choose to leave the study early, data collected until that point will remain in the study database and may not be removed.

The investigators conducting the study may need to remove you from the study. You may be removed from the study if:

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

ARE YOU PARTICIPATING OR CAN YOU PARTICIPATE IN ANOTHER RESEARCH STUDY AT THE SAME TIME AS PARTICIPATING IN THIS ONE?

You may take part in this study if you are currently involved in another research study.

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

If you believe you are hurt or if you get sick because of something that is due to the study, you should call Hilary Surratt, PhD at 859-562-2458 immediately. Hilary Surratt, PhD will determine what type of treatment, if any, is best for you at that time.

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

Medical costs related to your care and treatment because of study-related harm will be your responsibility.

You do not give up your legal rights by signing this form.

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

You will receive a $30 gift card payment for research visits at enrollment, 3 month and 6 month follow up. The study interviewer will provide you with a $30 gift card immediately after taking part in the enrollment and follow-up sessions. $10 gift cards will be provided to cover transportation expenses to attend intervention sessions and research follow-up visits. Approximately 30 participants will complete an additional one-time survey for which they will receive another $30 gift card.

If you earn $600 or more by participating in any research, it is potentially reportable for tax purposes.

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

If the researcher learns of new information in regard to this study, and it might change your willingness to stay in this study, the information will be provided to you. You may be asked to sign a new informed consent form if the information is provided to you after you have joined the study.

WILL WE CONTACT YOU WITH INFORMATION ABOUT PARTICIPATING IN FUTURE STUDIES?

The research staff would like to contact you in the future with information about participating in additional studies. If so, it will be limited to two times per year.

Do you give your permission to be contacted in the future by Dr. Hilary Surratt or a member of the research team regarding your willingness to participate in future research studies?

☐ **Yes** ☐ **No** **Initials**_____

WHAT ELSE DO YOU NEED TO KNOW?

You will be one of approximately 80 health department clients who enroll in this study through the University of Kentucky. The National Institutes of Health is providing financial support for this study.

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

WILL YOUR INFORMATION BE USED FOR FUTURE RESEARCH?

All identifiable information will be removed from the information collected in this study. This means that no link or code to your identity will be kept. After all identifiers have been removed, the information or samples may be used for future research or shared with other researchers without your additional informed consent. Once you give your permission to have your de-identified information stored, they will be available indefinitely and cannot be removed due to the inability to identify them.

INFORMED CONSENT SIGNATURES

This consent includes the following:

- **Key Information Page**
- **Detailed Consent**

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

_____ **Signature of research subject**	_____ **Date**
_____ **Printed name of research subject**	
_____ Printed name of [authorized] person obtaining informed consent	_____ Date

The RISE (Research Informing Syringe Exchange) Trial SPIRIT Protocol

Administrative information

Title	1	Integrated PrEP Interventions for People Who Inject Drugs in Rural Kentucky A randomized parallel group trial to compare the preliminary efficacy of Strengths-Based Case Management versus standard CDC PrEP counselling in the initiation of pre-exposure prophylaxis among rural people who inject drugs.
Trial registration	2a	ClinicalTrials.gov: NCT05037513 (August 5, 2021)
World Health Organization Trial Registration Data Set	2b	N/A
Protocol version	3	Issue Date: July 5, 2022; Protocol Number: 01
Funding	4	NIDA Grant Number R34DA053140-01A1. Project Period: 08/01/2021-07/31/2024.
Names, Affiliations and Roles of Protocol Contributors	5a	Hilary L. Surratt, Associate Professor, University of Kentucky, Principal Investigator Laura C. Fanucchi, Associate Professor, University of Kentucky, Co-Investigator Jennifer R. Havens, Professor, University of Kentucky, Co-Investigator Michele Staton, Professor, University of Kentucky, Co-Investigator Philip Westgate, Associate Professor, University of Kentucky, Co-Investigator HLS conceived the study and is the primary grant holder. MS, LF, and JH provide consultation on elements of study design. PW provides statistical expertise in clinical trial design and is conducting the primary statistical analysis.
Name and Contact Information of the Trial Sponsor	5b	N/A
Role of Study Sponsor and Funder	5c	NIDA had no role in the design of this study and will not have any role during its execution, analyses, interpretation of the data, or decision to submit results.
Committees	5d	see Item 21a for Data and Safety Monitoring Board

Introduction

Background and rationale	6a	Description of research question and justification for undertaking the trial, including summary of relevant studies (published and unpublished) examining benefits and harms for each intervention

Background

Rural areas in the United States are increasingly impacted by HIV, tied to the ongoing opioid epidemic, growing stimulant use, and widespread drug injection. Kentucky (KY) is among seven states identified with heavy rural HIV burden and increasing rates of new HIV diagnoses attributable to injection drug use: in 2018, 36% of HIV-diagnosed women in KY had injection drug use as a transmission factor, as did 10% of men. Rural HIV outbreaks among people who inject drugs (PWID) have occurred recently in KY's neighboring states, including Indiana, West Virginia, and North Carolina. With increases in HIV transmission among PWID expected to continue, there is an urgent need to implement proven HIV prevention and harm reduction strategies for PWID in KY's rural areas.

Existing Knowledge

A key pillar of Ending the HIV Epidemic (EHE): A Plan for America is the prevention of new HIV infections through scale up of evidence-based interventions, including syringe service programs (SSPs) and Pre-exposure prophylaxis (PrEP). SSPs are a proven structural HIV prevention tool and are currently operational in 62 KY counties. Research in KY's Appalachian region has demonstrated consistent use of rurally located SSPs by high-risk PWID, making SSPs a critical venue to scale delivery of comprehensive HIV prevention services in rural areas. While SSPs are increasing access to sterile injection equipment for rural PWID, several gaps remain in HIV prevention, including suboptimal uptake of HIV testing, inadequate syringe coverage, and low access to PrEP providers in rural communities.

Need for a Trial

The expansion of PrEP has been endorsed as a key strategy for impacting the course of the HIV epidemic, however, PrEP trials among PWID are largely absent from the literature, particularly in rural areas. Structural barriers to healthcare access, lack of providers, and inadequate infrastructure to deliver PrEP are challenges in many rural areas. In addition, PWID often have low PrEP knowledge, limited perception of risk, high HIV-related stigma, and other competing needs that act as barriers to PrEP uptake. This study will integrate PrEP education, screening, prescribing and monitoring within the SSP, a venue already routinely accessed by rural PWID, to reduce structural barriers to access to this evidence-based HIV prevention intervention through co-located comprehensive PrEP services.

	6b	Explanation for choice of comparators
		This study will adapt and integrate a novel PrEP initiation intervention at point of care in rural SSPs using strengths-based case management (SBCM) approaches to elicit and address structural, environmental and psychosocial barriers to PrEP care. Participants will be randomized into: CDC-PrEP (an in-use PrEP intervention based on CDC guidelines), or the experimental SBCM-PrEP intervention. CDC-PrEP utilizes structured risk assessments and educational materials recommended by the CDC and operates as a point of care model with embedded APRNs providing clinical screening, prescribing, and monitoring of patients in a single session. SBCM-PrEP provides up to 5 strengths-based sessions to deliver tailored PrEP education and engage in action planning to increase readiness for PrEP initiation. The rationale for the selection of the intervention comparators is threefold: 1) use of an active comparator (CDC-PrEP) meets an ethical standard to provide high-risk participants with needed basic education and the potential to access PrEP; 2) examination of a brief, in-use content specific intervention for PrEP based on CDC guidelines affords the opportunity to establish preliminary efficacy of an existing intervention that has not been formally tested within the SSP context, and whose brevity may contribute to scalability if efficacious; and 3) Comparison with the SBCM-PrEP will examine the value-added of a more robust, but brief, client-driven intervention that supports PrEP initiation through active advocacy to reduce multi-level barriers to uptake.
Objectives	7	Specific objectives or hypotheses The primary objective is to examine preliminary efficacy and effect sizes of the novel SBCM-PrEP and CDC-PrEP interventions on the primary outcome of PrEP initiation (measured by dispensed PrEP prescription) in HIV- participants who inject drugs.
Trial design	8	Description of trial design including type of trial (eg, parallel group, crossover, factorial, single group), allocation ratio, and framework (eg, superiority, equivalence, noninferiority, exploratory) The trial is designed as a randomized, controlled exploratory trial with two parallel groups and a primary endpoint of PrEP initiation during 3 months after enrollment. Randomization will be stratified by site and gender and performed with a 1:1 allocation.

Methods: Participants, interventions, and outcomes

Study setting	9	Description of study settings (eg, community clinic, academic hospital) and list of countries where data will be collected. Reference to where list of study sites can be obtained Rural HIV- PWID will be recruited and sampled from two participating SSP locations in Knox and Clay Counties in rural southeastern Kentucky. Both SSPs are operated by health departments that provide a wide range of health and clinical care and are integrated with other health department services. SSP locations were purposefully selected for inclusion in the study based on their robust operational SSPs serving relatively large numbers of unique clients and location in rural southeastern KY counties that are among the nation's top ten most vulnerable to HIV among PWID.
Eligibility criteria	10	Inclusion and exclusion criteria for participants. If applicable, eligibility criteria for study centres and individuals who will perform the interventions (eg, surgeons, psychotherapists) Eligible participants will: 1) be at least 18 years of age; 2) report at least one occasion of injection drug use in the past month; 3) report sharing of injection equipment at least once in the past six months consistent with CDC indications for PrEP; 4) be a documented client of the county SSP at the time of study entry; and, 5) express willingness to participate in a multi-session intervention and follow-up. Exclusion criteria will include: HIV+ status, and current PrEP care.
Interventions	11a	Interventions for each group with sufficient detail to allow replication, including how and when they will be administered Participants will be randomized into: CDC-PrEP or the experimental SBCM-PrEP intervention. CDC-PrEP is 1 session PrEP education following CDC guidelines delivered one on one by trained study staff to individual clients in the syringe service program setting. This session will occur withing one week of study enrollment. SBCM-PrEP is a multi-session Strengths-Based Case Management intervention adapted for PrEP related educational content delivered one on one by trained study staff to individual clients in the syringe service program setting within one week of enrollment. In both arms, participants interested in starting PrEP are referred to the onsite Advanced Practice Registered Nurse for clinical PrEP screening.
	11b	Criteria for discontinuing or modifying allocated interventions for a given trial participant (eg, drug dose change in response to harms, participant request, or improving/worsening disease)

-N/A

11c Strategies to improve adherence to intervention protocols, and any procedures for monitoring adherence (eg, drug tablet return, laboratory tests)

Study staff will attempt to contact participants to remind them of intervention session appointments the day before each scheduled session, and participants will be allowed to reschedule missed sessions. In sessions participants will be asked about PrEP adherence, and problems or barriers addressed.

11d Relevant concomitant care and interventions that are permitted or prohibited during the trial

N/A

Outcomes 12 Primary, secondary, and other outcomes, including the specific measurement variable (eg, systolic blood pressure), analysis metric (eg, change from baseline, final value, time to event), method of aggregation (eg, median, proportion), and time point for each outcome. Explanation of the clinical relevance of chosen efficacy and harm outcomes is strongly recommended

Primary Outcome Measure:
Difference between the two intervention arms in the number of participants initiating PrEP at 3 and 6 month follow-up.

1. Number of participants initiating PrEP

   Documented PrEP initiation, measured by dispensed PrEP prescription.

   [Time Frame: 3 months post-baseline]

2. Number of participants initiating PrEP

   Documented PrEP initiation, measured by dispensed PrEP prescription.

   [Time Frame: 6 months post-baseline]

Secondary Outcome Measures:

3. Level of Intervention Engagement assessed by session checklist

   5 item Session Checklist completed by Nurse-Interventionist post-session; range is 0-15, higher scores are higher engagement

[Time Frame: 8 weeks post-baseline]

4. Level of Intervention Satisfaction assessed by the IAQ

   8 item Intervention Acceptability Questionnaire (IAQ) completed by participants post-intervention; range is 0-32, higher scores are higher satisfaction

   [Time Frame: 8 weeks post-baseline]

Participant timeline	13	Time schedule of enrolment, interventions (including any run-ins and washouts), assessments, and visits for participants. A schematic diagram is highly recommended (see Figure) **-Figure 1 and Table 1**
Sample size	14	Estimated number of participants needed to achieve study objectives and how it was determined, including clinical and statistical assumptions supporting any sample size calculations The pilot RCT is not designed to establish superiority of the SBCM-PREP, but to generate valid parameter estimates and preliminary evidence of effect sizes for application in a subsequent large trial. The proposed sample size of 80 aligns with recommended sample sizes for two-arm pilot trials structured as planning for subsequent major trials. Assuming a retention rate of 90% at 6 months, there will be 36 participants per intervention group for analysis, which is sufficient.
Recruitment	15	Strategies for achieving adequate participant enrolment to reach target sample size Recruitment is balanced across the two SSP locations and by gender, targeting enrollment of 40 individuals per location, or 80 in total. Within the SSP settings, potential participants will be screened by research staff on rotating days of the week when the SSPs are operational and eligible participants will be invited to participate. Approximately 6-8 individuals will be enrolled into the study each month across the two sites; challenges meeting the enrollment target based on prior research in these settings and current volumes of SSP clients are not anticipated.

Methods: Assignment of interventions (for controlled trials)

Allocation:

Sequence generation	16a	Method of generating the allocation sequence (eg, computer-generated random numbers), and list of any factors for stratification. To reduce predictability of a random sequence, details of any planned restriction (eg, blocking) should be provided in a separate document that is unavailable to those who enroll participants or assign

		interventions Participants will be randomly assigned to either the CDC-PrEP or SBCM-PrEP with a 1:1 allocation per a computer-generated randomization schedule stratified by site and gender.
Allocation concealment mechanism	16b	Mechanism of implementing the allocation sequence (eg, central telephone; sequentially numbered, opaque, sealed envelopes), describing any steps to conceal the sequence until interventions are assigned -The study coordinator and PI are notified of the allocation via secure email.
Implementation	16c	Who will generate the allocation sequence, who will enroll participants, and who will assign participants to interventions -The study Co-I statistician will generate the allocation sequence. The study interviewer will enroll participants, and the study coordinator will assign participants to intervention arms.
Blinding (masking)	17a	Who will be blinded after assignment to interventions (eg, trial participants, care providers, outcome assessors, data analysts), and how -N/A – the study is not blinded
	17b	If blinded, circumstances under which unblinding is permissible, and procedure for revealing a participant's allocated intervention during the trial
Methods: Data collection, management, and analysis		
Data collection methods	18a	Plans for assessment and collection of outcome, baseline, and other trial data, including any related processes to promote data quality (eg, duplicate measurements, training of assessors) and a description of study instruments (eg, questionnaires, laboratory tests) along with their reliability and validity, if known. Reference to where data collection forms can be found, if not in the protocol All study staff complete training on study assessments. Primary outcomes include PrEP initiation (measured by dispensed PrEP prescription) 3- and 6- months post-baseline, and acceptability of the intervention (measured by intervention engagement and satisfaction) during the active intervention period. Acceptability will be measured by engagement in the intervention using an interventionist completed session checklist, and a client completed Intervention Acceptability Questionnaire (IAQ) will assess satisfaction.

		Study instrumentation will collect self-report information on participation in PrEP screening, prescription, and adherence, however, primary measures will be drawn from HD/SSP medical record data to be extracted from the Patient Encounter Form (PEF) and Adult History and Physical Form through chart review at 3-and 6-months post baseline. Data points planned for extraction include: visit date, visit location (including phone or telehealth), provider number, patient ID number, CPT visit type, ICD codes, current medications, laboratory tests conducted relevant to CDC PrEP guidelines (HIV testing, viral hepatitis testing, STI testing, kidney function, and pregnancy testing), and PrEP prescription issuance/refills. For participants who receive a PrEP prescription from the nurse-interventionist, provider-initiated pharmacy verification and/or participant prescription documentation will be used to verify that the prescription was dispensed to the patient. Well-validated measures will examine participant and risk environment characteristics that may influence intervention outcomes. These measures will be collected at baseline, 3-and 6- month follow-up. The primary data collection instrument contains abbreviated segments of: a. Global Appraisal of Individual Needs (GAIN, v. 5.4) to capture demographics, substance use, physical and mental health, violence, housing situation, transportation; b. Collaborative Injection Drug User Study III/Drug User Intervention Trial Assessment Instrument to capture injection behaviors and equipment sharing, and sources of injecting equipment including SSPs; c. items on secondary syringe exchange, syringe disposal, and syringe coverage, d. Community Stigma related to substance use; and, e. Law Enforcement Activity near or enroute to SSP locations. Validated measures of perceived HIV risk, HIV-related community stigma, PrEP awareness, acceptability, and use, dignity denial, and PrEP adherence at follow-up have been included.
	18b	Plans to promote participant retention and complete follow-up, including list of any outcome data to be collected for participants who discontinue or deviate from intervention protocols Participants will be located for follow-up using detailed locator information collected at baseline. Project staff will also have a routine presence in the SSPs to maintain ongoing contact with participants. Participants will receive a $25 payment for data collection and transportation costs at 3-month and 6-month follow-up.
Data management	19	Plans for data entry, coding, security, and storage, including any related processes to promote data quality (eg, double data entry;

		range checks for data values). Reference to where details of data management procedures can be found, if not in the protocol Interview data will be collected at two remote SSP sites on a laptop interface through a REDCap survey application, which is housed on secure servers at UK. The application will provide the technical functionality required to remotely collect interview data and ensure data security during transmission to UK. Branching logic and range checks for data values are built into the REDCap assessments to promote data quality. The interview dataset will be audited for quality control issues on a bi-weekly basis.
Statistical methods	20a	Statistical methods for analysing primary and secondary outcomes. Reference to where other details of the statistical analysis plan can be found, if not in the protocol A total of 80 HIV- rural PWID will be randomly assigned to the two intervention groups. The major interest in Specific Aim 3 is to evaluate the preliminary efficacy of the intervention conditions on PrEP initiation (measured by dispensed PrEP prescription) at 3- and 6-month follow-ups. With 36 participants per intervention condition, and utilizing a 95% confidence interval, we will be able to estimate the true probability of PrEP initiation for either trial arm within a maximum of ± 0.16. To address Aim 3, robust analytic methods will be used for descriptive purposes and data analyses. Descriptive statistics (e.g., frequencies, proportions, means, and standard deviations) will be used to describe process variables (e.g., the number of sessions attended, engagement scores). Bivariable analyses will be used to examine potential differences in feasibility and acceptability between the two study conditions. Conventional statistical methods, such as t-tests, Chi- square, ANOVA, ANCOVA, OLS, and logistic regression will be used for preliminary analyses of the demographic and risk environment characteristics of PWID, as well as those associated with PrEP initiation. Tests will be two-sided at the 0.05 level. Similarly, to examine initiation of PrEP, as well as continuation of PrEP among those who initiated by 3 months, we will utilize frequencies, proportions, and corresponding 95% confidence intervals. Additionally, logistic regression models will be utilized to assess for group differences, adjusting for site due to its use as a stratification factor.
	20b	Methods for any additional analyses (eg, subgroup and adjusted analyses) N/A
	20c	Definition of analysis population relating to protocol non-adherence (eg, as randomised analysis), and any statistical methods to handle

		missing data (eg, multiple imputation) We will use an intent-to-treat approach, analyzing data from all participants based on the trial arms to which they were randomized regardless of whether they receive or complete the randomized treatment to which they were assigned. Analysis of the primary outcome (PrEP initiation) should not be affected by patient withdrawals or loss to follow up, as we will have process and medical records data to document for each participant whether they had an initial meeting with the nurse practitioner and whether a PrEP prescription was issued. Analyses of secondary outcomes will utilize all available data. Multiple imputation of missing data may be considered for sensitivity analyses.
Methods: Monitoring		
Data monitoring	21a	Composition of data monitoring committee (DMC); summary of its role and reporting structure; statement of whether it is independent from the sponsor and competing interests; and reference to where further details about its charter can be found, if not in the protocol. Alternatively, an explanation of why a DMC is not needed A Data and Safety Monitoring Board has been established including the following members: William W. Stoops, Ph.D. (chair), Hannah K. Knudsen, Ph.D. (member), and Keisa Fallin-Bennett, MD (member). The DSMB is independent of the study organizers. The DSMB will meet before the trial is fielded to review the initial protocol elements. During the period of study enrollment the DSMB will hold regular meetings every 6 months to evaluate the progress, safety and efficacy of the trial: i. Admission data, including eligibility data, the participant flow chart, retention, and overall progress toward targeted goals. ii. Protocol compliance, including quality assurance reports and protocol deviations and violations iii. Human subjects safety reports, including individual SAEs (identity data removed) and aggregated, categorized AEs. iv. Aggregated efficacy data by study arm, including all outcome measures. The Chair of the DSMB may request special data reports in any format and at any time. v. Actions taken in response to prior recommendations of the DSMB. vi. Compliance with reporting of SAEs and AEs to the IRB and to NIDA as described in the DSMP.
	21b	Description of any interim analyses and stopping guidelines, including who will have access to these interim results and make the final decision to terminate the trial

		The DSMB will independently make recommendations to researchers to continue, amend or terminate the trial based on the interim analysis of the safety data, efficacy data, and/or performance data (e.g., protocol violations, improper entry criteria, slow accrual rate, low participation rate, failure of randomization, inadequate treatment adherence, inadequate follow-up rate, severely compromised validity) and to independently make recommendations for improvement or termination if the trial would be unable to prove anything meaningful, regardless of modifications.
Harms	22	Plans for collecting, assessing, reporting, and managing solicited and spontaneously reported adverse events and other unintended effects of trial interventions or trial conduct Adverse events (AEs) are collected and assessed at each study visit. AEs are summarized in regular reporting to the DSMB, and annual reports to the IRB and NIDA. Prompt reporting guidelines to NIDA, the IRB, and the DSMB regarding Serious Adverse Events are followed.
Auditing	23	Frequency and procedures for auditing trial conduct, if any, and whether the process will be independent from investigators and the sponsor The study statistician does audits of the trial conduct and the PI or study coordinator will verify that the study assessments are completed on schedule. Results are shared with the investigator team.

Ethics and dissemination

Research ethics approval	24	Plans for seeking research ethics committee/institutional review board (REC/IRB) approval **Approval obtained from:** Board Name: (Medical) Institutional Review Board Board Affiliation: University of Kentucky Phone: 859-323-7399 Email: IRBsubmission@uky.edu Address: Office of Research Integrity University of Kentucky 316 Kinkead Hall Lexington, KY 40506-0057
Protocol amendments	25	Plans for communicating important protocol modifications (eg, changes to eligibility criteria, outcomes, analyses) to relevant parties (eg, investigators, REC/IRBs, trial participants, trial registries, journals, regulators)

		NIDA, the IRB and DSMB will be informed of all protocol modifications on an ongoing basis.
Consent or assent	26a	Who will obtain informed consent or assent from potential trial participants or authorised surrogates, and how (see Item 32) -Trained and approved study staff who have completed required human subjects protection trainings will obtain informed consent.
	26b	Additional consent provisions for collection and use of participant data and biological specimens in ancillary studies, if applicable N/A
Confidentiality	27	How personal information about potential and enrolled participants will be collected, shared, and maintained in order to protect confidentiality before, during, and after the trial Participants receive a unique identifier, and all PHI is stored separately. Data are stripped of all PHI prior to analysis, and all reports are of the de-identified, aggregate data.
Declaration of interests	28	Financial and other competing interests for principal investigators for the overall trial and each study site The investigators have no competing interests
Access to data	29	Statement of who will have access to the final trial dataset, and disclosure of contractual agreements that limit such access for investigators There are no contractual agreements limiting investigators access to the final trial dataset.
Ancillary and post-trial care	30	Provisions, if any, for ancillary and post-trial care, and for compensation to those who suffer harm from trial participation -For PrEP care, participants will receive a referral for ongoing care elsewhere.
Dissemination policy	31a	Plans for investigators and sponsor to communicate trial results to participants, healthcare professionals, the public, and other relevant groups (eg, via publication, reporting in results databases, or other data sharing arrangements), including any publication restrictions -The investigators plan to present results to the study sites, at national conferences and to publish study results

	31b	Authorship eligibility guidelines and any intended use of professional writers -No plan for professional hired writers
	31c	Plans, if any, for granting public access to the full protocol, participant-level dataset, and statistical code -N/A at this time
Appendices		
Informed consent materials	32	Model consent form and other related documentation given to participants and authorised surrogates Stamped and approved study consent form is attached.
Biological specimens	33	Plans for collection, laboratory evaluation, and storage of biological specimens for genetic or molecular analysis in the current trial and for future use in ancillary studies, if applicable N/A

STATISTICAL DESIGN AND POWER: PWID

Aim 3 Analytic Plan and Sample Size Considerations. The overarching goal of this R34 is to adapt and feasibility test an evidence-based SBCM intervention, and examine preliminary efficacy of the intervention comparators (SBCM-PrEP and CDC-PrEP). Within this context, our Aim 3 pilot RCT is not designed to establish superiority of the SBCM-PREP, but to evaluate feasibility of our procedures and implementation processes, examine acceptability of methods, intervention content and format, to generate valid parameter estimates and preliminary evidence of effect sizes for application in a subsequent R01, which are preferred endpoints for many pilot trials. The proposed sample size of 80 aligns with rules of thumb and recommended sample sizes for two-arm pilot trials structured as planning for subsequent major trials. Assuming a retention rate of 90% at 6 months, there will be 36 participants per intervention group for analysis, which is sufficient for the Aim 3 pilot.

Precision Analysis. A total of 80 HIV- rural PWID will be randomly assigned into the two intervention groups. The major interest related to Specific Aim 3 is to evaluate the preliminary efficacy of the intervention conditions on the primary study outcome (PrEP initiation, measured by dispensed PrEP prescription) at 3- and 6- month follow-ups. With 36 participants per intervention condition, and utilizing a 95% confidence interval, we will be able to estimate the true probability of PrEP initiation for either trial arm within a maximum of ± 0.16.

To address Aim 3, robust analytic methods will be used for descriptive purposes and data analyses. Descriptive statistics (e.g., frequencies, proportions, means, and standard deviations) will be used to describe targeted process variables (e.g., proportion of women agreeing to enroll in the study, the number of sessions attended, engagement scores, etc.). Bivariable analyses will be used to examine potential differences in feasibility and acceptability between the two study conditions. Conventional statistical methods, such as t-tests, Chi-square, ANOVA, ANCOVA, OLS, and logistic regression will be used for preliminary analyses of the demographic and risk environment characteristics of PWID, as well as those associated with PrEP initiation. Tests will be two-sided at the 0.05 level. Similarly, to examine initiation of PrEP, as well as continuation of PrEP among those who initiated by 3 months, we will utilize frequencies, proportions, and corresponding 95% confidence intervals. Additionally, logistic regression models will be utilized to assess for group differences, adjusting for site due to its use as a stratification factor.