Building on Needle Exchange to Optimize Prevention and Treatment

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2. LIST OF ABBREVIATIONS

AIDS	Acquired immunodeficiency syndrome
ART	Antiretroviral therapy
BCHD	Baltimore City Health Department
ED	Emergency department
HCV	Hepatitis C virus
HIV	Human immunodeficiency virus
ICV	Integrated care van
JHU	Johns Hopkins University
MOUD	Medication for opioid use disorder
PrEP	Pre-exposure prophylaxis
PWID	People who inject drugs
SSP	Syringe service program
STI	Sexually transmitted infection

3. PROTOCOL SUMMARY

Building on Needle Exchange to Optimize Prevention and Treatment

Purpose:

Biomedical interventions that have direct applicability to people who inject drugs (PWID) have flourished over the past 15 years (HIV treatment as prevention, pre-exposure prophylaxis [PrEP], office-based medication for opioid use disorder [MOUD] with buprenorphine, and hepatitis C virus [HCV] treatment with direct acting agents). However, penetration of these interventions among PWID is low relative to the potential benefits. Syringe service programs (SSP) are an essential risk reduction service for PWID, and represent a potential, although under-used, interface to provide additional PWID services. The Baltimore City Health Department (BCHD) and investigators at Johns Hopkins University (JHU) have developed a dedicated integrated care van (ICV) to complement the city's mobile SSP, with the goal of extending needed biomedical interventions to PWID. The primary purpose of this trial is to determine if the ICV intervention reduces risk, improves health, and increases uptake of evidence-based services among PWID. Secondary purposes are to examine the ICV implementation, acceptability, coverage, and sustainability using a mixed methods approach, and to assess costs and cost-effectiveness.

Design:

Matched-pair cluster randomized trial.

Study Population:

PWID who are 18 years of age or older.

Study Size:

The study will be conducted at 12 neighborhood sites or clusters in Baltimore that are visited by the SSP. We aim to enroll 60 participants at each site (720 participants overall).

Treatment Regimen:

In addition to continuing weekly visits from the mobile SSP, sites assigned to the intervention will receive weekly visits by the ICV. Staffed by 1-2 medical providers, a case manager, and phlebotomist, the ICV will provide a spectrum of PWID services (e.g., rapid HIV and HCV testing, naloxone overdose kits, HIV treatment and linkage, HCV treatment and linkage, buprenorphine-based MOUD, and PrEP). The ICV will visit neighborhood sites once a week and offer services to anyone seeking them, irrespective of enrollment in the study cohort

Sites assigned to usual care will continue to receive weekly visits from the mobile SSP, but no additional services.

Study Duration:

The study duration will be approximately 36 months. Site selection and preparatory work will take 8 months. Participants will be enrolled by site, in staggered fashion, over 14

months, and followed for an additional 14 months.

Primary Objective:

To determine if the ICV intervention increases uptake of evidence-based services, reduces risk behaviors, and reduces adverse outcomes among PWID (assessed by a composite PWID score), compared with the control condition.

Secondary Objectives:

- To determine if the ICV intervention improves the HIV care continuum (among HIV-positive participants), compared with the control condition
- To determine if the ICV intervention increases HIV testing rates (among HIV-negative participants), compared with the control condition.
- To determine if the ICV intervention improves the PrEP continuum (among HIV-negative participants), compared with the control condition.
- To determine if the ICV intervention improves the HCV care continuum (among HCV-positive participants), compared with the control condition.
- To determine if the ICV intervention increases HCV testing rates (among HCV-negative participants), compared with the control condition.
- To determine if the ICV intervention increases use of MOUD (among all participants), compared with the control condition.
- To determine if the ICV intervention increases use of SSP (among all participants), compared with the control condition.
- To determine if the ICV intervention increases possession of a naloxone overdose kit (among all participants), compared with the control condition.
- To determine if the ICV intervention reduces injection drug use (among all participants), compared with the control condition.
- To determine if the ICV intervention reduces recent drug use (among all participants), compared with the control condition.
- To determine if the ICV intervention reduces sharing of drug paraphernalia (among all participants), compared with the control condition.
- To determine if the ICV intervention reduces non-fatal drug overdoses (among all participants), compared with the control condition.
- To determine if the ICV intervention reduces emergency department use (among all participants), compared with the control condition.

- To determine if the ICV intervention reduces HIV seroconversion (among HIV-negative participants), compared with the control condition.

- To determine if the ICV intervention reduces HCV seroconversion (among HCV-negative participants), compared with the control condition.

- To determine if the ICV intervention decreases mortality (among all participants), compared with the control condition.

- To describe and characterize service utilization on the ICV including, but not limited to, number of visits and unique clients served, client demographics, use of individual services (HIV testing, HCV testing, PrEP, buprenorphine-based MOUD, etc.), and overlap between ICV clients and the neighborhood PWID cohorts enrolled for the study.

Exploratory Objectives:

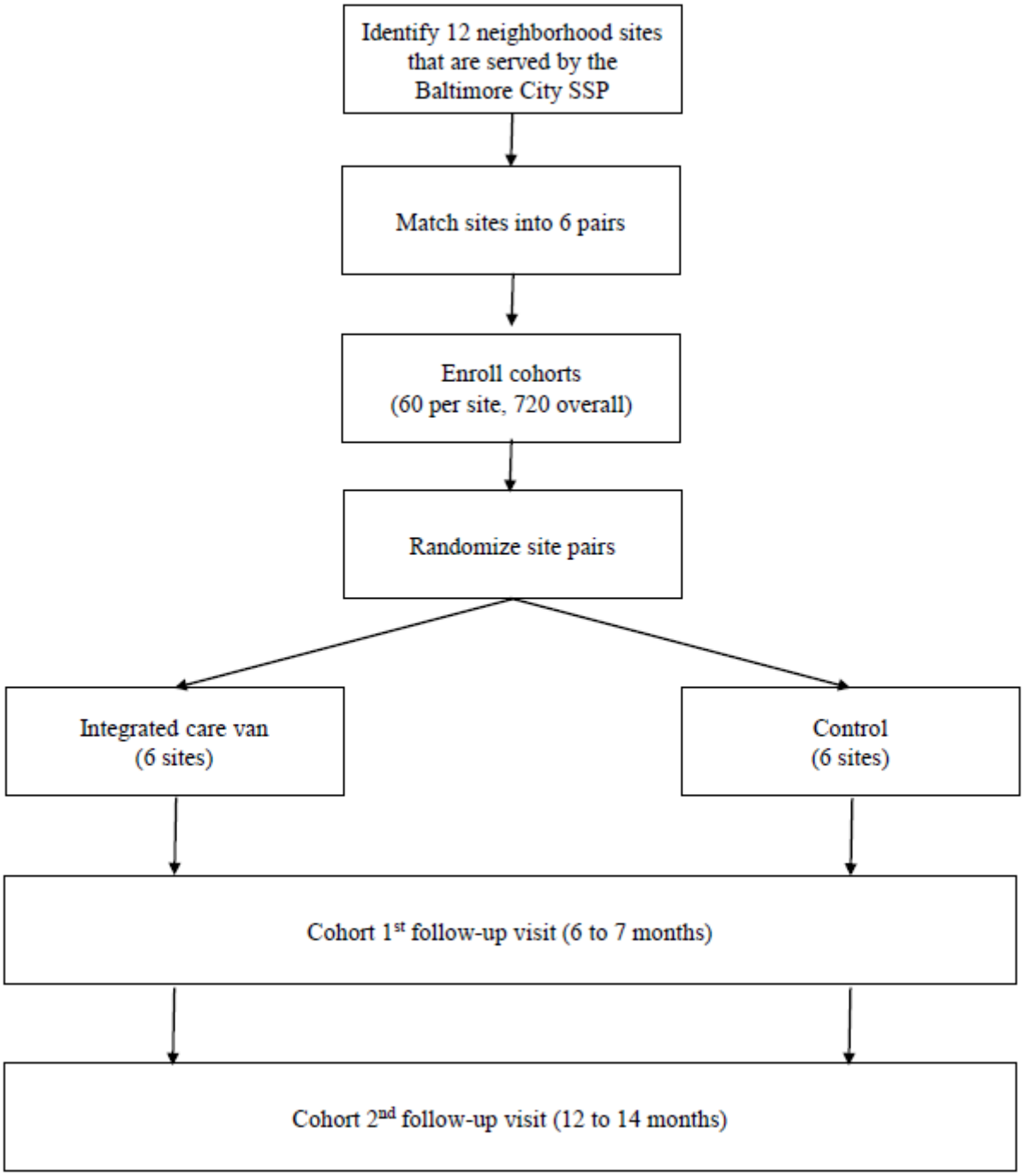
- To conduct a qualitative evaluation of barriers to service delivery for PWID, perceptions about the ICV, interest in services provided by and not provided by the ICV, and sustainability of the ICV from in-depth interviews with SSP, ICV staff, and PWID; and by key-informant interviews with policy stakeholders.

- To evaluate ICV cost and assess the potential cost-effectives of the ICV as a service delivery modality for PWID.

Study Sites:

The study will be conducted at 12 neighborhood locations (cross streets) where the Baltimore City mobile SSP provides clean needles and syringes

Overview of Study Design and Randomization Scheme:



4. INTRODUCTION

4.1 Background Information

Since the introduction of combination antiretroviral therapy (ART), studies (including many from our team) have consistently identified barriers and lower access to ART among PWID compared with other HIV risk groups.[1-6] While active substance use is a well-established barrier to adherence, it is also clear that clinicians often believe PWID are incapable of taking ART.[7] Despite dramatic strides in treating HIV-positive persons overall, PWID disparities remain. A large consortium of HIV cohorts in North America recently found that (compared with other risk groups) PWID were significantly less likely to initiate ART and to achieve viral suppression at 6- and 12-months after reaching guideline-eligibility for ART.[8] Strikingly, female PWID were 36% less likely (95% CI: 25%, 46%) to initiate ART when eligible than MSM. In another study by the NA ACCORD, of all factors assessed, PWID had the strongest association with non-retention to HIV care (68% increased risk of non-retention; 95% CI: 49%, 89%) compared with non-PWID. This pattern has emerged again with pre-exposure prophylaxis (PrEP) and hepatitis C virus (HCV) treatment. In a systematic review, PWID expressed similar levels of PrEP interest as other risk groups;[9] however a survey study found that primary care providers were significantly less willing to provide PrEP for PWID compared to all other risk groups.[10] In a PubMed search we combined the term "pre-exposure prophylaxis" with "MSM" or "men who have sex with men" and identified 373 published articles. In contrast when we combined "pre-exposure prophylaxis" with "PWID" or "people who inject drugs," only 34 published articles were identified. Tellingly, of the 34 articles, only 2 manuscripts reported actual implementation of PrEP among PWID, both from the Bangkok Tenofovir Study.[11,12] Finally, unpublished data by our group from the ALIVE study – a community-based cohort of PWID in Baltimore – found that among 269 HCV-positive participants enrolled in 2016-17, less than 10% reported linkage to HCV care and only 3% reported HCV treatment with cure. ***These data highlight the persistent pattern of disparities in access to evidence-based biomedical services by PWID.***

4.2 Rationale

A substantial body of literature supports the feasibility, acceptability, and efficacy of models in which substance use treatment and medical management are integrated in a single venue.[13,14] One small trial from over 20 years ago makes this simple point clearly: 51 methadone clients who had an untreated medical condition were randomized to either on-site treatment at the methadone clinic or referral to a nearby medical clinic, with treatment costs covered by the study. 76% assigned to integrated care attended ≥ 2 medical visits compared with 6% referred off-site (P<0.001).[15] Other randomized controlled trials, including work by our group, have found that integration of medication for opioid use disorder (MOUD) within general medical or HIV specialty clinics was associated with higher patient satisfaction, increased retention to medical and substance abuse treatment, and higher rates of negative urine drug tests, compared with separate models of care.[16-19] Pioneering work by Altice and colleagues has shown that a mobile health platform is acceptable, feasible, and effective for serving PWID populations, including vaccination, screening and treatment of latent tuberculosis, buprenorphine-based MOUD, HCV screening, and ART facilitation for HIV-positive persons.[20-24] ***We propose to build on the prior work of our team and others to implement and evaluate a PWID-focused multi-service van to bring needed biomedical services to this***

population.

4.3 Study Hypotheses

We hypothesize that a multi-service ICV will reduce risk behaviors, improve health, and increase uptake of evidence-based services among PWID.

5. OBJECTIVES

5.1 Primary Objective:

To determine if the ICV intervention increases uptake of evidence-based services, reduces risk behaviors, and reduces adverse outcomes among PWID (assessed by a composite PWID score), compared with the control condition.

5.2 Secondary Objectives:

- To determine if the ICV intervention improves the HIV care continuum (among HIV-positive participants), compared with the control condition
- To determine if the ICV intervention increases HIV testing rates (among HIV-negative participants), compared with the control condition.
- To determine if the ICV intervention improves the PrEP continuum (among HIV-negative participants), compared with the control condition.
- To determine if the ICV intervention improves the HCV care continuum (among HCV-positive participants), compared with the control condition.
- To determine if the ICV intervention increases HCV testing rates (among HCV-negative participants), compared with the control condition.
- To determine if the ICV intervention increases use of MOUD (among all participants), compared with the control condition.
- To determine if the ICV intervention increases use of SSP (among all participants), compared with the control condition.
- To determine if the ICV intervention increases possession of a naloxone overdose kit (among all participants), compared with the control condition.
- To determine if the ICV intervention reduces injection drug use (among all participants), compared with the control condition.
- To determine if the ICV intervention reduces recent drug use (among all participants), compared with the control condition.
- To determine if the ICV intervention reduces sharing of drug paraphernalia (among all participants), compared with the control condition.

- To determine if the ICV intervention reduces non-fatal drug overdoses (among all participants), compared with the control condition.

- To determine if the ICV intervention reduces emergency department use (among all participants), compared with the control condition.

- To determine if the ICV intervention reduces HIV seroconversion (among HIV-negative participants), compared with the control condition.

- To determine if the ICV intervention reduces HCV seroconversion (among HCV-negative participants), compared with the control condition.

- To determine if the ICV intervention decreases mortality (among all participants), compared with the control condition.

- To describe and characterize service utilization on the ICV including, but not limited to, number of visits and unique clients served, client demographics, use of individual services (HIV testing, HCV testing, PrEP, buprenorphine-based MOUD, etc.), and overlap between ICV clients and the neighborhood PWID cohorts enrolled for the study.

5.3 Exploratory Objectives:

- To conduct a qualitative evaluation of barriers to service delivery for PWID, perceptions about the ICV, interest in services provided by and not provided by the ICV, and sustainability of the ICV from in-depth interviews with SSP, ICV staff, and PWID; and by key-informant interviews with policy stakeholders.

- To evaluate ICV cost and assess the potential cost-effectives of the ICV as a service delivery modality for PWID.

6. STUDY DESIGN

This is a comparative effectiveness, two-arm, matched-pair cluster randomized trial. The study will be conducted in 12 neighborhood sites in Baltimore City that receive services from the mobile SSP. Eligible PWID will be recruited at each site prior to randomization. In each site pair, one site will be assigned to the control condition and the other site to the ICV intervention.

1. Control condition – Sites assigned to usual care will continue to receive weekly visits from the mobile SSP, but no additional services.
2. Intervention – In addition to continuing weekly visits from the mobile SSP, sites assigned to the intervention will receive weekly visits by the ICV. Staffed by a medical provider, nurse, and phlebotomist, the ICV will provide a spectrum of PWID services (e.g., rapid HIV and HCV testing, naloxone overdose kits, HIV treatment and linkage, HCV treatment and linkage, buprenorphine-based MOUD, and PrEP). The ICV will visit neighborhood sites once a week and offer services to anyone seeking them, irrespective of enrollment in the study cohort

In addition to the quantitative endpoints from the trial, we will also collect qualitative

data to understand whether the ICV was recognized by clients and how ICV service provision was perceived by different stakeholders. Additionally, a cost-effectiveness evaluation is planned.

The study duration will be approximately 36 months. Site selection and preparatory work will take 8 months. Participants will be enrolled by site, in staggered fashion, over 14 months, and followed for an additional 14 months.

7. STUDY POPULATION

We will recruit cohorts of PWID at each neighborhood site, with roll-out of the study arm allocation (intervention or control condition) near the conclusion of cohort enrollment. Cohort participants will be followed for 14 months during the intervention phase. The exploratory objectives require i) collection of qualitative data from key stakeholders, including PWID, SSP staff, ICV staff, and policymakers, ii) conduct cost-benefit analyses.

7.1 Enrollment Criteria

The enrollment criteria were designed to enroll high-risk PWID. To optimize enrollment of HIV-positive individuals, we structured the inclusion criteria so that HIV-positive individuals did not have to be recent injectors. HIV point-of-care rapid testing (with pre- and post-test counseling) will be conducted as part of study screening. An important component of study recruitment (and follow-up) will be the use of biometric identification (iris scans) to prevent duplicate enrollments of participants at different neighborhood sites (and to ensure proper attribution of follow-up visits). We have found this method to be highly acceptable to the target population, rapid (about 20 seconds), accurate, and safe (the program uses a proprietary algorithm to generate a unique, reproducible code from iris images, but does not store photographic images).

7.1.1 Participant Inclusion Criteria

Inclusion criteria for cohort participants

Men and women who meet all of the following criteria are eligible for inclusion as a cohort participants:

- 18 years of age or older
- Injection drug use history according to HIV status
    - If HIV-negative
        - Injected 4 or more days in the prior 30 days
          or
        - Shared needles/syringes in the prior 6 months
    - If HIV-positive
        - History of injection drug use

7.1.2 Participant Exclusion Criteria

Exclusion criteria for cohort participants

Men and women who meet any of the following criteria are ineligible for inclusion as a cohort participants:

- Not competent to provide written informed consent
- Unwilling or unable to provide a blood sample

7.2 Recruitment Process

We will enroll cohorts of participants at each of the 12 study sites, with a target enrollment of 60 participants at each site (720 overall). Data from the cohorts will be used to draw inferences about the acceptability and effectiveness of the ICV. We have taken steps to minimize selection or follow-up bias between the ICV and cohort activities. First, cohorts will be recruited prior to randomization (so research staff will not know which sites will receive the intervention when they are recruiting the cohorts). Second, the cohorts will be recruited and followed by a dedicated research team on a research van that is separate from the mobile SSP and the ICV. This separation of research from the ICV will minimize the risk that research activities affect ICV service utilization. The goal will be to recruit PWID clients of the mobile SSP and other PWID in the neighborhood who might access services on the ICV.

We will use a dedicated research van to recruit individuals at each of the neighborhood sites (near cross-street locations where the Baltimore City mobile SSP makes regular stops). The research van will accompany the SSP van to sites where it is actively recruiting cohorts. We will post study recruitment flyers on the SSP van and staff on the van will refer interested clients to the research van. Additionally, research staff will encourage word-of-mouth referrals from participants.

7.3 Participant Retention

Our experienced team is well aware of the challenges of PWID study retention. Once a participant enrolls in the cohort study, the research team will make every effort to retain him/her for the full study period (~14 months). Study site staff will develop and implement local standard operating procedures to target this goal. Components of such procedures include:

- Thorough explanation of the study visit schedule and procedural requirements during the informed consent process and re-emphasis at each study visit.
- An experienced van research team with a lifelong knowledge of Baltimore City.
- Collection of detailed and multifaceted locator information at the baseline visit, and active review and updating of this information at each subsequent visit.
- Use of mapping techniques to establish the location of participant residences and other locator venues.
- Visit reminder calls and letters.
- Reimbursed “check-in” phone contacts between the scheduled study visits (i.e., ~3 months and ~9 months)
- Regular communication with the PWID community at large to increase awareness about follow-up and the research van’s current and future location.
- Use the van to visit participants’ last known residence (“knocking on doors”).

8. INTERVENTIONS

Study sites (clusters) will be randomly allocated to either the ICV intervention or to the control condition.

Table 1. Comparison of services with the mobile SSP alone (control) and the SSP combined with the ICV (intervention).

Type of service	SSP (control)	ICV intervention
Risk reduction		
SSP	Confidential (ID-based) SSP using hybrid exchange/distributive model	Same
Overdose prevention /response	SSP program leads city-wide initiative to train and provide naloxone overdose kits to PWID, their friends, and family	Same, although ICV will provide increased opportunities for naloxone kit training and distribution
PrEP	Refer to PrEP program offered at BCHD clinics	Onsite provision of PrEP education, clinical /lab screening for PrEP eligibility, PrEP prescription, and monitoring
HIV care cascade		
HIV testing	Free (non-rapid) HIV and syphilis testing offered on the van once or twice a year	Free rapid HIV testing offered daily
Linkage to HIV care	No routine service	Intervention team tracks care cascade using Data to Care program, peer navigators link clients to care.
ART adherence /viral suppression	No routine service on mobile SSP.	ICV team communicates with HIV treatment providers in city, tracks patients who have lapsed with ART prescription fills, on-site case management to address barriers, laboratory testing on van to assist clinic, ART refills provided
Substance abuse treatment	Referral to buprenorphine- or methadone-based MOUD with dedicated slots for SSP clients	Low-barrier, same-day prescription of buprenorphine, with transition community-based MOUD
Additional PWID services		
HCV care cascade	Referral to BCHD clinics or elsewhere for testing, disease staging, and treatment	HCV antibody and HCV RNA testing on ICV, initiate HCV treatment on ICV with case management support. Referral for advanced liver disease.
Wound care	Referral to primary care provider or emergency department	Wound care-certified NP offers acute and chronic wound care management on the van, with referral for specialized treatment[25]

8.1 Control Condition

Control (usual care) sites will receive services currently provided by 2 Baltimore City Health Department mobile SSPs. Together, these vans visit ~15 sites around Baltimore City each week (busy sites are visited more than once per week). In 2015, the SSP had 16,164 visits by 4512 unduplicated clients, and distributed 1,071,927 clean syringes. In addition to needle/syringe services, the SSP vans offers outreach HIV and syphilis testing (not rapid testing) approximately twice a year (the SSP van is not normally staffed for phlebotomy). Second, the SSP provides opioid overdose reversal training and distributes naloxone nasal spray kits directly to clients. Third, the SSP can refer clients to opioid agonist treatment programs that have dedicated treatment slots for SSP referrals. For other services (HIV management, PrEP, HCV testing and treatment evaluation, wound care, etc.) the SSP provides no direct services.

8.2 ICV Intervention

The integrated care van (ICV) is a medically-staffed, mobile health facility that will provide PWID-oriented medical services and case management. ICV services will include 1) linkage, support, and medical management for HIV-positive clients, 2)

screening and initiation of pre-exposure prophylaxis (PrEP) for high-risk HIV-negative PWID, 3) low-barrier initiation of buprenorphine/naloxone and transfer to community-based medication assisted treatment, 4) HCV testing, liver disease staging, and HCV treatment with direct acting agents, and 5) wound care. The ICV will visit different neighborhood stops/sites according to an established weekly schedule. The ICV is a structural intervention that will provide the staff, physical space, equipment, and information technology to bring a package of evidence-based biomedical services to the outermost public health-PWID interface. The ICV is a 40-foot Freightliner that includes 2 patient exam rooms, a waiting space, a phlebotomy/laboratory area, and a bathroom. Electricity is provided by an on-board generator. The ICV will be staffed by BCHD employees, including one or two medical providers (physicians and mid-level practitioners), a case manager, and a phlebotomist/driver. The clinical staff are experienced in HIV treatment, PrEP screening and management, HCV treatment, buprenorphine (with Drug Enforcement Agency waiver), and wound care. Under the auspices of the BCHD, the ICV will provide services to anyone who visits the unit.

9. STUDY PROCEDURES/EVALUATIONS

9.1 Clinical Evaluations and Procedures

Eligible participants who meet inclusion criteria and provide written informed consent will be enrolled to the local cohort. Cohort participants will complete a baseline study visit, most often on the day of screening, and will be asked to complete follow-up visits at 7 months and 14 months, for a total of 3 study visits. Study visits will include the following evaluations:

- Biometric capture (iris scan) to assure identity
- Blood draw and urine sample
- Collection of contact and locator information
- Interviewer-administered survey covering the following domains
    - Demographics
    - Quality of life
    - Engagement/experience with HIV, HCV, PWID services
    - Alcohol and drug use
    - Injection- and sex-related risk behaviors
    - Depression symptoms
    - Health care utilization

9.2 Laboratory Evaluations

Table 2. Laboratory testing for cohort participants

Test	CLIA status	Visits measured	Participants included	
			HIV-negative	HIV-positive
bioLytical Laboratory INSTI HIV-1/HIV-2 point-of-care Rapid HIV test	Waived	SCR	●	●
CD4 cell count, flow cytometry, JHH	Certified	V00		●
HIV-1 antibody test	Certified	V14	●	
HIV RNA	Certified	V00, V07, V14		●

Table 2. Laboratory testing for cohort participants

Test	CLIA status	Visits measured	Participants included	
			HIV-negative	HIV-positive
Tenofovir diphosphate concentration in peripheral blood mononuclear cells	Non-certified	V00, V07, V14 (among subset reporting linkage to PrEP)	●	
Hepatitis C virus (HCV) serology	Certified	V00	●	●
HCV RNA	Certified	V00 & V14 (in HCV seropositive only)	●	●
Urine drug screening, high resolution accurate mass spectrometry	Certified	V00, V07, V14	●	●

SCR, screening; V00, baseline visit, V07, 7-month visit; V14, 14-month visit

9.2.1 Biohazard Containment

As the transmission of HIV and other blood-borne pathogens can occur through contact with contaminated needles, blood, blood products and body fluids, appropriate blood and secretion precautions will be employed by all personnel in the drawing of blood and shipping and handling of all specimens for this study, as currently recommended by the United States Centers for Disease Control and Prevention. All infectious specimens will be transported in accordance with United States regulations (42 CFR 72).

9.2.2 Total Blood Volume

We will draw a blood volume of 25 cc at the baseline, 7 month, and 14-month visits. The maximum amount of blood drawn over an 8-week period is 25 cc.

9.3 Schedule of Procedures/Evaluations: Timing and Definitions

Follow-up visits at ~7 months and ~14 months following the baseline visit.

9.3.1 Screening

Following oral consent (OCS) for screening (see **Figure** for flow diagram), participants will be asked to complete an iris scan to check for duplicate enrollment (individuals will not be able to enroll more than once). The iris scans are converted by proprietary software into long encrypted codes that are used to identify persons who have participated previously in the study (Iris ID, Inc.: EAC2500 Software and iCAM TD100 dual iris imager. The iris scan system protects participant confidentiality because the iris images are not saved in the system and codes derived from the scans cannot be used to reconstruct iris scan images. Finally, the codes generated by the iris scans at screening

will not be stored – they will only be used to cross-reference with the database to quickly identify individuals who have already participated and prevent such individuals from entering the study a second time. Participants with no match in the iris scan code database will be asked to answer screening questions. Participants that remain eligible after completing the screening questions, will be asked to provide written informed consent.

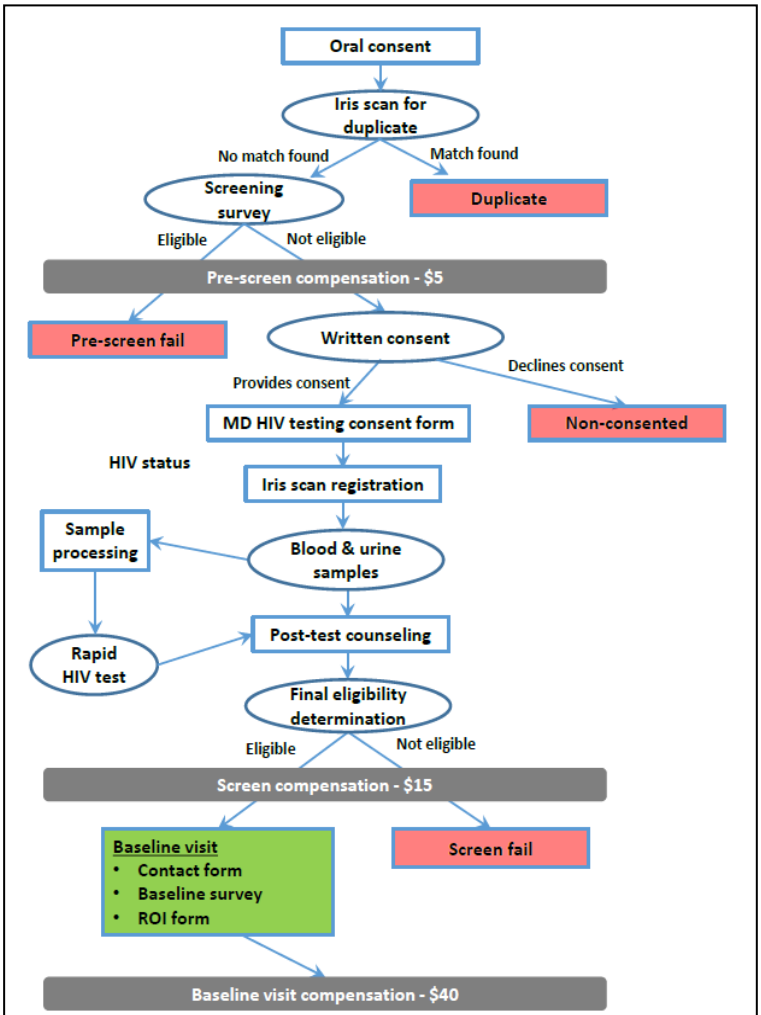


Figure. Screening/Enrollment Diagram

Following written informed consent, participant iris scan codes will be registered in the database to prevent duplicate enrollment in the future. Study staff will complete a State of Maryland HIV testing form and provide pre-test counseling. Participants will be asked to provide blood and urine samples, and have a fingerstick for a rapid HIV test. We will use the INSTI HIV-1/HIV-2 rapid test (bioLytical Laboratories, Richmond, BC, Canada), a 3rd generation HIV 1/2 test, which is also used by the BCHD. After specimen collection and rapid testing, research staff will provide post-test HIV counseling, discuss eligibility for the cohort study, and offer cohort enrollment to eligible individuals. Participants with negative HIV test results will be counselled to resume routine testing (every 6 to 12 months) depending on ongoing risk factors. Participants with invalid results will be advised to retest in the next 1 month. Participants with a positive HIV test (and who have not previously tested positive) will be referred to a BCHD facility for confirmatory HIV testing and linkage to care. After HIV post-test counseling, we will make a final eligibility determination on the basis of 1) the screening survey, 2) ability to provide a blood sample, and 3) results of the rapid HIV test. These data will be applied to the study inclusion/exclusion criteria described in **Section 7.1** to determine eligibility to join the cohort.

9.3.2 Enrollment

Participants that are eligible for the cohort will be offered enrollment. Research staff will conduct the baseline visit as soon as possible following screening (usually the same day).

9.3.3 Follow-up

There will be 2 follow-up cohort visits at ~7 and ~14 months. Study visits will include 1) collection of contact information, 2) an interviewer-administered questionnaire, 3) blood draw, and 4) urine sample. The questionnaire will cover the following domains: socio-demographics (age, race, sex, education, employment, geo-coding, incarceration), substance use (injection and non-injection drugs, alcohol [AUDIT]), drug using network, overdose history, injection practices (frequency, needle/syringe sharing, drugs used), sexual transmission risk behaviors (number of partners, concurrency, condom use, MSM, sex work), depression (PHQ-9), quality of life (SF-12), social support, and resource utilization (SSP, HIV care, HCV care, PrEP, MOUD, other substance abuse treatment modalities, emergency department use, hospitalizations, time and money spent obtaining medical care).

9.3.4 COVID-19 Impact on Study

The COVID-19 pandemic initially struck Baltimore, MD in March 2020 and had substantial effects on this study. The pandemic led to suspension of both study cohort follow-up visits and the ICV intervention for many months. The study achieved full enrollment (N=720, n=60 at each of the 12 sites) between July 2018 and August 2019. Two cohort follow-up visits were planned at 7 months and 14 months. At the time of pandemic-related shut downs we had completed the 7-month visits at all 12 sites. Additionally, we had completed the 14-month visit at 4 of the 12 sites. We switched to telephone-based follow-up visits, which included the participant survey but not laboratory tests. We also added questions to assess the effects of COVID-19 among the study cohort. We resumed in-person visits in July 2021. For the purposes of this trial, we decided to base primary analyses on the baseline visit and the first follow-up visit (7 months). Although this does not include the longer follow-up that we planned, it includes only data that was collected prior to the pandemic. In secondary analyses we will consider data collected during and after pandemic-related shut downs.

10. ASSESSMENT OF SAFETY

10.1 Safety Assessment Overview

This section provides information on the definition of adverse events (AE), serious adverse events (SAE) and the procedures for reporting. Procedures for prompt reporting of AE and SAE will be standardized across the field sites.

10.2 Definition of Adverse Events (AE)

An AE is any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or diagnosis that occurs in a study participant during the conduct of the study regardless of the attribution (i.e., relationship of event to medical treatment/study product/device or procedure/intervention). This includes any occurrence that is new in onset or aggravated in severity or frequency from the baseline condition.

10.3 Definition of serious adverse events (SAE)

An SAE is defined as any untoward medical occurrence that:

- Results in death
- Is life-threatening
- Requires inpatient hospitalization or prolongation of existing hospitalization
- Results in persistent or significant disability/incapacity
- Is a congenital anomaly/birth defect
- Is an important medical event that may not be immediately life-threatening or result in death or hospitalization but may jeopardize the patient or may require intervention to prevent one of the other outcomes listed in the definition above).

10.4 Adverse Event Procedures and Reporting Requirements

The research procedures in our study include study visits with cohort participants and key-informant interviews. These research procedures are minimal risk (involve only a blood draw), and do not include a drug or medical device. Furthermore, study sites (or clusters) are the unit of randomization, not individual participants. Participants at intervention sites have access to the intervention (ICV), but are not required to seek or accept the intervention. The intervention itself is being rolled out by the BCHD, and this study is a formalized assessment of the intervention. Finally, the study population of active PWID have substantially higher risks of morbidity and mortality than persons in the general population. Given these considerations, our reporting obligations for the trial focus only on events that are more likely than not to be associated with study procedures (study visits or key-informant interviews. Two types of events will be reportable:

1. Unanticipated problems involving risks to participants or others will be reported to the JHM IRB within 10 working days (unless the event is death, in which case # 2 applies). Such events are defined as:
    a. The information is unexpected in terms of nature, severity, or frequency, given:
        i. The research procedures described in the protocol and informed consent document; and
        ii. The characteristics of the subject population being studied
    b. The information indicates that the participants or others are at greater risk of harm (including physical, psychological, economic, or social harm) than was previously known or recognized.
2. Deaths of study participants in close association with study procedures will be reported to the IRB within 3 working days.

11. CLINICAL MANAGEMENT

11.1 Clinical Management of Adverse Events

Research staff will interact with participants at study visits and during the intervention (dispensing non-cash incentives). Research staff will refer participants to a clinic or hospital for medical conditions that arise.

11.2 Criteria for Permanent Intervention Discontinuation or Premature Study Discontinuation

Potential reasons for discontinuation of intervention or study are:

- Request by the participant to stop.
- Request of study coordinator if s/he thinks the intervention is no longer in the best interest of the participant.
- At the discretion of the IRB/Ethics Committee, Office for Human Research Protections (OHRP), other government agencies as part of their duties, or investigator

12. STATISTICAL CONSIDERATIONS

12.1 Overview and General Design Issues

The primary objective of this study is to determine whether provision of an ICV at neighborhood sites, served by the mobile SSP in Baltimore, reduces risk, improves health, and increases uptake of evidence-based services among PWID. We will address this objective with a two-arm, matched-pair, 12-site cluster randomized trial. Neighborhood sites allocated to the control condition, will continue to receive SSP services. Neighborhood effects will be assessed in cohorts of PWID participants enrolled at each study site, prior to intervention roll-out, and followed for up to 14 months. During the trial, we will collect qualitative data from PWID (who used and did not use ICV services), ICV staff, and other stakeholders. Finally we will collect costing data to facilitate evaluation of cost-effectiveness.

12.2 Study Endpoints

Primary and secondary study endpoints will be assessed at follow-up cohort visits on the basis of laboratory testing, structured interviews, and external sources of data, including treatment episodes (emergency department visits, hospitalizations, outpatient clinic visits) captured by Chesapeake Regional Information System for Our Patients (CRISP) and the National Death Index. Exploratory endpoints will be assessed on the basis i) costing data collected during the study, and ii) qualitative key informant interviews.

12.2.1 Primary Endpoint

Composite PWID score (service access, risk behaviors, adverse outcomes). This outcome will be assessed in participants at all visits. To capture the multi-faceted nature of the ICV intervention and the array of health issues relevant to PWID, we developed a composite score that will be captured at baseline and recalculated at each follow-up visit. We developed a scoring rubric (**Appendix**) based on WHO guidelines for evidence-based PWID services,[26] a predictive risk model for HIV seroconversion among PWID developed by the Baltimore-based ALIVE study,[27] the HCV care continuum,[28] and the overdose epidemic.[29]

12.2.2 Secondary Endpoints

- HIV care continuum (among HIV-positive participants).
- Recent HIV testing (among HIV-negative participants).
- PrEP continuum (among HIV-negative participants).
- HCV care continuum (among HCV-positive participants).

- HCV testing (among HCV-negative participants)
- Engagement in MOUD (among all participants).
- Engagement in SSP
- Possession of a naloxone overdose kit (among all participants).
- Injection drug use (among all participants)
- Recent drug use (among all participants) – Urine drug test positive for fentanyl (metabolite), heroin (morphine or 6MAM), cocaine (metabolite), or amphetamines
- Sharing drug paraphernalia (among all participants)
- Non-fatal drug overdoses (among all participants)
- Emergency department use (among all participants).
- HIV seroconversion
- HCV seroconversion
- All-cause mortality (among all participants).

12.2.3 Exploratory Endpoints

- Qualitative assessments among key stakeholders.
- Costs and cost-effectiveness

12.3 Study Hypothesis

We hypothesize that the availability of an ICV that provides evidence-based PWID-focused services will reduce risk, improve health, and increase uptake of evidence-based services among PWID.

12.4 Sample Size Considerations

To estimate the power to correctly reject a null hypothesis, we used simulation methods assuming a normally distributed composite PWID score. We adapted the methods of Arnold et al.[30] for using mixed effects logistic regression random intercepts for cluster (SD = .22) and participant (SD = 1.05) with one baseline and one follow-up assessment, 80% retention, and a similar treatment effect at each follow-up. With an initial sample size of 720 participants, we would have 80% power if the true person-level composite scores were .33 standard deviations higher at follow-up at the target sites than at the control sites, controlling for composite scores at baseline, random variation across study sites, and random variation across individuals. Using Cohen's criteria, this would correspond to a small-medium effect size.[31]

12.5 Study Site Selection and Pair Matching

We will use a parallel cluster randomized trial, in which random allocation to the experimental condition occurs at the site- (or cluster-) level rather than at the participant-level. Like other randomized designs, cluster randomized trials are methodologically rigorous and yield strong inferences about intervention effectiveness.[32,33] Cluster randomized trials are well-suited to implementation research because participant-level randomization is often impractical with multi-faceted or structural interventions and is susceptible to contamination bias in this setting. The SSP vans currently serve 15 neighborhood sites across the city. We will select 12 of the sites to include in the cluster randomized trial. Several factors are relevant to site selection. We must consider proximity of the sites. If two sites are very close together, there may be contamination, where the intervention delivered at one of sites affects the proximal site as well. Where there is a high risk of overlap between two sites, we will exclude one of the sites or consider the two sites to be a single site in the trial.

Because the number of randomly allocated units in this cluster randomized trial is small, we anticipate using a matched-pair design. The idea is to identify pairs of sites that are similar to one another in important characteristics, with one site in each pair randomized to the intervention and the other site to usual care. To assess for good site pairings, we will review all available BCHD data about the different SSP sites – number of clients accessing services each week, client demographic characteristics, and HIV prevalence. Additionally, we will interview current SSP staff to capture qualitative aspects of the different sites. At the conclusion of this process we will identify 12 sites (6 pairs) for the trial. Of note, cohort recruitment at the sties will be staggered, whereby recruitment will begin at the first 2 pair (4 sites), then move to a second set of 2 pair, and finally to a third set of 2-pair.

12.6 Randomization and Masking Procedures

Once the randomization scheme is finalized (including consideration of pair-matching) a statistician, who is independent of the study will randomize sites in pairs using a commercial software program. The statistician will withhold results until cohort enrollment is complete or nearly complete for a given pair of sites. When cohort enrollment in a given pair is complete or near complete, the statistician will notify the team of the random assignments for the sites in a given pair. The nature of the intervention precludes masking.

12.7 Analysis Plan

12.7.1 Analysis plan for primary and secondary endpoints

We will estimate the impact of the ICV on the composite primary outcome which incorporates the following: HIV prevention, testing, and treatment; HCV prevention, testing, and treatment; substance use and treatment; overdose; and healthcare utilization (see Appendix). We will also estimate the impact of the ICV on the separate measures that make up the composite outcome, including the HIV care cascade, the PrEP continuum, MAT engagement, and linkage to HCV treatment. The outcomes will be continuous (composite primary outcome), ordinal (HIV care cascade, PrEP continuum, HCV linkage), and dichotomous (MAT), and the analytic samples will vary depending on

the outcome. For all outcomes, the data will have the same structure, with time (*t*) nested within participants (*i*) nested within SSP sites (*j*). The three-level structure of the data will induce correlations in the outcomes within sites and within participants, and this will be addressed by using random intercepts for site and random intercepts for participants. Fixed effects will include covariates for calendar time (a linear, quadratic, spline terms, or indicators as indicated by exploratory data analysis), indicator for 6-month follow-up assessment, a time-varying indicator for ICV exposure status, and follow-up-by-ICV-status interaction terms. This general linear model can be expressed as:

$$\pi_{ijt} = \beta_0 + U_{0i} + U_{0j} + ICV_{ijt}\beta_1 + FU_{ijt}\beta_2 + ICVxFU_{ijt}\beta_3 + \boldsymbol{x}'_{ijt}\boldsymbol{\gamma} + \boldsymbol{z}'_j\boldsymbol{\zeta}$$

where: π_{ijt} denotes the linearized expected outcome for participant i at SSP site j on occasion t ; β_0 is the overall intercept; U_{0_i} and U_{0_j} are normally distributed person-level and site-level random intercepts; ICV_{ijt} is an indicator for participation being at an ICV site, FU_{ijt} is a binary indicator for the 6-month follow-up assessment; $ICVxFU_{ijt}$ is an ICV-by-follow-up interaction term; $\boldsymbol{x}_{ijt}$ is a vector of participant-level covariates with $\boldsymbol{\gamma}$ the vector of corresponding fixed-effects regression parameters; $\boldsymbol{z}'_j$ is a vector of SSP site covariates (including intervention phase) with $\boldsymbol{\zeta}$ the vector of corresponding fixed effects; and ε_{ijt} are error terms. The null hypothesis of no significant group-by-time interaction at the follow-ups can be tested using a 1-df F-test of H_0: $\beta_3 = \mathbf{0}$. The form of π_{ijt} and the expected distribution of the residuals will be specified based on the specific outcome. For the composite outcome, we will use mixed effects linear regression with an identity link function and normally distributed residuals.

The above-described model does not have a coefficient for matched-pair, and therefore "breaks the pairing." This approach may be more statistically powerful when the matching accounts for little variability among clusters,[33] and we expect that to the case given the limited information that was available for conducting the matching. How much variability is accounted for by the matching will be based on reduction in the variance of the cluster-level random intercept when including fixed effects for matched-pairs, and a likelihood ratio test comparing models with and without fixed effects for matched-pairs.

For ordinal outcomes, such as an individual's location along the HIV care cascade or PrEP continuum, mixed effects ordinal logistic regression is a natural analytic approach. Such a method assumes an underlying continuum of propensity for viral suppression or PrEP adherence. In a classic example, Aiken and colleagues[34] used ordinal logistic regression in a randomized trial to model movement along a mammography continuum with ordered outcome categories including doing nothing, contacting a healthcare provider, making an appointment, and actually receiving a mammogram—these outcomes parallel the care cascade and PrEP continuum. Gibbons and Hedeker[35] described using ordinal logistic regression in a three-level random effects model, as we propose here.

The ordinal logistic model is also referred to as the proportional odds model as it assumes that ICV exposure has the same effect on transitioning across the various cascade/continuum thresholds. Thus, the interaction between follow-up and ICV status

would be interpreted as the change in the log-odds of being past any given threshold in the care cascade (e.g., recent prescription for ART) with ICV exposure, controlling for other factors in the model, including person-specific and site-specific, random intercepts. In our analyses, we will evaluate the proportional odds assumption through the use of the Score test.[31] If the proportional odds assumption is violated, we will proceed with a nested dichotomies approach using a logit link function. It is also possible that the three-level ordinal logistic model may not converge. In that case, we will also use nested dichotomies. With nested dichotomies,[31] we would first dichotomize outcomes between the first and second steps of the care cascade (or PrEP continuum) and evaluate the effect of the intervention on the odds of being at least linked to care; in a second model limited to those at least linked to care, we would evaluate the effect of the intervention on the odds of being engaged in care; and so forth.

For the dichotomous outcome of MOUD use in the last 30 days, we will follow the same general formula described above using mixed effects logistic regression with a logit link function and a binomial residual distribution. Outcome analyses will be preceded by preliminary analyses examining bias in intervention assignment and potential baseline confounders of the relationship between assignment and the primary outcomes. We shall evaluate and adjust for any potential confounders in adjusted outcome analyses. All analyses will be conducted in Stata and will include the use of the random effects gllamm procedures with Huber/White variance-covariance estimators.

The composite PWID score will be calculated for each participant at each study visit according to the rubric in the **Appendix**, where a higher score indicates higher risk for adverse events or lower use of evidence-based PWID services. At the follow-up visits, we will calculate each participant's change in score from baseline. We will estimate the association between ICV cluster and change in the score with a multi-level linear regression model, similar to that shown above. In a supplementary analysis, we will convert follow-up scores to binary outcomes that indicate whether the score has decreased from baseline (improved) or not. In this case we will use a logistic regression model.

We are aware of the risk of attrition in this study, and our sample size estimates have accounted for up to 20% attrition, despite intensive retention efforts. We will examine whether missingness is associated with observed data using standard methods.[36-38] If we do identify predictors of missingness (i.e., data are not missing completely at random [MCAR]), we will conduct a second set of outcome analyses using multiple imputation to evaluate the robustness of the primary outcome analyses to missingness and report estimates based on multiple imputation that would be valid based on the assumption that the data are missing at random (MAR) as opposed to not missing at random (NMAR). As missing data are expected to follow multiple distributions, we will impute using chained equations.[39] We will produce imputed datasets ($m > 10$), run outcome analyses on all sets, and derive point and standard error estimates for treatment effects and other parameters from the distribution of estimates from the outcome analyses with imputed datasets. We will implement multiple imputation using the Stata "mi impute chained" and "mi estimate" procedures.

12.7.2 Analysis plan for qualitative evaluation of HIV treatment incentives

Qualitative data analysis involves the search for patterns in data and for ideas that help to explain the presence of those patterns. Transcripts from in-depth interviews (IDIs) with ICV and SSP staff, PWID participants, and city and state health department officials will be entered and managed in NVivo. Separate coding schemes will be developed for PWID (ICV and non-ICV clients) and the other two groups of city and state health department staff (city and state health department officials, ICV and SSP service providers). An iterative coding process in NVivo will be used to conceptually name the data and reduce it to manageable units of information that cover broad and general categories. Codes will be informed by the questions in the qualitative guides, and new themes that emerge from the data will be analyzed through a grounded theory approach, allowing for themes to emerge and ensuring that the knowledge assembled from the observational data is not subjected to the themes solely established through the interview guide. Two coders will conduct open-coding on three transcripts to develop initial coding schemes. After discussion and development of a combined draft scheme, two more interviews will be coded, and these will be further discussed and inform a final coding scheme under the guidance of Dr. Sherman. Through weekly meetings, a team approach to data analysis will be employed, whereby different analysts provide feedback on emerging interpretations and check emerging categories against the raw data. In this way, an "audit trail" will be used to help ensure trustworthiness of findings, gather input from multiple perspectives, and enhance reliability.

12.7.3 Analysis plan for cost-effectiveness

Overview. In accordance with the recommendations of the 2nd US Panel on Cost-Effectiveness in Heath and Medicine,[40] we will: inventory and value the resources consumed in the ICV intervention; estimate intervention effectiveness in regards to viral suppression, HIV infections averted, HCV treatment, and MOUD use; estimate treatment costs averted and QALYs saved for each type of effectiveness; and determine whether the ICV is cost-saving, cost-effective, or not cost-effective.

Cost analysis. We will estimate the cost of delivering the program locally from payer, societal, and health care perspectives. The societal perspective will incorporate broader costs, including non-medical costs to participants and costs reflected in the newly-recommended impact inventory.[41] We will use a micro-costing approach[42-44] to directly enumerate the cost of every output used in the intervention such as staff time spent on each intervention activity, facility space, equipment and materials. In-kind contributions will also be enumerated and costed. Sources of data will include project records, salaries, cost worksheets, project manager interviews and a project manager survey. The program manager will complete a survey to quantify per unit costs for program resources, including procedure-specific resources, general resources, fixed resources, and variable resources. The labor hours will be converted to labor cost by multiplying the staff time by hourly wage rate (including fringe benefits) of the specific staff person who performed the activity. Unit costs for in-kind contributions will be based on market rates. Costs for participant time, travel, and child or elder care will be based on prevailing local wage costs. Cost data for each type of resource will include a "best estimate", and a credible range for unit costs will be established by asking program staff to provide upper and lower bounds for any uncertain cost estimates. Questions will be added to the questionnaire to capture participant time spent in the intervention and money spent in

travel to and from the intervention. We will pilot-test and refine data collection instruments and methods during the formative phase. In addition to ongoing, integrated cost data collection, it is expected that intensive cost data collection will occur during at least two time periods during the intervention phase. During these periods members of the costing team will be on-site.

Upon completion of cost data collection, the costing team will conduct a preliminary cost analysis of the ICV intervention. We will estimate the cost overall of delivery the intervention as well as the cost per visit and cost per person-year. The cost estimate will allow us to establish effectiveness thresholds required for the interventions to be cost saving, cost-effective, or highly cost-effective. Cost-effectiveness analysis will be conducted following the final outcome analyses.

Effectiveness, medical costs, and QALYs. Expected outcomes among participants with and without the ICV will be based on the primary outcome analyses and will include HIV care engagement, adherent PrEP use, HCV treatment, and MOUD engagement. We will estimate HIV and HCV incidence among participants and contacts using Bernoulli process models[45] of intercourse and injecting with transmission probabilities based on an updated review of the literature and behavioral patterns based on participant assessments. We will also rely on the literature for estimates of lifetime treatment costs and quality-adjusted life years (QALYs) associated with different health states, both discounted at 3% per annum.[40,46]

Incremental cost-effectiveness. The cost-utility ratio will be computed based on the estimation of net incremental cost (difference between the incremental intervention costs and the incremental treatment costs averted) divided by the QALYs averted. The intervention will be considered cost-saving if the incremental intervention cost less than the incremental treatment cost averted, considered cost-effective if the net incremental cost per QALY saved is less than society's willingness to pay to save 1 QALY, and not cost-effective if net incremental cost per QALY is greater than society's willingness to pay.[47] We will use sensitivity analyses to reflect uncertainty in our parameter estimates and to examine the robustness of the cost-utility estimates.

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14. APPENDIX

Table. Rubric for composite PWID score (service access, risk behaviors, adverse outcomes)

Score component	Denominator	Category definitions
Service access		
HIV care continuum	HIV positive	0 – Suppressed (HIV RNA <200 c/mL) 1 – Not suppressed, and either i) took ARVs in prior 30 days (self-report) OR ii) had visit with HIV provider in prior 6 months 2 – Not suppressed AND did not take ART in prior 30 days AND did not have visit with HIV provider in prior 6 months (includes those unaware of HIV+ status) at the visit
HIV testing	HIV negative	0 – Had HIV test in past 6 months 1 – Did not have HIV test in past 6 months
PrEP continuum	HIV negative	0 – Used PrEP in prior 6 months (self-report) 1 – Did not use PrEP in prior 6 months
HCV care continuum	HCV positive i. all Ab(+) + RNA(+) or ii. Ab(+) + RNA(-) + treated	0 – HCV treatment history (self-report) and HCV RNA suppressed (<15) 1 – Not suppressed and either treated for HCV OR evaluated by HCV provider in prior 6 months 2 - Not suppressed AND not treated for HCV in prior 6 months AND not evaluated by HCV provider in prior 6 months.
HCV testing	HCV negative i. Ab(-) or ii. Ab(+) + RNA(-) + never treated	0 – Had HCV test in past 6 months 1 – Did not have HCV test in past 6 months
MOUD use	All	0 – Used MOUD in past 6 months 1 – Did not use MOUD in past 6 months
SSP use	Injected in prior 6 months	0 – Used SSP in past 6 months 1 – Did not use SSP in past 6 months
Available naloxone kit	All	0 – Has naloxone kit on person or where drugs used 1 – Does not have accessible naloxone kit
Risk behaviors		
Injection drug use	All	0 – No injection drug use in prior 6 months (self-report) 1 – Injection drug use in prior 6 months
Recent drug use	All	0 – Urine drug test negative for drugs of concern (*see footnote) 1 – Urine drug test positive for one or more drugs of concern (*see footnote)
Sharing injecting equipment	All	0 – No sharing syringe/works OR not using/injecting in prior 6 months 1 – Sharing works (cotton/cooker) only in prior 6 months 2 – Sharing needle/syringe in prior 6 months
Adverse outcomes		

Table. Rubric for composite PWID score (service access, risk behaviors, adverse outcomes)

Score component	Denominator	Category definitions
Non-fatal overdose	All	0 – No overdose in prior 6 months 1 – One or more overdose in prior 6 months
Emergency department use	All	0 – No ED visits in past 6 months 1 - One or more ED visits in past 6 months (Self-report, supplemented by CRISP
Clinical status change assessed at follow-up only		
HIV seroconversion	HIV negative	0 – No HIV seroconversion 2 - HIV seroconversion occurring between baseline and follow-up
HCV seroconversion	HCV negative	0 – No HCV seroconversion 1 - HCV seroconversion occurring between baseline and follow-up
Death	All	0 – Alive 15 (maximum points) – Confirmed death during follow-up

*Includes fentanyl (or metabolite), heroin (morphine or 6MAM), cocaine (or metabolite), amphetamine

Revised scoring system 25 OCT 2021

HIV status	HCV status	Maximum score
-	-	15
-	+	15
+	-	13
+	+	13