STATISTICAL ANALYSIS PLAN

INTEGRA: A Vanguard Study of Health Service Delivery in a Mobile Health Delivery Unit to Link Persons who Inject Drugs to Integrated Care and Prevention for Addiction, HIV, HCV, and Primary Care

HPTN 094 (Protocol Version #2.0)

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Protocol Name:	*INTEGRA: A Vanguard Study of Health Service Delivery in a Mobile Health Delivery Unit to Link Persons who Inject Drugs to Integrated Care and Prevention for Addiction, HIV, HCV and Primary Care*
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1. LIST OF ABBREVIATIONS AND ACRONYMS

A list of abbreviations used in the SAP

Term/Abbreviation	Definition
AE	Adverse Event
ART	Anti-Retroviral Therapy
COVID-19	Coronavirus disease 2019
DAIDS	Division of AIDS
DBS	Dried Blood Spot
FDA	Food and Drug Administration
GLM	Generalized Linear Model
HAV	Hepatitis A
HBV	Hepatitis B
HCV	Hepatitis C
HIV	Human Immunodeficiency Virus
HPTN	HIV Prevention Trials Network
mL	Milli-Liter
MOUD	Medication for Opioid Use Disorder
OUD	Opioid Use Disorder
PrEP	Pre-Exposure Prophylaxis
PWID	Persons Who Inject Drugs
RNA	Ribonucleic Acid
RSC	Radiation Safety Committee
SAE	Severe Adverse Event
SAP	Statistical Analysis Plan
SARS-CoV-2	Severe Acute Respiratory Syndrome Coronavirus 2
SMC	Safety Monitoring Committee
SSP	Study Specific Procedures
STI	Sexually Transmitted Infection
VL	Viral Load

2. INTRODUCTION

This statistical analysis plan (SAP) details the final analyses and statistical procedures that address the study objectives specified in Version 2.0 of Protocol HPTN 094: INTEGRA: A Vanguard Study of Health Service Delivery in a Mobile Health Delivery Unit to Link Persons who Inject Drugs to Integrated Care and Prevention for Addiction, HIV, HCV and Primary Care. New versions of the SAP will be issued to document updates and changes in the plan.

2.1 General Design Considerations

The following is a protocol summary of the study:

Protocol title:	INTEGRA: A Vanguard Study of Health Service Delivery in a Mobile Health Delivery Unit to Link Persons who Inject Drugs to Integrated Care and Prevention for Addiction, HIV, HCV, and Primary Care
IND Sponsor:	DAIDS
Protocol Chair(s):	Steve Shoptaw, PhD; Nabila El-Bassel, PhD
Sample Size:	A total of 450 participants allotted in a 1:1 ratio to intervention and active control arms, with targets of a minimum 25% women and 25% participants under 30 years of age, and 10% people living with HIV at enrollment.
Study Population:	People living with and without HIV and who inject drugs, have OUD, and are not receiving MOUD
Study Sites:	Five urban sites in the United States (US) with substantial populations of PWID with OUD. The locations are as follows: Houston, TX; Los Angeles, CA; Bronx, NY; Philadelphia, PA; Washington, DC
Study Design:	A two-arm, individually randomized, controlled, open label study
Study Duration:	Approximately three and a half years with a possibility of extension, with individual participants on study for approximately 52 weeks (26 weeks receiving the intervention or peer navigation and then an evaluation for durability of effect at the end of 52 weeks).
Study Products:	Mobile health delivery unit (“mobile unit”) to deliver “one stop” integrated health services – particularly medication for opioid use disorder (MOUD) and medication for HIV treatment and prevention – to people who inject drugs (PWID) with opioid use disorder (OUD). VS Health services available at community-based agencies
Study Regimen:	All potential study participants will provide biological samples and self-reported data via interview in the mobile unit at Screening and Enrollment Visits. Samples will be tested for HIV, hepatitis A (HAV), B (HBV) and C (HCV) and sexually transmitted infections (STIs). At the Enrollment Visit, participants who meet all inclusion and no exclusion criteria will be randomized to the intervention or active control arm and will receive harm reduction services and empiric treatment for STIs if symptomatic. Participants will also be assessed for COVID-19 at study visits; participants with suspected COVID-19 or recent

exposure will be referred for further evaluation, care and/or treatment, as available.

Intervention Arm: Participants in the intervention arm will be provided integrated health services delivered in the mobile unit and peer navigation for 26 weeks. The integrated health services in the mobile unit will include:
MOUD and harm reduction services for OUD
HIV testing
HIV treatment for people living with HIV not already in care
PrEP for people without HIV
Testing and referral for vaccination or treatment for HAV and HBV
Testing and referral for treatment for HCV
STI testing and treatment
Primary care
Harm reduction services

Peer navigation in the intervention arm will coordinate and facilitate integrated care in the mobile unit through 26 weeks. As participants become established in care, navigation will help transition participants to community-based services by 26 weeks after randomization.

Active Control Arm: Participants in the active control arm will be provided 26 weeks of peer navigation to connect them to health services available at community-based agencies.

All participants (both arms) will have study visits at 26 and 52 weeks for evaluation of study endpoints.

2.2 Study Objectives and Endpoints

Objectives:

Primary:

To evaluate whether 26 weeks of "one stop" integrated health services delivered in a mobile unit, supported by peer navigation, improves use of MOUD and increases use of PrEP, as measured at 26 weeks among people without HIV, when compared to 26 weeks of peer navigation to similar health services available at community-based agencies.

Secondary:

1) To evaluate whether 26 weeks of "one stop" integrated health services delivered in a mobile unit, supported by peer navigation, compared to 26 weeks of peer navigation to similar health services available at community-based agencies:
   a) improves use of MOUD at 52 weeks
   b) increases rates of viral suppression among people living with HIV at 26 and 52 weeks
   c) increases use of PrEP among people without HIV at 26 and 52 weeks
   d) decreases opioid and polysubstance use at 26 and 52 weeks
   e) decreases prevalence of bacterial STIs at 26 and 52 weeks
   f) decreases fatal and non-fatal overdose events by 26 and 52 weeks
   g) increases the proportion of participants with undetectable HCV RNA at 26 and 52 weeks among those with chronic HCV infection at enrollment

h) decreases HCV incidence at 52 weeks, for those who are HCV negative at enrollment

2) To evaluate whether 26 weeks of "one stop" integrated health services delivered in a mobile unit, supported by peer navigation, increases MOUD use, viral suppression, and PrEP use at 26 and 52 weeks compared to Enrollment

3) To evaluate whether 26 weeks of peer navigation to similar health services available at community-based agencies increases MOUD use, viral suppression, and PrEP use at 26 and 52 weeks compared to Enrollment

4) To document the prevalence of seropositivity for SARS-CoV-2 at baseline, 26 and 52 weeks

5) To document the impact of the COVID-19 epidemic on participants' experiences of seeking, obtaining and/or maintaining health services, housing, food security and drugs

6) To evaluate implementation of "one-stop" integrated health services using a mobile unit, supported by peer navigation, across study sites to identify mechanisms at multiple levels to:
   a) Guide real-time improvements and refinements in the conduct of the study to ensure primary and secondary outcomes are met with fidelity
   b) Examine the quality and process of services delivered in each study arm, particularly as these affect primary and secondary outcomes
   c) Develop evidence-based guidance for policymakers on the uptake and implementation of integrated health services using peer navigation and mobile health units in urban US regions to address HIV prevention in PWID
   d) Identify factors that enhance or impede the delivery of integrated health services using a mobile unit, supported by peer navigation, on primary and secondary outcomes, including responding to the impact of COVID-19 on service delivery

7) To use mathematical modeling methods to:
   a) Estimate the effect of integrated health services delivered in a mobile unit, supported by peer navigation, on reducing HIV incidence in PWID and their sexual and injection partners
   b) Estimate the cost-effectiveness of the integrated health services provided in a mobile unit and supported by peer navigation

Process:

For participants in the intervention arm, assess:
1. Time to provide MOUD treatment, ART (among those who are living with HIV and not on ART at Enrollment) and PrEP (among those who are without HIV at Enrollment)
2. The proportion of participants linked to community based MOUD, ART and PrEP services at 26 weeks

Exploratory Objectives:

Stored samples may be used to analyze HIV subtypes/strains, HIV drug resistance, and the duration of HIV infection. Phylogenetic methods may be used to evaluate behavioral, demographic, and clinical factors associated with viral clusters and transmission dynamics. Stored samples may also be used to characterize HCV strains and the relationship between HIV and HCV infections, and to explore issues related to COVID-19.

Endpoints:

Primary:

Consistent with the primary study objective to evaluate whether the intervention improves use of MOUD and increases use of PrEP, as measured at 26 weeks among people without HIV, the following endpoints will be assessed:

1. Documented current use of MOUD. At the Week 26 visit:
   a) Alive
   b) Retained
   c) Biological evidence of MOUD (any detectable Methadone or Buprenorphine)
   d) A MOUD prescription current at the week 26 visit or proof of current receipt of MOUD from a clinic that does not provide individual MOUD prescriptions (e.g., methadone clinics)
2. Among participants who were without HIV at enrollment: alive, retained, without HIV, with detectable PrEP drugs (Truvada or Descovy in dried blood spot (DBS) samples, or Cabotegravir in plasma samples at the week 26 visit

Secondary:

1. To evaluate whether "one stop" integrated health services delivered in a mobile unit, supported by peer navigation, compared to peer navigation to similar health services available at community-based agencies, the following endpoint(s) will be assessed:

   a. The intervention improves use of MOUD at 52 weeks
      - Documented current use of MOUD: alive, retained, with biological evidence of MOUD (any detectable medications) at the week 52 visit and a MOUD prescription current at 52 weeks after enrollment or proof of current receipt of MOUD from a clinic that does not provide individual MOUD prescriptions (e.g., methadone clinics) at the week 52 visit
      - Documented use of MOUD during the study: a MOUD prescription documented during the 52 weeks of study follow-up or proof of current receipt of MOUD from a clinic that does not provide individual MOUD prescriptions (e.g., methadone clinics) during the 52 weeks of study follow-up

   b. The intervention increases rates of viral suppression among people living with HIV at 26 and 52 weeks
      - Among participants living with HIV at enrollment: alive, retained, and virally suppressed (VL <200 copies/mL) at the week 26 and week 52 visits, separately.

   c. The intervention increases use of PrEP among people without HIV at 26 and 52 weeks
      - Among participants without HIV at enrollment: alive, retained, HIV negative, with detectable PrEP drugs in DBS at the week 52 visit
      - Among participants without HIV at enrollment: alive, retained, HIV negative, with protective levels of PrEP drugs in DBS samples at the week 26 and 52 visits

   d. The intervention decreases opioid and polysubstance use at 26 and 52 weeks
      - Alive, retained, and no opioids (natural or synthetic), stimulants (methamphetamine, cocaine) or benzodiazepines detected in urine samples at week 26 and 52 visits

   e. The intervention decreases prevalence of bacterial STIs at 26 and 52 weeks
      - Alive, retained and no evidence of gonorrhea, chlamydia, or new or recurrent syphilis infection detected at the week 26 and 52 visits

f. The intervention reduces the rate of fatal and non-fatal overdose events by 26 and 52 weeks,
   - Death, with overdose as cause
   - Self-report of non-fatal overdose, collected at week 26 and 52 visits

g. The intervention increases the proportion of participants with undetectable HCV RNA among those with chronic HCV infection at enrollment
   - Undetectable HCV RNA at the week 26 and 52 visits among participants with chronic HCV at enrollment

h. The intervention reduces HCV incidence
   - HCV antibody positive at the week 52 visit among participants who are HCV antibody negative at enrollment

2. To evaluate whether 26 weeks of "one stop" integrated health services delivered in a mobile health delivery unit, supported by peer navigation, increases MOUD use, viral suppression, and PrEP use at 26 and 52 weeks compared to enrollment, the following endpoint(s) will be assessed:
   - In the intervention arm, change over time in the use of MOUD during the study, comparing documented use of MOUD (biological evidence of MOUD - any detectable medications - and a current MOUD prescription or proof of current receipt of MOUD from a clinic that does not provide individual MOUD prescriptions (e.g., methadone clinics)) at 26 and 52 weeks to documented use of MOUD at enrollment. MOUD use is assumed to be zero at enrollment due to study exclusion criteria. Follow-up endpoints will be defined as alive, retained, and having documented MOUD use.
   - Among participants living with HIV at enrollment: change over time in the proportion of people with viral suppression (VL<200 copies/mL), comparing 26 and 52 weeks to enrollment. Follow-up endpoints will be defined as alive, retained, and virally suppressed.
   - Among participants who were without HIV at enrollment: change over time in the proportion of people with detectable PrEP drugs in DBS at 26 and 52 weeks compared to enrollment. Follow-up endpoints will be defined as alive, retained, and having detectable PrEP.

3. To evaluate whether 26 weeks of peer navigation to similar health services available at community-based agencies increases MOUD use, viral suppression, and PrEP use at 26 and 52 weeks compared to enrollment, the following endpoint(s) will be assessed:
   - In the active control arm, change over time in the use of MOUD during the study, comparing documented use of MOUD (biological evidence of MOUD - any detectable medications - and a current MOUD prescription or proof of current receipt of MOUD from a clinic that does not provide individual MOUD prescriptions (e.g., methadone clinics)) at 26 and 52 weeks to documented MOUD use at enrollment. MOUD use is assumed to be zero at enrollment due to study exclusion criteria. Follow-up endpoints will be defined as alive, retained, and having documented MOUD use.
   - In the active control arm among participants living with HIV at enrollment: change over time in the proportion of people with viral suppression (VL<200 copies/mL), comparing 26 and 52 weeks to enrollment. Follow-up endpoints will be defined as alive, retained, and virally suppressed.
   - In the active control arm among participants who were without HIV at enrollment: change over time in the proportion of people with detectable PrEP drugs in DBS at 26

and 52 weeks compared to enrollment. Follow-up endpoints will be defined as alive, retained, and having detectable PrEP.

4. To assess the prevalence of SARS-CoV-2 seropositivity at baseline, 26 and 52 weeks, the following endpoint will be assessed:
   - Laboratory evidence of antibodies to SARS-CoV-2

The rest of the endpoints will be handled separately in a different SAP or will be added later.

2.3 Randomization

Random treatment-arm allocation will occur at a 1:1 ratio, stratified by study site and by HIV status. Permuted-block randomization will be used to assure balanced groups within each study site and HIV-status subgroup with 30 blocks per site/HIV-status stratum. A list of size 240 [10*(6+8+10)] would allow each site more than enough randomization slots in case a site is called upon to enroll greater than the projected sample size (approx. n=80 HIV negative participants and approx. n= 10 HIV positive participants per site), or in case of dropouts or randomization errors.

2.4 Blinding

This study is unblinded.

2.5 Sample Size and Power

Sample sizes are chosen to provide sufficient power for both the HIV-related and MOUD-related primary outcomes. By computing sample sizes based on each individual outcome separately and choosing the largest sample size needed for either outcome, high power is achieved for both individual outcomes. Prior work in PWID populations suggests that uptake of MOUD, ART, and PrEP in the control condition will likely be modest;[1,2] we anticipate 25% uptake of MOUD, 42.5% achieving viral suppression, and 5% uptake of PrEP in the control arm.

Sample sizes are computed to provide 90% power to detect a fifteen-percentage point difference in the proportion of participants achieving success, assuming a 5% type-I error rate (two-sided). A sample of 400 participants is needed to detect a 15-point difference in MOUD use (25% vs. 40%) between the active control and intervention arm at 26 weeks. Approximately 216 people without HIV would be needed to see a 15-point difference in PrEP uptake (5% vs. 20%). To cover both HIV and MOUD outcomes, 400 people without HIV will be needed. Approximately 10% of the study population is expected to be living with HIV – insufficient to accommodate a fully powered subgroup - but because this subgroup is expected to have very different rates of HIV-related success than the people without HIV subgroup, it will be important to analyze these participants separately. To assure 400 people without HIV, the target sample size will be augmented by 50 for a combined total of 450 participants, where 40-50 of those are expected to be people living with HIV.

2.6 Accrual and Retention

The study cohort (n=450) will be enrolled over the course of approximately 2.5 years and followed for 52 weeks each. This corresponds to a rate of approximately 15 new enrollees per month, or approximately 3 new enrollees per month at each of the five sites.

3. GENERAL DATA ANALYSIS CONSIDERATIONS

3.1 Analysis Set(s)

- **Intent to Treat (ITT):**
  All participants enrolled, excluding those who were inappropriately enrolled.

- **Safety:**
  There is no formal safety analysis in this study, however, serious adverse events (SAE) will be monitored for all randomized participants.

3.2 Statistical Analysis Issues

- **Missing Data:**
  In anticipation of the potential for missing data in this unstable study population, a missing-data strategy has been built into the primary endpoints. A positive result for each endpoint is defined as being "alive, retained," and meeting the MOUD, ART, or PrEP criteria at 26 weeks from enrollment. If the 26-week visit is missing for any individual, that individual is "not retained" at 26 weeks, and the 26-week result for that person will be considered "negative".

  Secondary endpoints are defined similarly. If missing data rates are higher than anticipated (over 15%) for primary or secondary endpoints, sensitivity analyses will be conducted to assess the impact of assuming missed visits represent negative outcomes.

  - **Missing Start and Stop Dates:**
    Start date:
    - If start date is completely missing, start date will not be imputed.
    - If year is present and month and day are missing, then set month and day to January 1 or date of enrollment whichever is later.
    - If year and day are present and month is missing, the set month to January or date of enrollment whichever is later.
    - If year and month are present and day is missing, set day to the 1st day of month or date of enrollment whichever is later.

    Stop date:
    - If end date is completely missing, end date will not be imputed.
    - If year is present and month and day are missing, then set month and day to December 31st or date of termination whichever is earlier.
    - If year and day are present and month is missing, set month to December or date of termination whichever is earlier.
    - If year and month are present and day is missing, set day to the last day of month.

- **Out of window visits:**
  For each required study visit, there is an allowable visit window specifying on which study days (post-enrollment) the visit is "allowed" to be completed. The allowable visit windows are contiguous between week 26 and week 52 and do not overlap. Within each allowable visit window, there is a target visit window and study visits should ideally be conducted within this window. Further details about visit windows are defined at section 6.8 of the Protocol V2.0.

  All data will be tabulated per the evaluation visit as recorded on the CRF even if the assessment is outside of the visit window. In data listings, actual visit dates will be presented alongside nominal visit types.

4. INTERIM ANALYSIS AND DATA MONITORING COMMITTEE

No interim analyses are planned.

HPTN SMC oversight is planned for this study. The SMC will conduct interim reviews of study progress, including rates of participant accrual, visit retention, completion of primary and secondary endpoint collection, and, in a closed report, endpoint and safety data by arm. The frequency and content of SMC reviews will be determined prior to the start of the study and outlined in the SSP Manual but will occur at least once per calendar year.

5. GENERAL ANALYSIS METHODS

Participants characteristics at baseline will include the number of subjects with non-missing value (n), plus frequency and percentage for the categorical variables; and mean, median, standard deviation (SD), minimum (min), and maximum (max) for the continuous variables. Baseline is defined as Enrollment visit, except for data collected at screening and not at enrollment visit. For example, opioids data collected at screening visit will be considered as baseline data.

Any deviations from this statistical plan will be described in the final report.Primary and secondary outcomes will be limited to data collected within the allowable visit window for the week 26 and week 52 visits, respectively.

For all outcomes below, “retained” at 26 weeks is defined as having completed the 26-week visit within the allowable window of 126-308 days from enrollment, and “retained” at 52 weeks is defined as having completed the 52-week visit within the allowable window of 309-449 days from enrollment.

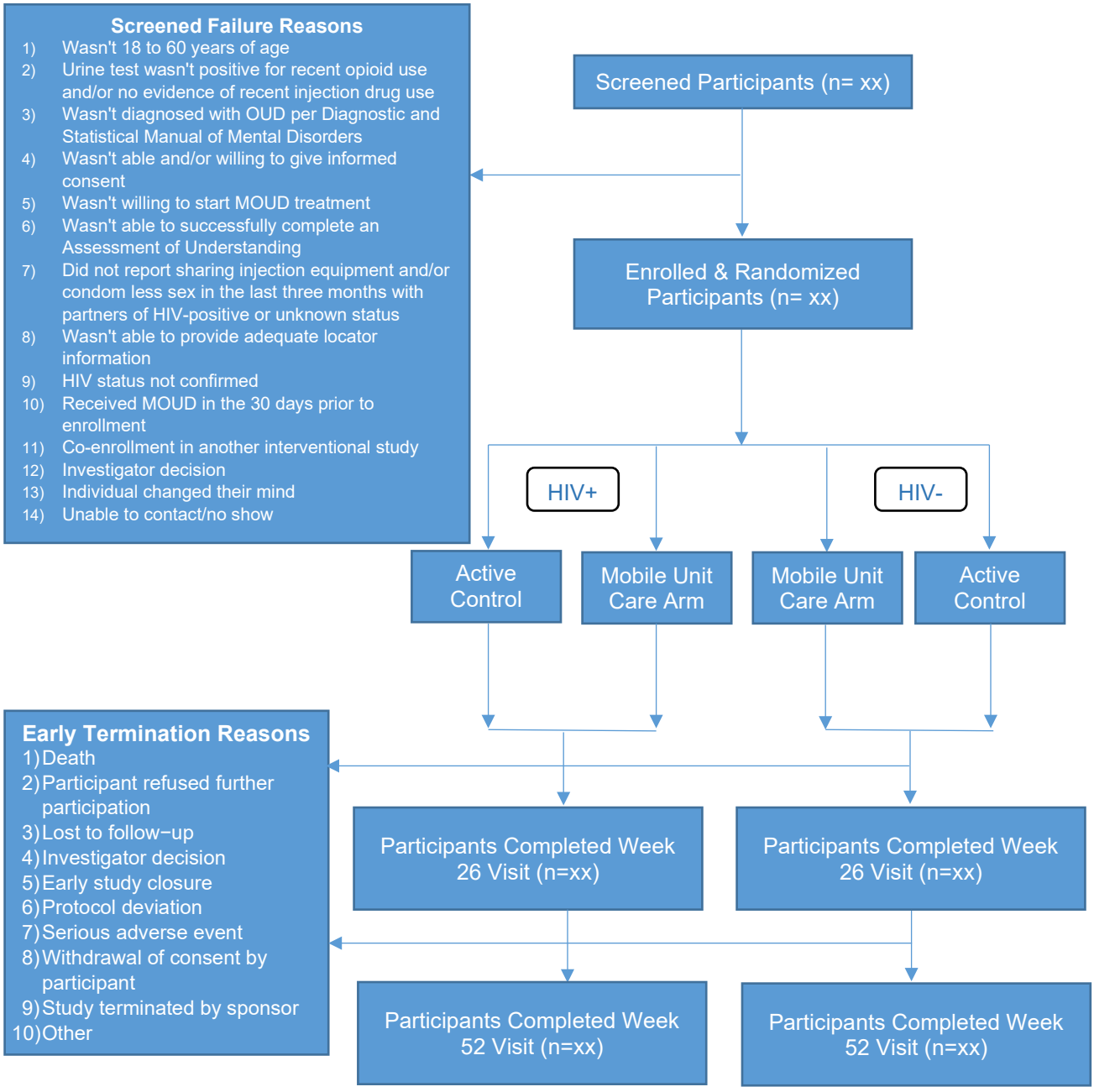
For MOUD outcomes, biological detection of Buprenorphine (or Norbuprenorphine or Buprenorphine Glucuronide) or Methadone (or EDDP) will be performed via laboratory analysis of plasma and urine samples. Detectable MOUD is defined as a value above the lower limit of quantitation (LLOQ) for any of the medications or metabolites mentioned above, in either plasma or urine.

For PrEP outcomes, the PrEP regimen tested (Truvada or Descovy in DBS, or CAB-LA in plasma) is determined based upon reported PrEP use. If there is no reported PrEP usage, the default regimen is Truvada. Detectable PrEP is defined as a value above the lower limit of quantitation (LLOQ) for the PrEP regimen tested.

6. TRIAL PARTICIPANT DISPOSITION

6.1 Disposition of Participants

Final disposition for all study participants will be summarized using the following CONSORT flow chart.



6.2 Protocol Deviations

Protocol deviations related to study inclusion or exclusion criteria, the conduct of the study, and inappropriate enrollment will be summarized by site, and overall, in the form of tables and listings. The following protocol deviations will be summarized:

- Inappropriate enrollment
- Failure to follow randomization or blinding procedures
- Conduct of non-protocol procedure
- Improper SAE
- Unreported SAE
- Breach of confidentiality
- Physical assessment deviation
- Lab assessment deviation
- Staff performing duties that they are not qualified to perform
- Use of non-IRB/EC-approved materials
- Informed consent process deviation
- Other

7. BASELINE DATA

Participants' baseline characteristics will be presented by site, HIV status, study arm, and overall.

- Demographics, including age, race, ethnicity, self-identified gender and sexual orientation.
- Drug use and overdose history including: the types of drugs taken (stimulants, opioids, other); ways the drugs were taken; and the number of days drugs were taken in the past month. Overdose history will be summarized by the type of drug leading to overdose on and the number of times overdosed.
- Delivery of the intervention will be described by summarizing the number of navigation sessions per participant, the location and length of the sessions, and the topics addressed.

8. EFFICACY/EFFECTIVENESS ANALYSES

Primary Outcomes:

Among the enrolled HIV-negative cohort:

- Documented current use of MOUD defined as: alive, retained, with biological evidence of MOUD (defined in section 5) and a current MOUD prescription or proof of current receipt of MOUD from a clinic that does not provide individual MOUD prescriptions (e.g., methadone clinics) at the week 26 visit

- Current use of PrEP defined as: alive, retained, HIV-negative, with detectable PrEP (defined in section 5) at the week 26 visit

For the primary outcome of MOUD use, a Generalized Linear Model (GLM) for binary outcomes using the identity link will be performed with treatment arm and site as covariates. The proportions of participants who meet the MOUD endpoint criteria (by-arm, and by-site-by-arm) at week 26 will be provided along with the estimate and 95% confidence interval for the difference in proportions.

For the primary outcome of PrEP use, a Generalized Linear Model (GLM) for binary outcomes using the identity link will be performed with treatment arm and site as covariates. The proportions of participants who meet the PrEP endpoint criteria (by-arm, and by-site-by-arm) at week 26 will be provided along with the estimate and 95% confidence interval for the difference in proportions.

9. SAFETY ANALYSES

In this study, the only drugs that will be dispensed or prescribed will be US FDA-approved medications for treatment or prevention of OUD, HIV, and STIs and prescriptions for contraceptives, primary care concerns, and chronic conditions, if indicated. There are no investigational products in this protocol. Therefore, there will be no monitoring or reporting of unanticipated treatment-related risks with the following exception: site investigators will report to the FDA any serious adverse events that are "unexpected" per the current version of the package insert for drugs provided for MOUD, ART or PrEP via the FDA's MedWatch form, copying the RSC Safety Office.

9.1 Adverse Events and Deaths

Adverse events (AEs) that study staff become aware of will be recorded in source documentation and will be assessed for seriousness. Non-serious AEs will not be reported in the study database and referrals for care will be provided as necessary. Only Serious adverse events (SAEs) will be reported in form of tables and listings categorized by system organ class, severity grade (The Division of AIDS Table for Grading the Severity of Adult and Pediatric Adverse Events, Corrected Version 2.1, July 2017. https://rsc.niaid.nih.gov/clinical-research-sites/daids-adverse-event-grading-tables), HIV status and arm. Serious adverse events (SAEs) are those AEs that result in one or more of the following outcomes:

- Death
- A life-threatening (i.e., an immediate threat to life) event
- Requires in-patient hospitalization or prolongation of an existing hospitalization
- A persistent or significant incapacity or substantial disruption of the ability to conduct normal life functions
- A congenital anomaly/birth defect
- A medically important 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

Examples of SAEs that can be expected to occur during this study include deaths (e.g., overdoses or other addiction-related deaths) and life-threatening events requiring intervention (e.g., overdose reversals).

9.2 Other Safety Measures

Pregnancy will be presented in the form of listings by site, study arm and HIV-status.

10. SECONDARY ENDPOINTS

1. **To evaluate whether "one stop" integrated health services delivered in a mobile unit, supported by peer navigation, compared to peer navigation to similar health services available at community-based agencies, the following endpoint(s) will be assessed:**

   a) Improves use of MOUD at 52 weeks compared to the active control condition

Outcomes:

- Documented current use of MOUD: alive, retained, with biological evidence of MOUD (as defined above) at the week 52 visit and a MOUD prescription current at 52 weeks after enrollment or proof of current receipt of MOUD from a clinic that does not provide individual MOUD prescriptions (e.g., methadone clinics) at the week 52 visit
- Documented use of MOUD during the study: a MOUD prescription documented during the 52 weeks of study follow-up or proof of current receipt of MOUD from a clinic that does not provide individual MOUD prescriptions (e.g., methadone clinics) during the 52 weeks of study follow-up

These outcomes will be modeled and summarized using the same strategy as specified for the primary outcome in section 8 above.

b) Increases rates of viral suppression among people enrolled living with HIV, at 26 and 52 weeks

Outcome:

- Among participants living with HIV at enrollment: alive, retained, and virally suppressed (VL <200 copies/mL) at the week 26 and 52 visits, separately.

The proportion of participants achieving the viral suppression outcome will be computed and presented by arm and within site by arm, along with exact Clopper-Pearson 95% confidence intervals using F-quantiles based on the Binomial distribution. No statistical comparisons between treatment arms will be made.

c) The intervention increases use of PrEP among people without HIV at 26 and 52 weeks

Outcome:

- Among participants without HIV at enrollment: alive, retained, HIV negative, with detectable PrEP drugs in DBS at the week 52 visit
- Among participants without HIV at enrollment: alive, retained, HIV negative, with protective levels of PrEP drugs in DBS samples at the week 26 and 52 visits

A protective level of oral PrEP[3] is defined as:
TFV-DP concentrations ≥ 800 fmol/punch in DBS among those tested for Truvada (TDF-FTC)
TFV-DP concentrations ≥ 950 fmol/punch in DBS among those tested for Descovy (TAF-FTC)

A protective level of long-acting PrEP (Cabotegravir) is defined as plasma concentrations above the four times the PA-IC_{90} of 166 ng/mL – that is, above 664 ng/mL.

These outcomes will be modeled and summarized using the same strategy as specified for the primary outcome in section 8 above.

d) Decreases opioid and polysubstance use at 26 and 52 weeks

Outcome:

- Opioids (natural or synthetic) detected in urine samples for those retained at the week 26 and 52 visits (visits analyzed separately).
- Opioids (natural or synthetic) detected, along with stimulants (methamphetamine, cocaine), xylazine and/or benzodiazepines detected in urine samples at the week 26 and 52 visits (visits analyzed separately).

This objective will be analyzed only in those giving a urine sample at the respective visit (week 26 or week 52).

Opioids (natural or synthetic) include opiates, fentanyls and synthetic opioids.

Opiate detection includes 6-mam, codeine, dihydrocodeine, heroin, hydrocodone, hydromorphone, morphine, morphine glucuronide naloxone, and normorphine.

Fentanyl detection includes 4-ANPP, acetyl fentanyl, alfentanil, fentanyl, FIBF, furanyl fentanyl, methoxyacetyl fentanyl, norfentanyl, para-chlorofentanyl, para-fluorofentanyl, and valeryl fentanyl.

Synthetic Opioid detection includes isotonitazene, meperidine, metonitazene, noroxycodone, oxycodone, oxymorphone, tapentadol, tramadol, and U-47700.

Stimulant detection includes amphetamine, MDA, MDEA, MDMA, methamphetamine, methylphenidate, phentermine, benzoylecgonine, cocaethylene, and cocaine.

Benzodiazepine detection includes alpha-hydroxyalprazolam, alprazolam, carisoprodol, chlordiazepoxide, clonazepam, diazepam, flurazepam, lorazepam, nordiazepam, oxazepam, and temazepam.

These outcomes will be modeled and summarized using the same strategy as specified for the primary outcome in section 8 above.

e) Decreases prevalence of bacterial STIs at 26 and 52 weeks
Outcome:

- Gonorrhea, chlamydia, or new or prevalent syphilis infection detected via local labs for those retained at the week 26 and 52 visits (visits analyzed separately).

This objective will be analyzed only in those giving a specimen and having a valid test result at the respective visit (week 26 or week 52).

Negative for syphilis, at any visit, is defined as a negative/not-detected non-treponemal test; or a positive non-treponemal test and a negative/not-detected treponemal test (this would be considered a false-positive test and thus considered negative for the visit).

Prevalent syphilis is defined as a positive non-treponemal test and a positive treponemal test, with a titer value >= 1:8.

Note: Participants can be non-prevalent (positive tests with tier < 1:8) but also not negative for syphilis. Thus, they had syphilis previously, but it is not a prevalent infection.

New syphilis is defined as a positive non-treponemal test and positive treponemal test (regardless of titer value) at a follow-up visit when they were negative at the previous visit.

These outcomes will be modeled and summarized using the same strategy as specified for the primary outcome in section 8 above.

f) Decreases fatal and non-fatal overdose events by 26 and 52 weeks
Outcomes:

- Death, with overdose as cause, collected on or before 26- and on or before 52-week visits, separately.
- Self-report of non-fatal overdose, collected on or before week 26- and on or before 52-week visits, separately.

These outcomes are reported on the SAE log form.

Death, caused by overdose, will be modeled with a time-to-event cox proportional hazards model with treatment arm as a covariate.

Person-time for fatal overdoses will be calculated as follows:
- For those retained (alive) at the visit: time between enrollment and the week 26 or week 52 visit date.
- For those reported deceased by the visit date: time between enrollment and recorded date of death.
- If deceased and no recorded date of death: time between enrollment and the midpoint of last attended visit and termination date.
- Those with no reported death and not retained at week 26 and/or week 52 (or terminated before the visit): use time between enrollment and the last attended visit (or termination date). If no other visit besides enrollment is documented: exclude from the analysis.

Note: Last attended visit can include the enrollment or week 26 visits, an interim visit, or a navigation session

Self-reported non-fatal overdoses will use a Poisson regression model (GLM with log link) with treatment arm as a covariate. We will use the number of reported non-fatal overdoses in the 30 days prior to the respective visit to compare treatment arms.

g) Increases the proportion of participants with undetectable HCV RNA at 26 and 52 weeks among those with chronic HCV infection at enrollment

Outcome:
- Undetectable HCV RNA at the week 26 and 52 visits (visits analyzed separately) among participants with chronic HCV at enrollment.

The HCV treatment outcome will be modeled and summarized using the same strategy as specified for the primary outcome in section 8 above.

h) Decreases HCV incidence at 52 weeks, for those who are HCV negative at enrollment

Outcome:
- HCV antibody positive at the week 52 visit among participants who are HCV antibody negative at enrollment.

HCV incidence will be modeled using Poisson regression (GLM with log link), with treatment arm and site as covariates and person years as an offset. Person time will be computed as the number of years from enrollment to the visit date where infection is first detected for participants with incident HCV infection, and from enrollment to the week 52 visit date (or last available visit) for HCV-negative participants with no incident infection.

2. **To evaluate whether 26 weeks of "one stop" integrated health services delivered in a mobile health delivery unit, supported by peer navigation, increases MOUD use, viral suppression, and PrEP use at 26 and 52 weeks compared to enrollment, the following endpoint(s) will be assessed:**

- In the intervention arm, change over time in the use of MOUD during the study, comparing documented use of MOUD (biological evidence of MOUD - any detectable medications - and a current MOUD prescription or proof of current receipt of MOUD from a clinic that does not provide individual MOUD prescriptions (e.g., methadone clinics)) at 26 and 52 weeks to documented use of MOUD at enrollment. MOUD use is assumed to be zero at enrollment due to study exclusion criteria. Follow-up endpoints will be defined as alive, retained, and having documented MOUD use.
- Among participants living with HIV at enrollment: change over time in the proportion of people with viral suppression (VL<200 copies/mL), comparing 26 and 52 weeks to enrollment. Follow-up endpoints will be defined as alive, retained, and virally suppressed.

- Among participants who were without HIV at enrollment: change over time in the proportion of people with detectable PrEP drugs in DBS at 26 and 52 weeks compared to enrollment. Follow-up endpoints will be defined as alive, retained, and having detectable PrEP.

The viral suppression outcome will not be modelled. We will report the proportions at enrollment, 26 week and 52-week visits, along with exact Clopper-Pearson 95% confidence intervals using F-quantiles based on the Binomial distribution.

Change over time in the MOUD endpoint will be modeled using GEE (one model for 26 weeks compared to enrollment, and another model for 52 weeks compared to enrollment) with a linear link and an exchangeable correlation structure accounting for within-person repeated measures over time. Each model will include an indicator for time point (26 weeks vs enrollment, or 52 weeks vs enrollment) and a covariate for site. The proportion of participants achieving the outcome at each time point will be summarized, along with the estimated difference in proportions and corresponding 95% confidence interval.
Change over time in the PrEP outcome will be modeling and summarized using the same strategy as defined above for MOUD.

3. **To evaluate whether 26 weeks of peer navigation to similar health services available at community-based agencies increases MOUD use, viral suppression, and PrEP use at 26 and 52 weeks compared to enrollment, the following endpoint(s) will be assessed:**

- In the active control arm, change over time in the use of MOUD during the study, comparing documented use of MOUD (biological evidence of MOUD - any detectable medications - and a current MOUD prescription or proof of current receipt of MOUD from a clinic that does not provide individual MOUD prescriptions (e.g., methadone clinics)) at 26 and 52 weeks to documented MOUD use at enrollment. MOUD use is assumed to be zero at enrollment due to study exclusion criteria. Follow-up endpoints will be defined as alive, retained, and having documented MOUD use.
- In the active control arm among participants living with HIV at enrollment: change over time in the proportion of people with viral suppression (VL<200 copies/mL), comparing 26 and 52 weeks to enrollment. Follow-up endpoints will be defined as alive, retained, and virally suppressed.
- In the active control arm among participants who were without HIV at enrollment: change over time in the proportion of people with detectable PrEP drugs in DBS at 26 and 52 weeks compared to enrollment. Follow-up endpoints will be defined as alive, retained, and having detectable PrEP.

The viral suppression outcome will not be modelled. We will report the proportions at enrollment, 26 week and 52-week visits, along with 95% confidence intervals using exact binomial distribution.

For participants in the control arm, change over time in the MOUD and PrEP outcomes will be modeled and presented using the same strategy as defined in section 2 above for the intervention arm.

4. **To document the prevalence of seropositivity for SARS-CoV-2 at baseline, 26 and 52 weeks, the following endpoint(s) will be assessed:**

- Laboratory evidence of antibodies to SARS-CoV-2 Overall and by Site (and by arm).

At each of the three timepoints, we will report the proportion of participants with lab evidence of SARS-CoV-2 antibodies (by-arm and by-site-by-arm) at week 26 and week 52. Laboratory evidence of antibodies to SARS-CoV-2

Analyses for Secondary Objectives 5, 6, and 7, along with Process Objectives 1 and 2, will be outlined in a different Analysis Plan document.

11. REFERENCES

1. Miller WC, Hoffman IF, Hanscom BS, et al. A scalable, integrated intervention to engage people who inject drugs in HIV care and medication-assisted treatment (HPTN 074): a randomised, controlled phase 3 feasibility and efficacy study. Lancet 2018; 392(10149): 747-59.

2. Morgan JR, Schackman BR, Leff JA, Linas BP, Walley AY. Injectable naltrexone, oral naltrexone, and buprenorphine utilization and discontinuation among individuals treated for opioid use disorder in a United States commercially insured population. J Subst Abuse Treat 2018; 85: 90-6.

3. HPTN LC Pharmacology Core (Marzinke, Anderson).

12. CHANGE HISTORY

Version		Affected Section(s)	Activity Description
Number	Effective Date		
v1.0	14JUL2023	N/A	First version
v2.0	Date of last signature	2.2, 5, 8, 10, 11, 12	Defining cohorts and endpoints, including biological evidence of MOUD, more clearly. Updating general analysis methods with definitions of endpoints including PrEP regimen testing. Updating protective levels of PrEP for Truvada, Descovy and CAB-LA (with references added).