9. Clinical and Counseling Procedures

9.1 Overview of Section 9

This section provides information on the clinical and counseling procedures for participants in HPTN 094. The Schedule of Procedures and Evaluations in Appendices IA-IC of the protocol indicates when specific clinical, counseling, and ACASI procedures and relevant laboratory testing are required.

9.2 Clinical Procedures

9.2.1 Assessment of Recent Injection Drug Use

An enrollment criterion for HPTN 094 is evidence of recent injection drug use ("track marks"). Site clinicians may assess evidence of recent injection drug use ("track marks") at the screening visit to screen out persons without recent injection evidence from further evaluation. Sites must see evidence of recent injection drug use at the enrollment visit in order to randomize (enroll). Clinicians will assess the evidence of recent injection using clinical judgment when determining participant eligibility. Appendix A of this SSP section provides a visual guide for assistance in interpreting skin lesions related to injection drug use.

9.2.2 Medical History at Screening and Enrollment

A targeted medical history will be collected at screening and enrollment. This history should focus on conditions that have occurred since the participant started using drugs, and probe for the most accurate information available on the participant's current health status. At the Screening visit the medical history will assist in determining a participant's eligibility for study enrollment. Sites may choose whether to collect a more limited medical history at screening and a more extensive medical history at enrollment, or a more extensive medical history at screening which will be reviewed, updated, and completed at enrollment.

When collecting past medical history from the participant, the clinician should ask probing questions in order to collect the most complete and accurate information possible, especially with regard to HIV history and treatments. In all cases, information obtained at Screening, Enrollment, and all follow-up visits should be documented in the participant's chart and on appropriate e-case report forms.

The targeted medical history collected in HPTN 094 should:

- Include a review of medical information by major body systems
- Record both chronic and acute conditions, including psychiatric conditions
- Record symptoms, illnesses, allergies, and surgeries
- Investigate history of or current pregnancy, breast-feeding, birth control use

- Focus on history of drug use (including medical complications of drug use including HIV or hepatitis, serious bloodborne infections and soft tissue infections, overdoses requiring Narcan or medical care), prior treatment using MOUD, and concomitant drugs.
- Include HIV risk behaviors
- STI & HIV history
- Prior or current participation in other research studies

9.2.2.1 Pre-existing Conditions

Pre-existing Conditions are a subset of a participant's medical history and consist of all ongoing and/or relevant medical conditions, problems, signs, symptoms, and abnormal findings that are observed and/or reported prior to enrollment into the study. For this population, it will be important to inquire about ongoing injuries or chronic pain syndromes. Recurring or chronic conditions are considered ongoing whether or not they are active at baseline. For example, oral Herpes Simplex Virus could be listed as a pre-existing condition if the participant has a history of recurrent oral herpetic lesions. Other examples of pre-existing conditions that a participant reports but are not apparent during screening, such as asthma, untreated latent or treated active TB, and skin conditions, will also be reported as a pre-existing condition. As appropriate, participants may be referred for care for pre-existing conditions, and participants in the intervention arm may receive care or counseling from clinicians for these conditions in the mobile unit between enrollment and 26 weeks.

Pre-existing conditions are entered into the study database via the medical history log form. Because conditions reported by prospective participants at screening may change or resolve prior to enrollment (randomization) and new conditions may arise even on the day of enrollment, sites may decide not to complete and submit the medical history log forms until the day of randomization. If sites choose to submit pre-existing conditions into the database prior to the date of enrollment, they will need to review these conditions on the day of enrollment: if conditions have resolved or changed, the site will need to delete or update the relevant previously submitted forms

9.2.3 Targeted Medical History at Care Visits

Targeted medical history at care visits will be collected as needed for participants in the active arm receiving care in the mobile health units, e.g., to identify and better understand new or persistent symptoms or conditions, to guide treatment decisions and to document changes in frequency or severity of symptoms.

At a minimum, it is recommended that the interim medical history include:

- Review of medications being taken at the last visit and inquiries about any new medications begun since then
    - Note: All medications, including traditional medicines, vitamins, etc., should be recorded on Concomitant Medications Log
- Adherence to MOUD and ART/PrEP

- Follow up on any ongoing medical issues identified at the previous visit
- An open-ended question, such as "Have you had any new health problems since your last exam?"]
- Ongoing substance use

9.2.4 Targeted Medical History at Week 26 and Week 52 Visits

Targeted interim medical history at the Week 26 and Week 52 Visits will include participation in other interventional studies, overdose events and follow-up of unresolved AEs/SAEs identified previously. Clinicians should inquire about and document resolution or changes in severity or frequency of ongoing medical issues identified at the previous visits. If participants volunteer new symptoms, illnesses, or conditions that have occurred since the previous visit these should be documented, and (if reported at the 26 week visit) followed up at the 52 week visit.

9.2.5 Physical Exams at Enrollment

A basic physical exam is required at the enrollment visit. The exam will be performed according to standard procedures at the site but at a minimum is recommended to include assessment and documentation of:

- Height
- Weight
- Vital signs (temperature, blood pressure, pulse)

And examination of the following body systems/components:

- Mouth and throat
- Neck
- Chest
- Abdomen
- Skin
- Extremities

Additional exam elements may be completed at the clinician's discretion for patient care.

Any abnormal findings should be documented in the chart notes. It is important to grade these pre-existing conditions in the source document so that adverse events (AEs) can be identified if the severity of the conditions increases.

9.2.6 Targeted Physical Exams at Care Visits

Targeted physical exams will be performed at care visits (active arm only) as needed.

9.2.7 Screening for Mental Health Needs

All participants will be screened for mental health needs at the Enrollment, Week 26, and Week 52 Visits and referred for community-based services as needed. Screening tools for alcoholism, anxiety disorder, depression and PTSD (AUDIT-3, GAD-7, CESD 10 and PC-PTSD-adapted) are included in the "Behavioral Questionnaire Part A & B" CRFs that will be completed at enrollment, 26 and 52 weeks. Responses on these screeners should be scored (see Appendix B for screener scoring instructions) and should inform discussions with the participant, and referrals as appropriate. Study clinicians should use their clinical judgement about whether screening for additional needs is indicated and how to complete additional screening. At care visits (active arm only), mental health screenings and referrals will be provided as indicated. The clinician will work with the peer navigators to coordinate the provision of appropriate referrals. If any participant appears to be at risk of harming themselves or others, site staff will call 911 will follow relevant local/institutional protocols.

9.2.8 OUD Assessment

Clinicians will assess for opioid use disorder (OUD) for each participant at either the Screening or Enrollment Visit by completing the tool provided as Appendix C of this SSP section. This tool will be the source document for OUD diagnosis. The site must determine whether participant name or PTID will be included on the form, and whether a printed copy of the form will be used or if the form will be completed in an appropriate electronic record system. If OUD is confirmed at screening, it does not need to be re-confirmed at enrollment.

9.3 COVID-19 Assessment

Participants will be assessed for symptoms of COVID-19 at every contact with the mobile unit (e.g., Screening, Enrollment, Follow Up and Care Visits). Persons presenting with suspected COVID-19 at the Screening Visit will be deferred from screening and referred for community available services. Likewise, eligible participants presenting with suspected COVID-19 at the Enrolment Visit will have their enrollment deferred until they meet criteria for discontinuation of isolation per CDC and/or local guidelines. Enrolled participants presenting with symptoms of COVID-19 will have Care and Follow-Up visits deferred until they meet criteria for discontinuation of isolation per CDC and/or local guidelines. Sites are encouraged to implement remote pre-screening for COVID-19 prior to a participant visit using text, telephony, etc.

It will be sites' responsibility to remain up-to-date on CDC and local policies regarding screening for COVID-19 and discontinuation of isolation. As of the time of the writing of this version of the SSP, the CDC screening tool for facilities was available at: https://www.cdc.gov/screening/paper-version.pdf

9.4 Clinical Management of OUD, HIV Infection, and PrEP

9.4.1 Management of OUD

In the active control arm, OUD-related clinical activities will be minimal (refer to protocol section 5.4, Table 1 and protocol appendices IA and IB). The clinician will confirm OUD and injection drug use as part of eligibility determination. At the enrollment visit, the clinician will counsel the participant regarding their OUD and

provide information about MOUD therapy. The clinician and participant will develop a care plan based on the participant's priorities informed by clinician input. It is anticipated that this plan will include preparing to start MOUD. The clinician and peer navigator will collaborate to make an appropriate referral to an MOUD provider in the community.

In the intervention arm, as for the control arm, the clinician will confirm OUD and injection drug use as part of eligibility determination and will counsel the participant during the enrollment visit regarding their OUD and provide information about MOUD therapy. Also, as for the control arm, the clinician and participant will develop a care plan based on the participant's priorities informed by clinician input. It is anticipated that this plan will include preparing to start MOUD. If the participant is ready to start MOUD immediately with buprenorphine-based therapy, the clinician will transmit a prescription to the research pharmacy. Few if any participants are expected to be in withdrawal at their enrollment visit and so will be counseled to return the next day in withdrawal to receive induction at the mobile unit. This will allow the pharmacy to prepare the product for that participant and have it available on the mobile unit the next day. A COWS assessment will be administered to participants prior to initiation of MOUD. Clinicians will follow the local induction protocols and clinical judgement for starting participants on buprenorphine. Although this is the expected "standard" approach to initiating MOUD therapy for active arm participants, it is understood that some, perhaps many, will follow a different course. Some participants may need days or weeks of time and encouragement before they are ready to initiate MOUD. Some may ultimately refuse MOUD and that is their prerogative, though not what is hoped for. Some participants may prefer methadone treatment or detox with long-acting naltrexone; these participants will be referred to an appropriate program.

Although the standard approach to induction in the study is envisioned as research pharmacy delivery of buprenorphine to the participant at the van and observed induction at the van, clinical practice concerning induction has been evolving rapidly in response to the COVID-19 epidemic. Home induction has become widespread and early reports from the field indicate that few problems have been seen with this approach and many benefits. Sites may therefore decide to implement home induction. If they choose to offer home induction, the site must create an SOP or modify (an) existing SOP(s) to address the following:

- Confirmation that home induction is allowed in their jurisdiction and by their institution
- What preparation and instructions will be provided to the participant prior to home induction, including what the participant is expected to do if they encounter problems during induction (see example instructions for home induction in Appendix D to this SSP section).
- Expectations for how and when the clinician will engage with the participant during and after induction, prior to the next appointment with the clinician at the mobile unit to receive the next dispensation of medication. If participant-clinician check-ins will be allowed to take place remotely by telephone or video chat, what protocols and technology will be used for that and what safeguards will be in place to protect participant confidentiality?

- Describe how source documentation for these visits will be recorded, making sure that it will be clearly documented which inductions are at home vs at the van.

The expectation for all sites is that the initial dispensation of MOUD in the mobile unit will be for one week's worth of treatment, and that participants will return to the unit at the end of the week to see the clinician and receive their next dispensation, which will also be for a week's worth of medication. The participant will receive a week's medication each week for the first four weeks, and then, if the clinician believes they are stable, transition to returning to the unit for clinician visit and dispensation of medication at 30-day intervals after that. This is the standard expectation, and as a clinical trial, sites should endeavor to provide services in a consistent way from site to site and participant to participant. However, circumstances may dictate a different approach for a particular participant. Examples of such variations include:

- A participant who has been stably in care on buprenorphine until recently and becomes quickly re-stabilized after enrolling may move to 30-day dispensations prior to the fourth week.
- A participant who (per the participant or clinician judgement) needs weekly visits for longer than four weeks to get firmly established in care, or who has logistical difficulties managing more than seven days' medication at a time.
- Situations in which a site/pharmacy delivers medications to a participant (for example, a participant who cannot travel due to a medical condition or house arrest). These should be rare occasions.
- Participants who collect their prescription from a retail pharmacy, for example, because they are pregnant and require buprenorphine without naloxone, or because they have insurance and find it easier to obtain medication from a local pharmacy where they live than to come to the mobile unit.
- It will be up to clinician judgment, in accordance with local standards and procedures, how to provide clinical management of the participant, i.e., if the clinician can conduct some or all check-ins remotely or will need to see the participant at the mobile unit. As noted above, sites providing clinical visits to participants via telephone or video should document what protocols and technology will be used for that and what safeguards will be in place to protect participant confidentiality.

Withdrawal from opioid use can be challenging. Clinicians can prescribe comfort medications for withdrawal symptoms, but these drugs will not be provided from the van. Clinicians are advised against prescribing benzodiazepines for withdrawal. Clinicians will record prescriptions for comfort medications (as they would for any other prescription) in the participant chart.

Even as clinicians begin to work with a participant, they must keep in mind that the end goal of the intervention is to get the participant transitioned stably to care at bricks and mortar facilities in the community by 26 weeks. To do this, the clinician and navigator will work toward having participants begin to receive care at community providers approximately four months into the intervention. This will allow approximately two months before the end of the intervention for participants to get established stably at community-based providers while still receiving support from peer navigators and having access to the clinicians in the mobile unit if initial attempts at transition are not

successful. Clinicians (and navigators) will reinforce these goals and timelines from the beginning of their work with each participant**.** Although initiating care from community providers at four months is the standard expectation, it is recognized that for any individual, timelines may be different and will be determined by participant situation and clinician (and navigator) judgment. Some participants may only need a short period of van-based care before they are stabilized and may be eager to begin receiving clinic-based services prior to four months. Other participants may experience some sort of relapse or set back close to the four-month mark that requires re-stabilization prior to transition. But as a clinical trial, sites should endeavor to target transition at four months to keep the intervention broadly consistent from site to site and participant to participant.

Clinicians will provide MOUD counseling at care visits (intervention arm) and at the Week 26 and 52 Visits (all participants). Testing by urine for MOUD will occur at the Week 26 and 52 Visits. Urine testing for substances of abuse will also take place at the Week 26 and 52 Visits and (for intervention arm) at care visits. Clinicians/staff may share these results with the participant as part of MOUD counseling.

Clinicians and pharmacists are expected to follow national and local requirements/procedures for documenting the distribution of buprenorphine in their state's prescription drug monitoring program (PDMP). This is typically done by pharmacies after distribution of the product to the patient. Clinicians will look up a participant in the PDMP before writing a prescription for/dispensing buprenorphine (new or refill), per any national and/or local requirements or practice. Note that evidence of recent prescription of MOUD in the PDMP is not a study exclusion criterion. If a participant has an open prescription for buprenorphine, clinicians will be expected not to prescribe or dispense more buprenorphine. The clinician will either contact the provider (with participant's permission) to close the open prescription, or the participant will need to wait to receive buprenorphine (or a buprenorphine prescription) until the open prescription has expired. Site clinicians are not expected to query local methadone programs to see if a participant is enrolled. If a participant has an open prescription for any opioids other than buprenorphine in the PDMP, the clinician will have a conversation with the participant about what is going on and will use clinical judgment regarding dispensing or prescribing buprenorphine. If the clinician has any uncertainty about the correct course of action, they should contact the HPTN 094 Clinical Monitoring Committee (CMC) for advice by emailing 094CMC@HPTN.org.

If a clinician suspects that a participant is diverting rather than taking study provided (or prescribed) buprenorphine, the clinician should report this to the HPTN 094 CMC and should address their concern with the participant to try to determine the problem and correct the behavior. If the clinician continues to have concerns that the participant is diverting, they will stop dispensing/prescribing buprenorphine based upon clinical judgment and consultation with the CMC. Suspected or confirmed diversion is not a reason to terminate a participant's participation in the study; such participants can still receive other support and care and will contribute to the data of the study.

9.4.2 Management of HIV Infection

In this study, management of HIV infection is a top priority for participants living with HIV. An overview of HIV management expectations can be found in the protocol in

Section 5.4 and Tables 1 and 2. Clinicians will provide information and counseling about HIV care and ART treatment for HIV to all participants living with HIV at the enrollment visit and as indicated at subsequent visits. For participants in the active control arm, clinicians will provide referrals to an ART provider in the community in consultation with the navigator. For participants in the intervention arm, clinicians should initiate ART as soon as possible, taking into account the complex lives and competing priorities of this population and the wishes of the participant. Although some clinicians may prefer to stabilize participants on MOUD before adding ART (or participants may request this), in other scenarios, a participant might prioritize initiating ART before MOUD, or clinician judgement may be that a participant can handle initiating MOUD and ART simultaneously.

Clinicians managing HIV for intervention arm participants are expected to follow guidelines and protocols established for HIV care, in terms of screening for advanced disease, resistance testing, viral load and CD4 cell count monitoring, etc. Participants identified as having AIDS with a CD4 count of less than 200 cells/mL should also be offered prophylaxis against PCP with either Bactrim or, in the case of a history of sulfa allergy, atovaquone. Both of these medications will provide prophylaxis against toxoplasmosis for those with CD4 counts less than 100 cells/mL.

Some HIV positive participants will have known or suspected ART resistance. Clinicians on the mobile unit with the appropriate skills and experience may manage treatment of these cases, on their own or in consultation with more senior or experienced colleagues. It is expected that study clinicians may need to provide such cases with prescriptions for ART drugs additional to or different from the single regimen available on the van. If the clinician at the site is not comfortable managing the case, the participant will be referred for care, with referral support provided by the peer navigator. Care of participants with known or suspected ART resistance will be managed according to local practice and clinician judgment.

9.4.2.1 Choice of Regimen and Provider

Clinicians taking care of participants in the intervention arm living with HIV who are not engaged in HIV care/taking ART will decide what medication to use based upon the participant's prior history of ART, concerns for or known HIV resistance, and renal and hepatitis B status informed by laboratory testing. Clinicians will attempt to initiate DHHS first line therapy whenever possible. Clinicians will be able to offer Biktarvy® at no cost to intervention arm participants from the van, so this should be a first option if appropriate for the participant. Clinicians in the van may prescribe any appropriate medication to manage a participant's HIV but should be mindful of what the participant's insurance will cover. The clinician should work with the navigator to prioritize (re)securing health insurance for participants living with HIV so that paying for HIV prescriptions does not delay initiation of ART.

Participants in both arms who are in care with an HIV provider in the community will be encouraged to continue their care with that provider. However, if a participant in the intervention arm prefers to receive HIV care from the study clinician (for example because of perceived poor treatment by their prior provider), that is acceptable. In such a scenario, however, the clinician must remind the participant that by 26 weeks they will

need to resume care in the community and should be working with the navigator to find an acceptable community-based provider. If a participant in the active control arm is unhappy with their HIV care provider, the navigator can try to help the participant find a new provider, as available and appropriate.

9.4.3 Management of PrEP

In this study, prevention of HIV infection is a top priority and uptake of PrEP by HIV negative participants is a protocol objective. An overview of expectations related to PrEP can be found in the protocol in Section 5.4 and Tables 1 and 2. Clinicians should follow national and/or local guidelines for whether PrEP is indicated for any individual participant, but the enrollment criteria for the study should mean that participants in the trial not already living with HIV should be eligible for PrEP.

Clinicians will provide information and counseling about PrEP and HIV risk reduction to all participants not living with HIV at the enrollment visit and as indicated at subsequent visits. As part of this consultation, the clinician will review the additional considerations for PrEP use by people with chronic hepatitis B infection. For participants in the control arm, clinicians will provide referrals to a PrEP provider in the community in consultation with the navigator. Arrangements should be made to provide HBV test results to the provider, when possible. For participants in the intervention arm whose laboratory testing indicates they are not infected with hepatitis B, clinicians should initiate PrEP as soon as possible, taking into account the complex lives and competing priorities of this population and of course the wishes of the participant. Although some clinicians may prefer to get participants stabilized on MOUD before adding PrEP (or participants may request this), in other scenarios, a participant might prioritize initiating PrEP before MOUD, or clinician judgement may be that a participant can handle initiating MOUD and PrEP simultaneously. For participants with laboratory evidence of hepatitis B infection, the decision whether to start PrEP will be taken after further discussion of the potential risks and benefits.

Clinicians managing PrEP for intervention arm participants are expected to follow normal guidelines and protocols established for such care.

9.4.3.1 Choice of Regimen and Provider

Clinicians will be able to offer Descovy® or Truvada® for PrEP at no cost to intervention arm participants from the van. Donations of these drugs to the study have been given in quantities to allow Descovy® to be used for all participants except those who were assigned female at birth and are at risk for HIV acquisition from sex; those who were assigned female at birth and are at risk of HIV from sex should be provided with Truvada®. Clinicians in the van may prescribe PrEP medication instead of arranging dispensation from the study, if that is the participant's preference, but should be mindful of what the participant's insurance will cover. The clinician should work with the navigator to prioritize (re)securing health insurance for participants so that paying for PrEP medications (active control arm; intervention arm after 26 weeks) is not a barrier to participants receiving PrEP.

Participants in both arms who have established care with a PrEP provider in the community will be encouraged to continue their care with that provider. However, if a participant in the intervention arm prefers to receive PrEP from the study clinician (for example because of perceived poor treatment by their prior provider), that is acceptable. In such a scenario, however, the clinician must remind the participant that by 26 weeks they will need to resume care in the community and should be working with the navigator to find an acceptable community-based provider. If a participant in the active control arm is unhappy with their PrEP care provider, the navigator can try to help the participant find a new provider, as available and appropriate.

9.4.3.2 Management of HIV Seroconversion Post-Enrollment

In the event a participant has a reactive rapid HIV test after enrollment, participants will undergo confirmatory HIV testing per local guidelines. After confirmation of new HIV diagnosis, participants will receive HIV counseling and will be encouraged to initiate HIV treatment as soon as possible, even if the results of the CD4 count and HIV viral load are not available, in order to prevent further transmission of the HIV. For clinical considerations regarding HIV treatment, see Section 9.5.2 above. For counseling considerations, see section 9.7 below.

9.5 Other Clinical Care

In addition to OUD management and HIV infection treatment or prevention, clinicians will provide other (limited) primary care services from the van. The scope of these services is described in the protocol in Tables 1 & 2. Additional commentary on the scope of these services is provided below. Note that for both arms:

- At any visit (Screening through week 52), the clinician should provide presumptive treatment for STIs if the participant is symptomatic.

- Mental health concerns are addressed above in Section 9.3.6

- Clinicians and other study team members must abide by local reportable disease requirements, e.g., for HIV, gonorrhea, chlamydia, or syphilis.

9.5.1 Active Control Arm Participants

At screening and again at enrollment, rapid test results that are available during the visit (e.g., HIV, pregnancy) should be shared and appropriate information and/or counseling provided by the clinician or qualified staff member, with referral for care as indicated.

At enrollment and again at weeks 26 and 52, samples will be collected for laboratory testing for which results will not be available the same day (e.g., STI test results). Participants should be informed quickly of these results once they are available, through appropriate mechanisms (e.g., telephone call, medical app, letter, in-person) and by the appropriate staff person per local guidelines and practices. The mechanism for reporting may differ based on the nature of the result (e.g., a positive vs. a negative STI result). If there is a result that should be acted upon with urgency by the participant, such as incident syphilis, gonorrhea or Chlamydia, the clinician in collaboration with the navigator and other staff will endeavor to get the participant informed of their result as soon as possible and quickly engaged with proper care in the community (prior to the

Week 26 Visit) or provided information about community resources for care (Week 26 and 52 Visits).

At any visit (Screening through week 52), the clinician should provide presumptive treatment for STIs if the participant is symptomatic.

9.5.2 Intervention Arm Participants

As described above for active control arm participants, intervention arm participants should be informed of laboratory results as soon as they are available, and provided counseling as appropriate regarding their significance, per local guidelines and practices.

Unlike the active control arm, however, intervention arm participants are expected to return to the van for care during the first 26 weeks of their participation, and these visits may be relatively frequent in the first month of the study. These visits will provide one opportunity for the clinician to review test results, explain their significance and provide care, treatment, or referral for care.

As noted in the protocol, locally-supplied medications will be available in the van to treat bacterial STIs and clinicians should treat participants presumptively (if symptomatic) or as indicated by laboratory results. Clinicians may prescribe other regimens or refer participants to community services if the medications available on the van are not sufficient.

Based upon hepatitis testing, the clinician will refer for vaccination or treatment (see protocol) though appropriate ART or PrEP regimens may be prescribed or provided for those with HBV infection (again, see guidance in protocol)

Participants using stimulants will be referred to 12-step meetings or community-based services as available.

Per the protocol, participants who are pregnant will continue to be seen for MOUD, ART, PrEP and other services on the mobile unit. Sites that have access to buprenorphine monotherapy may provide MOUD medication to pregnant participants. Sites that only have the ability to provide combination buprenorphine/naloxone for MOUD will provide pregnant participants with prescriptions for buprenorphine monotherapy or, if the participant prefers, referral to a methadone program. Sites will refer all pregnant participants for obstetric care with an OB/GYN provider comfortable treating pregnant persons who inject drugs treated with MOUD. Study clinicians will endeavor to coordinate with the obstetric care provider to optimize care.

Study clinicians will provide limited reproductive health services in the form of prescriptions for oral contraception, condoms and lube. Referrals should be provided to participants needing or requesting other reproductive health services that go beyond the contraception methods above and basic primary care, as described below.

Clinicians will provide basic primary care to intervention arm participants on the mobile unit. This will include diagnosis and management of minor acute illnesses and infections such as upper respiratory tract infections, colds, flu, diarrheal illness and providing

prescriptions for such conditions if indicated. For more complex care needs and chronic conditions, the clinician will refer the participant for diagnostic and care services available in the community. Clinicians on the mobile unit may provide prescriptions for medications for chronic conditions that have been lost or stolen or are needed for continuity of care, including communication and coordination, as possible, with the provider managing the care of the chronic condition.

Starting with the Week 26 Visit, intervention arm participants will no longer receive medical care or consultation from the study clinician beyond presumptive treatment at the Week 26 and 52 Visits for symptomatic STIs, and provision of study results and referrals for study required clinical testing.

9.6 Timing of Care Visits in the Intervention Arm

The frequency of care visits in the intervention arm will be determined by the clinical need, clinician judgment and the willingness of the participant.

9.7 Specimen Collection

Blood specimens, urine specimens, and swabs for STI assessment will be collected throughout the study. The protocol outlines the clinical procedures and corresponding testing to be performed on the specimens in protocol Appendices 1A-C. Sections 6 and 11 (checklists and laboratory sections) of the SSP should also be consulted for further specifications. The following additional considerations should be noted:

- Blood collection from persons who inject drugs can be challenging. Sites may find it helpful to allow the participant to suggest blood draw sites, to use small needles, to provide hydration to participants prior to sample collection and to solicit supplemental phlebotomy training from colleagues with experience working with this population.
- Guidance regarding guidelines for sample collection can be found in SSP Section 11 (Laboratory).
- As noted in SSP Section 11, it is anticipated that some participants may refuse collection of rectal and/or vaginal swabs and this is their right as study participants.
- The HPTN Laboratory Center specifies a preference for laboratory testing for vaginal GC/CT by swab because it is more sensitive. This may be by self-collection or by clinician collection. If a participant does not want to have a vaginal swab, or this is not the local practice or per clinician judgment, testing for vaginal GC/CT can be by urine instead.
- The expectation is that rectal swabs will be self-collected after brief instruction by the clinician, though those who prefer collection by the clinician should be accommodated.

9.8 Counseling Procedures

9.8.1 Pre- and Post- HIV Testing Counseling

Each site is required to develop a local SOP for providing HIV pre- and post- test

counseling whenever a participant is tested for HIV. Although this SOP will be site-specific and should at a minimum reflect the site's local requirements for HIV counseling and testing, the SOP should contain the following elements:

- Each individual should be provided with information that allows them to decide for themselves whether to be tested (informed decision with informed consent).
- The HIV testing procedure should be organized to maximize confidentiality.
- All individuals being tested for HIV should be provided with information about HIV that allows them to understand the results of their HIV test.
- All individuals should be provided appropriate HIV post-test counseling including appropriate referrals and tailored risk reduction counseling according to the site-specific SOP on post-test counseling.
- Disclosing HIV status to others should be discussed with all participants.
- The need for additional and appropriate referrals should be addressed where possible.

9.8.2 Counseling Following Collection of Data Concerning Behavior and Life History

At the enrollment, 26 and 52 week visits, data concerning behavior and life history will be collected from participants by staff interview and by ACASI questionnaire. These questions will cover such sensitive topics as history of abuse, experiences of sexual violence, and experiences of stigma.

For the participant, exploring these topics may be painful and may bring up powerful emotions, leaving the participant in a vulnerable or distraught condition. Staff should use judgment when administering the questionnaire and if the participant appears to be becoming upset by the process, check in with the participant, acknowledging that these are difficult questions, or offering to pause to give the participant a moment to collect themselves. If the participant is very upset, the staff member may wish to remind the participant that they do not have to complete the entire interview.

At the end of the interview, and also when the participant has completed the ACASI, the staff member should check in with the participant so see how the experience was for them and how they are doing. If the participant reports being distressed, the staff member should ask the participant if they would like to talk a more about how they are feeling or if they would like to talk to a professional therapist. If the participant would like to talk with a therapist, the staff member will provide a referral to a local resource or arrange for a therapist to speak with the participant during the visit if that is a possibility. If, in extreme situations, the staff member feels that the participant is so distraught that they are at risk of harming themselves or others, the staff member should dial 911 and/or follow local escalation procedures.

9.9 Clinical Management Committee

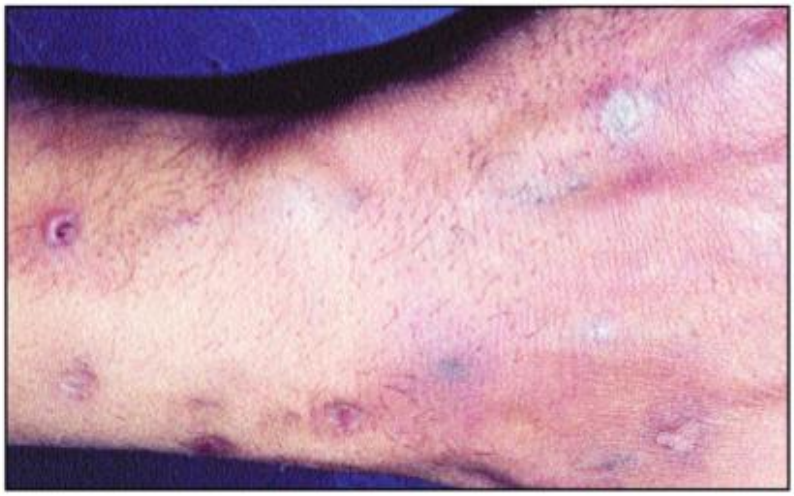
As outlined in the HPTN Manual of Operations (MOP), a CMC is constituted for each HPTN study with a biomedical intervention. The HPTN 094 CMC will provide consultation and decision-making regarding eligibility criteria, SAE management and reporting, and social impacts to participants as needed to ensure consistent case management, documentation, and information-sharing across sites. The CMC will be comprised of site clinicians, Protocol Chair and Co-Chair, DAIDS Medical Officer, and representatives from the HPTN LOC, HPTN LC, and the HPTN SDMC.

Queries from sites are submitted to the following email alias list: 094CMC@HPTN.org.

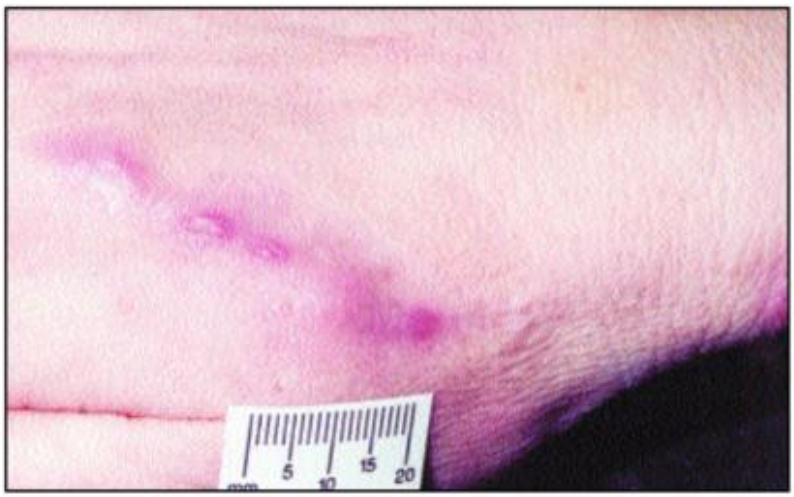
Appendix A
Skin lesion chart

Classifications

1 Recent/Old: Lesions appear to be recent (e.g., inflammation, infection, or nonhealed puncture wounds) and are *paired with* older evidence, such as scars, old granulomas, and atrophy or pigment changes at multiple locations.



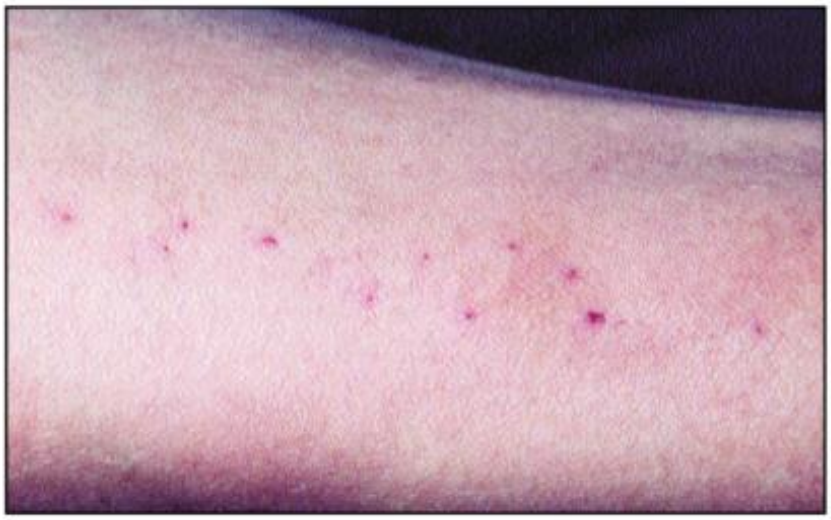
Hispanic/Latino, Left Hand. Old lesions consist of scars, post-inflammatory linear and nonlinear changes in pigmentation, and skin atrophy (note shiny skin). New lesions consist of healing with fresh eschar (scabs).



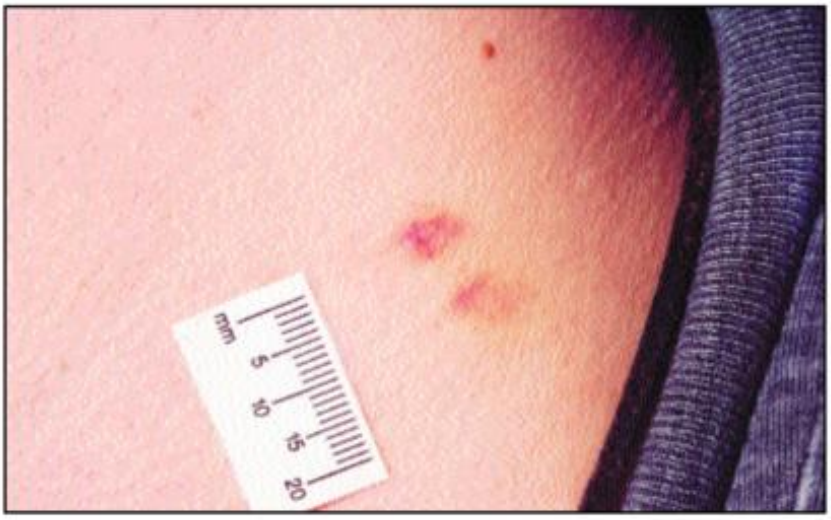
Caucasian, Right Hand. Old lesions consist mainly of post-inflammatory linear changes in pigmentation. New lesions consist of nonhealed puncture wounds with accompanying acute inflammatory changes.

Classifications

2 Recent Only: Lesions appear to be recent (e.g. scabs, punctures, acute or subacute inflammations, thrombosis with wounds, abscesses, or granulomas).



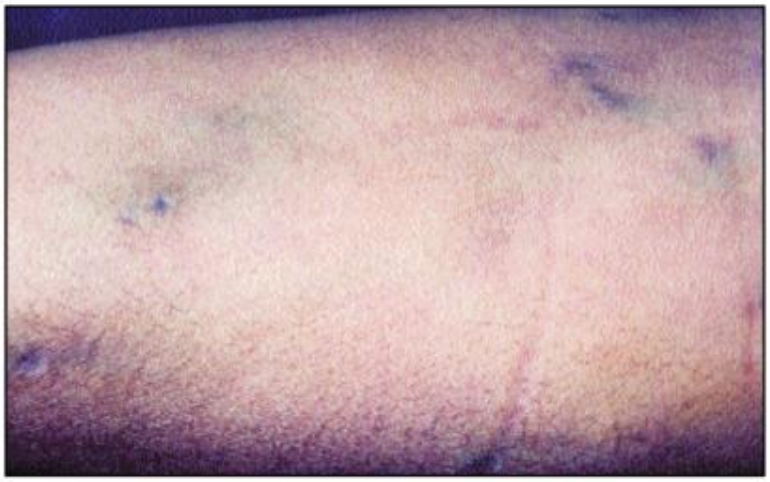
Alaska Native, Right Forearm. New lesions consist of fresh linear skin punctures with accompanying fresh eschar (scabs).



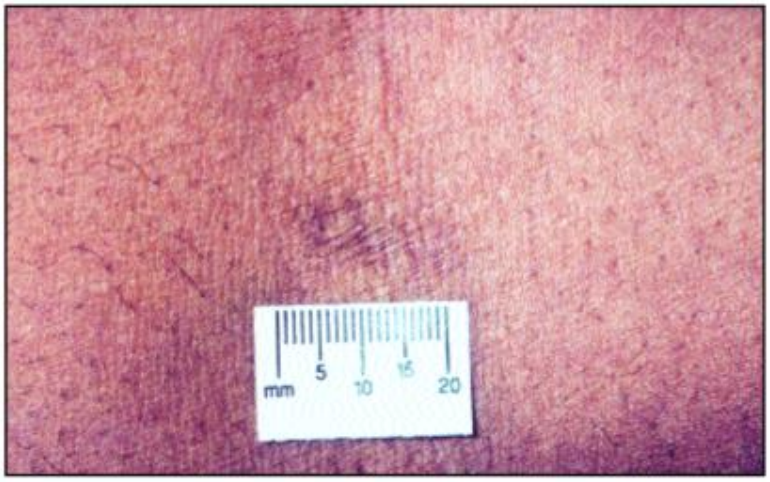
Caucasian, Neck. New lesions consist of recent puncture wounds with accompanying subacute inflammation.

Classifications

3 Old Only: Lesion characteristics include scars, atrophy, hyper- or hypo-pigmentation, pigmented granulomas, or noninflamed thrombosis.



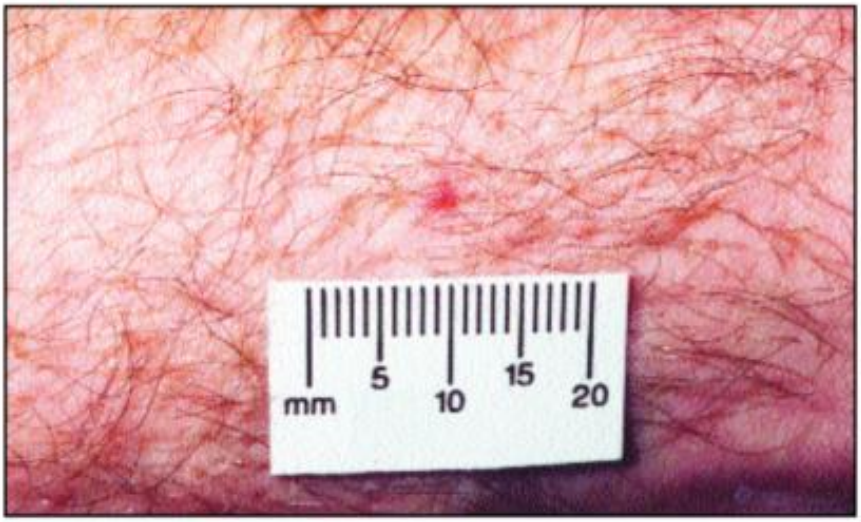
Hispanic/Latino, Left Forearm. Old lesions consist of punctate scars (tiny spots or prick marks) with post-inflammatory pigmentary changes that are both linear and nonlinear.



African American, Right Forearm. Old lesion consists of scarring with accompanying atrophy of the surrounding tissues and slight pigmentary changes.

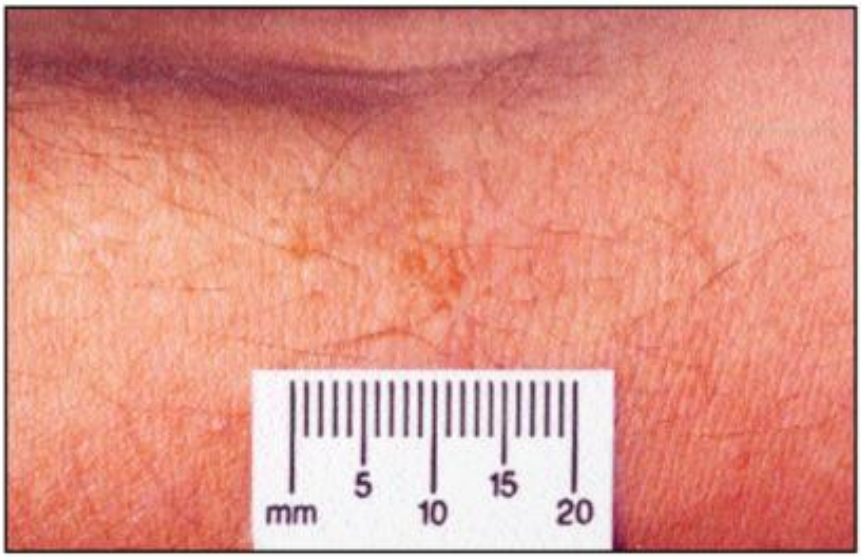
Classifications

4 Conflictive: Lesion characteristics are indiscernible.



Caucasian, Left Forearm. This single inflammatory lesion represents what may be folliculitis (an inflammation of hair follicles), an insect bite, or some other condition or wound.

5 Unsure: Specific nature of lesion is difficult to determine.

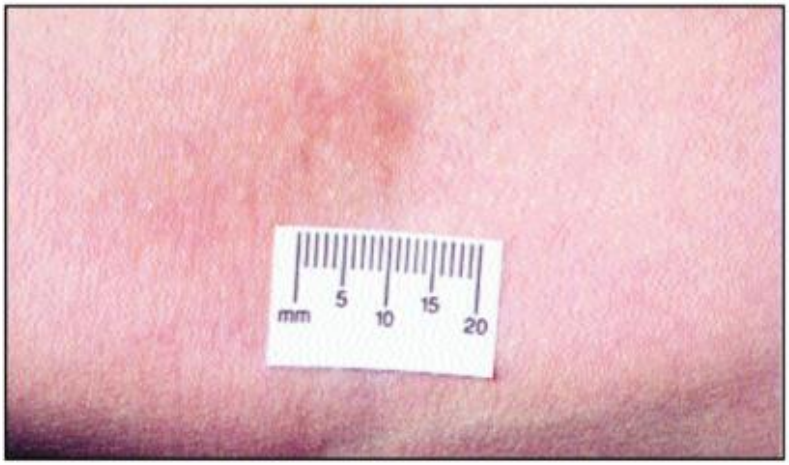


American Indian, Left Forearm. Lesions are subtle, unremarkable, and defy a good description, based upon evidence presented.

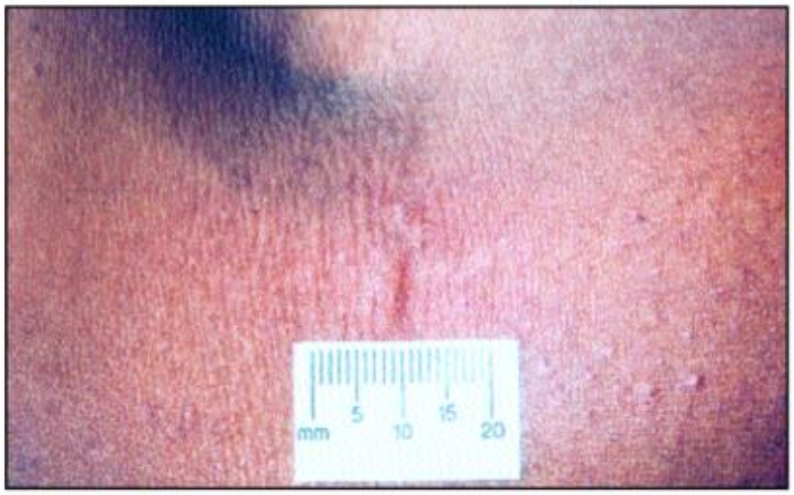
Center for Substance Abuse Treatment

Classifications

6 Inconsistent: Lesion may not be or probably is not an injection site; evidence is insufficient.



Alaska Native, Left Forearm. Lesions are subtle; slight pigmentary changes may or may not be consistent with injection drug use.



African American, Right Forearm. Lesions are subtle; puncture wound may or may not be consistent with injection drug use.

Note: Classification levels 4, 5, and 6 are similar enough that, in practice, they could collectively be considered as a singular classification labeled as "Indeterminate" or "Unsure."

Appendix B

Scoring Screeners for Mental Health Included in HPTN 094 Behavioral CRFs

AUDIT-C

The AUDIT-C, a screening tool for alcohol use disorders, has 3 questions and is scored on a scale of 0-12. Each AUDIT-C question has 5 answer choices valued from 0 points to 4 points. In men, a score of 4 or more is considered positive, optimal for identifying hazardous drinking or active alcohol use disorders. In women, a score of 3 or more is considered positive.

GAD-7:

The GAD-7, a screening tool for anxiety disorder, is calculated by assigning scores of 0, 1, 2, and 3 to the response categories, respectively, of "not at all," "several days," "more than half the days," and "nearly every day." GAD-7 total score for the seven items ranges from 0 to 21. 0–4: minimal anxiety 5–9: mild anxiety 10–14: moderate anxiety 15–21: severe anxiety.

CESD-10:

The CESD-10 is a screening tool for depression. The clinician needs to score "rarely or none" as zero up to "most or all of the time" as 3. But needs to flip the scoring around for items 5 and 8…the two questions addressing positive emotions. A score of 10 or above will be considered a positive screen for possibility of depression.

PC-PTSD (adapted by HPTN 094 team):

The PC-PTSD-5, a screening tool for post-traumatic stress disorder, has five questions and does not specify a timeframe for when a traumatic event may have happened. In that scale, a cutoff of 3 for optimal sensitivity and 4 for optimal efficiency is recommended for probable PTSD. The adapted version included in the HPTN 094 CRF restricts the timeline to an event in the last 6 months and there are only 4 questions, as the final question in the PC-PTSD-5 about guilt has been dropped. Because the 094 adapted screener has been altered in these ways, a formal cut-off number does not apply; the clinician should use their judgment as to whether they feel the participant's responses should initiate a conversation about a referral for psychotherapy/counseling.

References

- AUDIT-C: https://cde.drugabuse.gov/instrument/f229c68a-67ce-9a58-e040-bb89ad432be4#:~:text=The%20AUDIT%2DC%20has%203,or%20active%20alcohol%20use%20disorders
- GAD-7: https://adaa.org/sites/default/files/GAD-7_Anxiety-updated_0.pdf
- CESD-10: American Journal of Preventive Medicine, Volume 10, Issue 2, March–April 1994, Pages 77-84, Screening for Depression in Well Older Adults: Evaluation of a Short

Form of the CES-D, Elena M. Andresen, Judith A. Malmgren, William B. Carter, Donald L. Patrick

- PC-PTSD: https://www.ptsd.va.gov/professional/assessment/screens/pc-ptsd.asp

Appendix C

Tool for Diagnosis of Opioid Use Disorder per DSM-V

[PTID or Participant Name] *(site to determine which based on local documentation practices)*: _____

Clinician: _____

Clinician initials: _____ Date: _____

Which of the following are reported by the participant or observed by the clinician in the 12-months prior to the date of assessment?

- ☐ Opioids are often taken in larger amounts or over a longer period than was intended.
- ☐ There is a persistent desire or unsuccessful efforts to cut down or control opioid use.
- ☐ A great deal of time is spent in activities necessary to obtain the opioid, use the opioid, or recover from its effects.
- ☐ Craving, or a strong desire or urge to use opioids.
- ☐ Recurrent opioid use resulting in a failure to fulfill major role obligations at work, school, or home.
- ☐ Continued opioid use despite having persistent or recurrent social or interpersonal problems caused or exacerbated by the effects of opioids.
- ☐ Important social, occupational, or recreational activities are given up or reduced because of opioid use.
- ☐ Recurrent opioid use in situations in which it is physically hazardous.
- ☐ Continued opioid use despite knowledge of having a persistent or recurrent physical or psychological problem that is likely to have been caused or exacerbated by the substance.
- ☐ Exhibits tolerance (see below).
- ☐ Exhibits withdrawal (see below).

Does the participant meet at least two of the above criteria? Yes / No

If yes, the participant has opioid use disorder.

Tolerance and Withdrawal Diagnostic Criteria

The last two diagnostic criteria, related to tolerance and withdrawal, are not considered to be met for individuals taking opioids solely under appropriate medical supervision.

Tolerance

Tolerance is defined as either: 1) a need for markedly increased amounts of opioids to achieve intoxication or desired effect, or 2) a markedly diminished effect with continued use of the same amount of an opioid.

Withdrawal

You can refer specifically to DSM-5 Criteria A and B for opioid withdrawal syndrome:

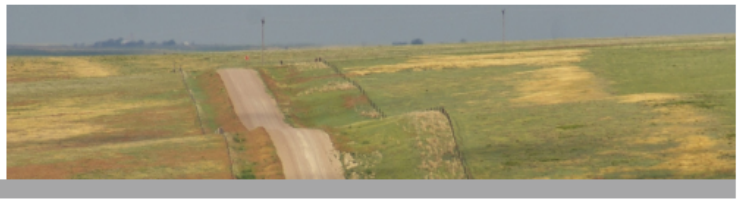
A) Either of the following: 1) Cessation of (or reduction in) opioid use that has been heavy and prolonged (several weeks or longer), or 2) administration of an opioid antagonist after a period of opioid use

B) Three (or more) of the following, developing within minutes to several days after Criterion A: dysphoric mood; nausea or vomiting; muscle aches; lacrimation or rhinorrhea; pupillary dilation, piloerection, or sweating; diarrhea; yawning; fever; or insomnia

Reference: CDC Training for Providers Opioid Overdose Manual accessed 04 Feb 2021 at: https://www.cdc.gov/drugoverdose/training/oud/

Appendix D

IT MATTTRs™



A Patient's Guide to Starting Buprenorphine at Home

PREPARATION

Receiving Medication Assisted Treatment (MAT) with Buprenorphone

Medication assisted treatment (MAT) with buprenorphine is a safe and effective method to help people with an opioid use disorder stop using prescription pain medications, heroin, and other opioids. There are three main phases of MAT: induction (first 1-2 days), stabilization (several weeks), and maintenance (as long as it takes). Before you start treatment, be sure to talk with your health care provider about your plans for treatment.

Your care team should schedule an MAT Procedure Review Appointment with you. This is a great time to discuss your decision to receive MAT, your goals and motivations, concerns, and receive important information. Before starting treatment, your health care team will also conduct a physical evaluation and some lab tests.

Home or Doctor's Office?

This process of getting started on buprenorphine is called Induction. You can be at your doctor's office to get started, or you can do this at home. Talk with your doctor and care team about which option is better for you. There are pros and cons for both options. Which option do you prefer?

Induction at the Doctor's Office		Induction at Home	
Pros	**Cons**	**Pros**	**Cons**
• Your care team is there to check on you and answer questions. • You can build a connection and relationships with your care team. • In some practices, a peer counselor or a behavioral health provider might be there to talk with you.	• You might not be as comfortable as home. • Someone should drive you there and home, ideally.	• You might be more comfortable at home. • You do not need to drive anywhere.	• Waiting to be in withdrawal before taking your first dose of buprenorphine can be difficult. If you take your first dose too soon, you increase the chance of an intense withdrawal that comes on very quickly (precipitated withdrawal). • Your health care team is not there to check on you and talk with you.

When to Stop Taking Opioids

Your treatment will more successful if you prepare for your first dose of buprenorphine (or induction). Before starting your medication, you will need to stop using opioids for a required period. This period of time when you are not using opioids protects you from undesirable side effects, which could delay you from feeling normal again. Be truthful with yourself and your health care team about when you last used opioids and what you used.

Type of Opiold	Examples	When to stop
Short-acting	Percocet, Vicodin (hydrocodone), Heroin	12-24 hours before first dose. *Example: Stop at Sunday at 12 noon for a Monday induction.*
Long-acting	Oxycontin, MS Contin/ Morphine, Methadone	• 36 hours before first dose for Oxycontin, Morphine • >48 hours for Methadone *Example: Stop at Saturday at 12 noon for a Monday induction*

MAT Procedure Review Appointment

Before you start taking buprenorphine and receiving MAT, you and your care team should meet for about 30 minutes. At this meeting, you will receive important information and be able to ask questions. This includes:

- ❑ Review and sign your Consent Form and Treatment Agreement Form.
- ❑ Discuss treatment steps, your goals and motivations, and buprenorphine information.
- ❑ Review the Subjective Opioid Withdrawal Scale (SOWS). This will ensure that you take your first dose of buprenorphine when it will be most effective. Your SOWS score should be ≥17 before starting your first dose.
- ❑ Identify whom you should call to check in.
- ❑ Map out a follow-up plan.
- ❑ Discuss safety, including interaction risks, avoid driving, safe storage

DAY 1

Checklist

Check the boxes next to each step to help you track your progress. Be patient — you're close to feeling better!

Before taking your first dose, stop taking all opioids for 12-36 hours. You should feel pretty lousy, like having the flu. These symptoms are normal. You will feel better soon.

- ❑ Before your first dose of medication, you should feel **at least three** of the following:
  - ❍ Very restless, can't sit still
  - ❍ Twitching, termors, or shaking
  - ❍ Enlarged pupils
  - ❍ Bad chills or sweating
  - ❍ Heavy yawning
  - ❍ Joint and bone aches
  - ❍ Runny nose, tears in your eyes
  - ❍ Goose flesh (or goose bumps)
  - ❍ Cramps, nausea, vomiting or diarrhea
  - ❍ Anxious or irritable
- ❑ Complete the SOWS. You need your SOWS score to be ≥17 before taking your first dose of buprenorphine.

Schedule

- ❑ **Take 4 mg** of buprenorphine under the tongue (tablet or film strip). (Half of an 8 mg tablet, or two 2 mg tablets). Usually one film strip.
- ❑ Put the tablet or film under your tongue. Do not swallow it. Buprenorphine does not work if swallowed.
- ❑ Wait an hour.
  - If you feel fine, do not take any more medication today. Record your total for the day dose below.
  - If you continue to have withdrawal symptoms, take a second dose under your tongue (4 mg).
  - If you are feeling worse than when you started, you might have precipitated withdrawal. Call and talk with your provider about treatment options.
- ❑ Call your provider or office staff to check in.
- ❑ Wait 1-2 hours.
  - If you feel fine, do not take any more medication today. Record your total for the day dose below.
  - If you continue to have withdrawal symptoms, take a third dose under your tongue (4 mg).
- ❑ Call your provider or office staff to check in.
- ❑ Wait 1-2 hours.
  - If you feel fine, do not take any more medication today. Record your total for the day dose below.
  - If you continue to have withdrawal symptoms,

DAY 1 Dose Summary

Dose	Amount	Time
1st dose (if needed)	4 mg	
2nd dose (if needed)	mg	
3rd dose (if needed)	mg	
4th dose (if needed)	mg	
Total mg on Day 1	mg	

Do not take more than 16 mg total of buprenorphine on Day 1.
If you have taken up to 16mg of buprenorphine and still fee bad, call your doctor right away.

Congratulations! You are through Day 1. See Instructions for Day 2 on the next page. You're doing great.

DAY 2

Total from Day 1

What was the total amount of buprenorphine you took yesterday (Day 1)?

Total buprenorphine taken on Day 1	mg

If your Day 1 total was 4 mg:

- ❑ If you feel fine, take 4 mg this morning; however, if you feel some withdrawal symptoms, start with 8 mg this morning.
- ❑ Later in the day, see how you feel. If you feel okay, do not take more. If you still feel withdrawal, take another 4 mg dose.
- ❑ Talk with your provider or office staff.

If your Day 1 total was 8 mg:

- ❑ If you feel fine, take 8 mg this morning; however, if you feel some withdrawal symptoms, start with 12 mg this morning.
- ❑ Later in the day, see how you feel. If you feel okay, do not take more. If you still feel withdrawal, try another 4 mg dose.
- ❑ Talk with your provider or office staff.

If your Day 1 total was 12 mg:

- ❑ If you feel fine, take 12 mg this morning. You might want to split the dose into a morning dose (6 mg) and afternoon dose (6 mg).
- ❑ If you feel some withdrawal symptoms, start with 16 mg this morning.
- ❑ Later in the day, see how you feel. If you feel okay, do not take more. If you still feel withdrawal, try another 4 mg dose.
- ❑ Talk with your provider or office staff.

DAY 2 Dose Summary

Dose	Amount	Time
1st dose (if needed)	mg	
2nd dose (if needed)	mg	
Total mg on Day 2	mg	

NOTES, IDEAS & THOUGHTS

DAY 3

❑ If you felt good at the end of Day 2, repeat the dose you took on Day 2. If the dose was more than 8 mg, you might want to split the dose into a morning dose (6 mg) and afternoon dose (6 mg).

If you felt too tired, groggy, or over-sedated on Day 2, take a lower dose on Day 3 (2-4 mg less).

If you still felt some withdrawal at the end of Day 2, take the same total dose you took on Day 2 plus another 4 mg dose.

❑ See how you feel as the day goes on. If withdrawal symptoms persist, take another dose.

Different people need different doses of buprenorphine. If symptoms persist, consider seeing your provide in the office. Talk with your provider about additional withdrawal treatments that might help.

Do not take more than 32 mg of Buprenorphine in one day.

DAY 3 Dose Summary

Dose	Amount	Time
1st dose (if needed)	4 mg	
2nd dose (if needed)	mg	
Total mg on Day 2	mg	

DAY 4 & BEYOND

On Day 4 and beyond, take the total dose you used on Day 2. You can take more or less medication, depending on how you feel overall, if you still have cravings, or if you are still using.

At this point, you should discuss any dose adjustments with your doctor. If you need to increase your dose, you should not change it by more than 4 mg per day.

NOTES, IDEAS & THOUGHTS

Adapted from NYU School of Medicine Division of General Internal Medicine and PCSS-MAT. Created in partnership with the High Plains Research Network Community Advisory Council for IT MATTTRs. For permission to use outside of IT MATTTRs, please contact ITMATTTRsColorado@ucdenver.edu.