SAN FRANCISCO DEPARTMENT OF PUBLIC HEALTH

STUDY PROTOCOL

Study Title:	Repeated-dose behavioral intervention to reduce opioid overdose: A two-site randomized-controlled efficacy trial
Sponsor:	National Institute on Drug Abuse at the National Institutes of Health
IND No.:	N/A
Indication:	At-risk for opioid overdose
Principal Investigator:	Phillip O. Coffin, MD MIA Director of Substance Use Research San Francisco Department of Public Health 25 Van Ness Ave, Suite 500 San Francisco, CA 94102 Telephone: 415-437-6282 E-mail: Phillip.coffin@sfdph.org
Regulatory Affairs:	This study is overseen by the following IRB: UCSF Committee on Human Research 3333 California Street, Suite 315 University of California, San Francisco, CA 94118 Phone: 415-476-1814 Fax: 415-502-1347 Email: irb@ucsf.edu

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PROTOCOL SYNOPSIS

San Francisco Department of Public Health

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Study Title:	Repeated-dose behavioral intervention to reduce opioid overdose: a two-site randomized-controlled efficacy trial
IND Number:	N/A
Study Center(s) Planned:	2 sites in the United States: San Francisco Department of Public Health in San Francisco, CA and Boston Medical Center in Boston, MA.
Number of Subjects Planned:	At least 300 subjects (150 subjects at each site)
Target Population:	Adult naloxone recipients with moderate to severe opioid use disorder (OUD) who have overdosed
Duration of Treatment:	Subjects will be enrolled in trial for approximately 16 months
Objectives:	The primary objectives of this study are as follows: 1) To adapt REBOOT intervention to ensure relevance in a setting heavily affected by fentanyl using the ADAPT-ITT process. 2) To determine if REBOOT, compared to attention control, reduces during 16 months of follow-up a. the number of opioid overdose events, or b. the occurrence of any opioid overdose. 3) To determine if REBOOT, compared to attention control, increases a. the number of days abstinent from opioid use, or b. days in substance use treatment. The exploratory objectives of this study are as follows: 1) To determine the efficacy of REBOOT first by site, then in affecting several secondary outcomes, such as modifiable risk behaviors and management of witnessed overdose.

Study Design:	We will enroll at least 300 (150 at each site) naloxone recipients with opioid use disorder and a prior opioid overdose who will be randomized 1:1 to receive repeated doses of a 30-45-minute IMB (Informational-Motivational-Behavior)-based counseling session in overdose prevention versus attention control. All participants will complete opioid urine screening at all in-person visits and assessments at enrollment and months 4, 8, 12, and 16. Participants will either receive counseling sessions or control (i.e., viewing videos or listening to podcasts), at months 0 (enrollment), 4, 8, and 12.
Inclusion Criteria:	(1) Age 18-65 years; (2) Self-reported use of non-prescribed opioids in past 14 days; (3) Current moderate to severe opioid use disorder by DSM-5; (4) Urine positive for opioids during screening by point-of-care testing (or self-reported illicit opioid use in the past 4 days, confirmed by a trusted source, for remote or other visits in which urine cannot be collected); (5) History of prior opioid overdose within past 3 years; (6) Previously received take-home naloxone; (7) No life-threatening illness likely to progress clinically during trial; (8) Able and willing to provide informed consent, provide adequate locator information, communicate in English, adhere to visit schedule.
Exclusion Criteria:	(1) Suicide plan or attempt within 12 months prior to screening; (2) Urine positive only for prescribed agonist maintenance therapy and negative for cocaine and methamphetamine (or self-report of ongoing receipt of agonist maintenance therapy for remote or other visits in which urine cannot be collected); (3) Currently participating in another interventional research study that could possibly impact the study's outcomes of interest; (4) Planning to leave San Francisco/Boston metro area during study; (5) Previously exposed to REBOOT counseling intervention; (6) Any condition that, in the Principal Investigator's judgment, interferes with safe study participation or adherence to study procedures.
Study Procedures/ Frequency:	All subjects will complete the following study visits: prescreening, screening, enrollment, study visits every 4 months for a total of 16 months. All study visits, including screening visits, may be done remotely when COVID-19 safety precautions do not permit in-person visits. Follow-up visits may be done remotely when other events restrict a participant from attending in-person visits (e.g. hospitalization, incarceration, inpatient rehabilitation, moving to another part of the country, etc.). Participants may complete a mix of both in-person and remote visits throughout their 16-month participation in the study. A subset of participants will be asked to

attend one final visit after 16 weeks for a validation substudy. Remote visits are conducted by phone or by video, using the Zoom video conference platform.

Prescreening: Prior to conducting informed consent procedures, research staff will administer a brief prescreener questionnaire to interested individuals either in person or over the phone. If participants meet prescreen eligibility criteria, they will be invited to complete an in-person or remote screening visit.

Screening visit: Informed consent will be obtained at the beginning of the screening visit. After consent is obtained and eligibility is determined, a locator form is completed and HIPAA and release of information (ROI) forms are signed. In the case of remote screening visits, verbal HIPAA authorization will be obtained, and the ROI will be omitted or postponed until the participant's written signature can be obtained. The screening visit will also include an evaluation of opioid use disorder by DSM-5 criteria, a screening for suicide risk, and a urine drug screen with expanded opioids, including fentanyl. For remote screening visits or other visits that do not permit urine collection, in lieu of a urine drug screen, the name of a trusted source, provided by the participant, will be asked to verify the participant's recent opioid use. Consent will be obtained from the participant to contact the trusted source and the trusted source will be informed of this agreement through either signed consent or verbal consent (e.g. 3-way call).

Enrollment (month 0): At the enrollment visit, participants will provide a urine for toxicology testing, update the locator form, have their picture taken to store with their locator form (if not done at screening), and will undergo the baseline assessment (administered by a staff-person blinded to study assignment). The photo for the locator form will be omitted for remote enrollment visits; urine drug screening will be omitted for enrollment visits that are remote or otherwise do not allow for collection of urine.

Participants will then be randomized to receive either the behavioral intervention (n=150) or attention control (n=150). **Randomization** will be 1:1, stratified by site, using permuted blocks of randomly selected sizes. Participants will then undergo the initial counseling visit for the intervention or attention control for the control arm. Attention control will involve watching videos during in-person visits and listening to podcasts during remote visits.

The next visit will be scheduled and participants will be compensated for their time.

	Months 2, 6, 10, 14: Participants will be contacted by study staff to update locator form. If contact is successful, participants will be reimbursed $3 at that time or at their next visit. Staff may attempt more frequent contact with participants at-risk to being lost-to-follow-up, but participants will not be compensated for these additional contacts. **Follow-Up Visits (Months 4, 8, 12, and 16):** At months 4, 8, and 12, participant will be seen for urine drug screen (in-person visits only), updating of their locator form, assessment (administered by a staff-person blinded to participant's study assignment), followed by counseling for the intervention arm or video or podcast for the control arm. At month 16, participants will complete activities listed for the monthly visits. Participants in the treatment arm will not receive counseling at month 16 and participants in the control arm will not watch a video nor listen to a podcast, at month 16. Participants will not update their locator form at month 16. The assessment, which is administered at enrollment and months 4, 8, 12, and 16 includes demographic information (enrollment only); drug use history (enrollment only); extensive opiate overdose questions; drug use, treatment and drug-related risk behaviors; questions about incarceration, severity of dependence, hopelessness, impulsivity, participant satisfaction with the study. The assessment also includes a COVID-19 Impact Assessment with questions about COVID-19 risk, testing, and vaccination history; drug use behaviors; and access to resources during the COVID-19 pandemic. **Validation Substudy Visit:** Participants may be invited to complete an additional interview after study completion in which they will complete one repeat assessment to assess the validity of the data collection methodology.
Treatment Arm:	REBOOT participants in the treatment arm will receive repeated doses of a 30-45-minute IMB (Informational-Motivational-Behavior)-based counseling session in overdose prevention at enrollment and months 4, 8, and 12.
Reference Arm:	Participants in the reference arm will receive attention control, which consists of 30-45-minute videos or podcasts, unrelated to overdose, substance use, or health issues such as HIV. Attention control videos will be administered at enrollment and months 4, 8, and 12.

Statistical Methods

Specific Aim 1: We will utilize ADAPT-ITT to ensure REBOOT's relevance in the context of fentanyl. We will produce a manuscript describing the process and outcomes, similar to that which we produced for a prior adaptation study of Personalized Cognitive Counseling that was accepted as a CDC Evidence-Based Intervention (https://tinyurl.com/ybx3oqep). While the manuscript will describe the process and outcomes from each ADAPT-ITT Phase, a major element of this analysis will be the theater test and focus group (Phase 3). Sessions will be audio-recorded and transcribed verbatim. Two independent analysts will develop a codebook and independently code the focus group transcript. The transcript will then be analyzed using standard thematic content analysis. The topical expert review (Phase 6) will also be a key element in describing the adaptation process, as well as the final product of the adapted intervention manual.

Specific Aim 2a: To determine if REBOOT, compared to attention control, reduces the occurrence of any opioid overdose event, we will use generalized estimating equations (GEE) models for the occurrence of any overdose event in each reporting period, with robust standard errors to account for within-subject correlation of the repeated measures. Overdose events will be determined by a modified time-line follow-back every 4 months to determine the approximate date(s) of non-fatal overdose(s). We will review EMS and ED records for fatal episodes and to verify reliability of self-report data for a subset of participants. Based on patterns observed in our pilot, the overdose rate in controls will be flexibly modeled by treating visit as categorical, while the treatment effect—that is, the between-group difference in overdose risk—will be modeled as linearly increasing over follow-up. Because odds-ratios can be misleading when interpreted as relative risks in contexts where outcomes are common, we will use log-link rather than logistic models to obtain relative risks directly. Further, because log-link binomial models do not reliably converge, we will use instead the Poisson model, noting that robust standard errors accommodate the violation of the Poisson assumption of variance equal to the mean. The primary analysis will be by intention to treat, without regard to adherence. Several sensitivity analyses will be performed: 1) with multiple imputation of missing outcomes; 2) with adjustment for any prognostic baseline covariates; 3) using an alternative model assuming a constant rather than linearly increasing treatment effect; and 4) using inverse probability of retention weights to account for potentially informative loss to follow-up. In view of the excellent participant retention and visit adherence in our past studies, we do not expect these sensitivity analyses to affect conclusions.

Specific Aim 2b: To determine if REBOOT, compared to attention control, reduces the number of opioid overdose events, we will use

GEE Poisson models for the number of overdose events in each reporting period, set up in the same way as the model for Aim 1. In this case, robust standard errors will be needed to account for within-subject correlation and potential over-dispersion (rather than under-dispersion) of the count outcome. We expect that repeated overdose events may be reasonably common in a subset of higher risk participants. The sensitivity analyses proposed for Aim 1 will be repeated for this outcome.

Specific Aim 3: To determine if REBOOT, compared to attention control, increases the number of days abstinent from opioid use or days in substance use treatment, we will use GEE Poisson models for each of these outcomes, both set up in the same way as the models for Aims 1 and 2. In addition, we will implement a Number-of-Beyond-threshold-Weeks-of-Success (NOBWOS) analysis, which will track by week the proportions of participants in each group who have achieved abstinence lasting through the end of the study.

Sample size justification: We estimate that the proposed sample of 300 participants, randomized 1:1 to REBOOT and attention control, will provide 80% power to detect net 59% reductions in the prevalence of any overdose by the final reporting period in the REBOOT group, conservatively accounting for net loss of 15% of participants by the end of the study. This is considerably smaller than the 83% net reduction observed in the pilot study. In making these calculations, we used data from the pilot to estimate baseline outcome rates by visit in the control condition, as well as the intra-class correlation of the repeated outcomes.

Exploratory Aims: Exploratory analyses will estimate the efficacy of REBOOT first by site, then in affecting several secondary outcomes. Some of these include modifiable risk behaviors and management of witnessed overdose. To estimate the effect of REBOOT, compared to attention control on overdose risk behaviors, as measured by frequency of using opioids concomitant with alcohol or benzodiazepines (the most common modifiable overdose risk behavior), we will use GEE Poisson models with robust standard errors. We will also use GEE Poisson models with robust standard errors to assess evidence that the intervention increases the use of naloxone during overdose events witnessed by participants. We will also conduct descriptive analyses of overdose risk behaviors and events in the prospectively-followed and sizable control population. Results will also be analyzed by pre and post-COVID-19 pandemic and remote versus in-person visits.

Biological Variables: Sex and age may affect the efficacy of REBOOT for primary as well as secondary outcomes. We will conduct

	additional analyses assessing modification of the REBOOT intervention by these factors.

This study will be conducted in accordance with the guidelines of Good Clinical Practices (GCPs) including archiving of essential documents.

1. INTRODUCTION

1.1. Background

The United States is amidst an opioid crisis, with increasing rates of opioid overdose mortality. While naloxone distribution has demonstrated benefits in reducing opioid overdose mortality, more is needed, particularly interventions to reduce the risk of overdose occurring in the first place. We developed a brief motivational interviewing intervention, based on the IMB model of behavior change, to address opioid overdose among persons who already have access to naloxone but remain at high risk for opioid overdose.

1.2. Overall Risk/Benefit Assessment

Primary Patient Risks:
We do not anticipate any moderate, severe, or life-threatening adverse events as a result of study participation. If a participant should report or display urgent medical or mental health concerns (such as hyperventilation, active suicidal ideation, serious emotional distress, or similar problems) study staff will suggest that a call be placed to an appropriate referral agency or crisis hotline. The staff member may also call 911 if deemed necessary. For remote visits, participants will be asked for their location in the event 911 needs to be called. Referral lists for mental health and substance abuse services and crisis hotlines will be available for reference at all times and provided to participants upon request. Study staff will be trained in how to identify, manage, and respond to these events. If needed, study staff will arrange for counselors or medical personnel to provide assistance to those participants that experience any serious effects during the course of the study.
Potential risks from study participation will be explained through the informed consent process. The study will not dispense naloxone to participants. Prior to enrollment, participants will have received naloxone; prior receipt of take-home naloxone is one of the study inclusion criteria. Therefore, this behavioral study does not pose any additional risks of pharmacologic agents nor does it raise ethical concerns about withholding this potentially life-saving agent. However, participants are informed of potential risks involved in study participation. Potential risks to participants include: unauthorized disclosure of confidential information; discomfort or embarrassment related to specimen collection or questionnaires dealing with personal habits and lifestyle, including drug or alcohol use; possible unwanted encounters with friends or associates in the research setting; possible cell phone charges from the participant's cell phone carrier from study texts and calls; and continued drug use, with its attendant risks, including risk of overdose.

There is potentially an increased risk to the participant's privacy when participating in remote visit procedures as the environment in remote settings may be more difficult to control than in an office setting. Additionally, participants who agree to the trusted source verification process may experience discomfort or embarrassment at having their drug use discussed among study staff and their trusted source. Study staff will provide guidance to participants to help minimize these risks (e.g., to be in a private setting for remote visits, to choose confidential trusted sources).

Alternative treatments and procedures in place to mitigate patient risks: Participants have the alternative of not participating in the study. We will explain to participants that their decision

will in no way influence their treatment by any universities, hospitals, programs or organizations affiliated with the study sites. We will also offer referrals to inpatient and outpatient substance use treatment facilities and services in San Francisco and Boston, upon request.

Benefits: Potential benefits to participants include: possibly becoming more aware of ways to reduce risk of overdose, however participants may not receive any benefit. Potential benefits to society include determining whether an IMB (Informational-Motivational-Behavior)-based intervention reduces opioid overdose risk among persons with opioid use disorder.

1.3. Compliance

This study will be conducted in compliance with this protocol, Good Clinical Practice (GCP), and all applicable regulatory requirements. There is a DSMB for this study.

2. OBJECTIVES

The primary objectives of this study are:

1) To adapt REBOOT intervention to ensure relevance in a setting heavily affected by fentanyl using the ADAPT-ITT process.
2) To determine if REBOOT, compared to attention control, reduces during 16 months of follow-up
    a. the number of opioid overdose events, or
    b. the occurrence of any opioid overdose.
3) To determine if REBOOT, compared to attention control, increases
    a. the number of days abstinent from opioid use, or
    b. days in substance use treatment.

Exploratory objectives of this study are:

1) To determine the efficacy of REBOOT first by site, then in affecting several secondary outcomes, including modifiable risk behaviors and management of witnessed overdose.

3. STUDY DESIGN

3.1. Adaptation

To ensure REBOOT can impact participants in a region hit by synthetic opioids, **we will complete an "ADAPT-ITT" process**, modified as some phases of the process do not apply to designing a full trial of an intervention. The intervention is already selected (Phase 2) and a needs assessment (Phase 1) has been completed by the CDC and affiliated investigators, including numerous qualitative interviews. We have already utilized these data to determine adjustments to the REBOOT intervention and, without changing the core elements and underlying theory of REBOOT, we will produce a first draft of an adapted intervention (early Phase 4). This draft will, for example, incorporate (a) the use of "tester shots", an approach to reducing risk that had fallen out of favor, but has again become common due to the extreme variations in potency of street opioids; (b) the importance of evaluating the appearance of the drug as products containing fentanyl/analogues tend to appear different both as solids and in solution; and (c) the importance of contacting EMS, employing chest compressions as cardiac arrest may be more rapid, and administering sufficient naloxone. We will then implement theater testing (Phase 3), in which 12 persons representative of the Boston target population (i.e., illicit opioid users who have previously experienced opioid overdose events) will observe a mock session, complete a survey and engage in a discussion about the strengths, weaknesses, and potential ways to improve the intervention. From this we will produce the second draft (Phase 4). Phase 5 involves review by topical experts, the results of which are integrated in Phase 6. The final phases, testing the intervention, will occur within the context of the full trial, with a **single, flexible curriculum utilized in both sites**.

3.2. Study Treatment and Duration of Treatment

This is a two-site full randomized-controlled trial of REBOOT, combining an established overdose education curriculum with motivational interviewing principles to leverage personal and witnessed overdose to reduce opioid overdose events.

Three hundred subjects (150 at each site) will be enrolled in one of the following two study arms.

Group 1: IMB Counseling (REBOOT)

- Treatment arm participants will receive a single 30-45 minute session of IMB counseling on overdose prevention at enrollment and months 4, 8, and 12.

Group 2: Attention control

- Participants in the reference arm will receive attention control, which consists of 30-45 minute videos or, for remote visits, podcasts, unrelated to overdose, substance use or health issues such as HIV.

3.3. Treatment Discontinuation Criteria

There are no formal trial-stopping rules for this study. However, a formal interim efficacy analysis will be conducted. Please see DSMP section 7.1 for details of the interim analysis and stopping rules, including stopping for benefit, harm, or futility.

If it becomes clear that the trial puts undue safety risk on study participants, outcomes are poor, or the trial will not achieve its enrollment goals, consideration will be given to stopping the trial, after consultation with the IRB and NIDA program officer (PO).

The overall safety risk to study participants will be determined through regular monitoring procedures. Safety issues will be evaluated as they arise. Study staff will consult with Dr. Coffin, the study Principal Investigator and San Francisco site medical director, or Dr. Walley, the study Co-Investigator and Boston site Principal Investigator, on these safety issues on a case-by-case basis as they are reported by the participant. Non-urgent clinical issues that arise during the course of the study are discussed at the next weekly meeting with Drs. Coffin or Walley. During weekly meetings, study staff will review all the safety issues and incident adverse events for the study overall, by system category, and by possible relationship to the behavioral intervention. The PI will alert the NIDA PO immediately if at any point the team observes an unexpected frequency of serious AEs possibly related to the intervention.

4. SUBJECT POPULATION

4.1. Number of Subjects and Subject Selection

At least 300 subjects will be enrolled in this study (150 at each site).

4.2. Inclusion Criteria

Subjects must meet *all* of the following inclusion criteria to be eligible for participation in this study.

(1) Age 18-65 years;

(2) Self-reported use of non-prescribed opioids in past 14 days;

(3) Current moderate-to-severe opioid use disorder by DSM-5;

(4) Urine positive for opioids by point-of-care testing during screening (or self-reported illicit opioid use in the past 4 days, confirmed by a trusted source, for remote or other visits in which urine cannot be collected)

(5) History of prior opioid overdose within past 3 years;

(6) Previously received take-home naloxone;

(7) No life-threatening illnesses likely to progress clinically during trial;

(8) Able and willing to provide informed consent, provide adequate locator information, communicate in English, adhere to visit schedule.

4.3. Exclusion Criteria

Subjects who meet *any* of the following exclusion criteria are not to be enrolled in this study.

(1) Suicide plan or attempt within 12 months prior to screening;

(2) Urine positive only for prescribed agonist maintenance therapy and negative for cocaine and methamphetamine (if urine cannot be collected precautions, this criterion will not apply);

(3) Currently participating in another interventional research study that could possibly impact the study's outcomes of interest;

(4) Planning to leave San Francisco/Boston metro area during study;

(5) Previously exposed to REBOOT counseling intervention;

(6) Any condition that, in the Principal Investigator's judgment, interferes with safe study participation or adherence to study procedures.

5. STUDY PROCEDURES

The study procedures to be conducted for each subject enrolled in the study are presented in tabular form in **Error! Reference source not found.**1 and described in the text that follows.

The investigator will document any deviation from protocol procedures and notify appropriate regulatory authorities (e.g., IRB and/or NIH).

5.1. Subject Enrollment and Treatment Assignment

Active recruitment will occur at a variety of community locations including, but not limited to, syringe access sites, naloxone distribution sites, the Boston Public Health Commission Engagement Center (Boston site only), local community-based organizations, and SUD treatment centers. Additionally, we will utilize passive recruitment methods through distribution of recruitment materials such as posters, cards, and flyers which will be left at places frequented by opioid users. We will also recruit participants via snowball sampling. Any enrolled REBOOT participant (who was consented, screened, and completed the baseline visit) may refer individuals to the study. Participants will be compensated $40 per person who they refer who is eligible and enrolls in the study (for a total of up to 5 people or $200). Participants will be informed of the snowball sampling process during study visits.

Individuals who express interest will complete a brief prescreening questionnaire administered by staff either over the phone or in person. Those deemed eligible per the prescreener will then be scheduled for a screening visit where informed consent will be signed, or verbal consent will be given (for remote or other visits in which urine cannot be collected), and final eligibility will be determined. Eligible participants will be scheduled for an enrollment visit at which time they will complete the baseline assessment and be randomized to either the counseling intervention or the attention control group, as described below. Follow-up visits will occur every four months for 16 months and will be completed primarily in person, but may also be completed over the phone if necessary.

5.2. Pretreatment Assessments

N/A

5.3. Screening Visit

Participants will be prescreened by trained research staff using IRB-approved procedures. Staff will inform participants of the study, emphasize that participation is voluntary, and provide them with IRB-approved flyers that describe the study. Research staff will administer the prescreening questionnaire to interested participants either over the phone or in person. Those who remain eligible will complete an in-person or remote screening visit. Participants will be informed before the visit that they may still be found ineligible for the study but that they will be compensated for their time.

Informed consent will be obtained at the beginning of the screening visit. After consent is obtained and eligibility is determined, a locator form is completed and HIPAA and release of information forms are signed for review of medical/criminal records. In the case of remote screening visits, verbal consent will be obtained for the informed consent and HIPAA, and the release of information will be omitted. The screening visit will also include Structured Clinical Interview for DSM-5 for opioid use disorder and assessment for suicidal ideation, as well as a urine drug screen with expanded opioids and fentanyl.

Subjects meeting all of the inclusion criteria and none of the exclusion criteria will return to the study site within 28 days after screening for enrollment into the study; enrollment may occur remotely if absolutely necessary due to COVID-19 precautions. Subjects who do not complete enrollment within 28 days may be considered for rescreening on a case-by-case basis, dependent upon the reason for non-enrollment.

Participants will be compensated $20 for the screening visit. Participants will not be compensated for completing the prescreener.

5.3.1. Enrollment Visit

Enrollment procedures will be completed prior to randomization and receipt of the first counseling or attention control session.

For in-person enrollment visits, participants will provide a urine sample for toxicology testing and research staff will administer the baseline assessment. Participants will update the locator form and have their picture taken to store with their locator form (this may also be done at screening if deemed appropriate). In the event of an remote enrollment visit, urine sample and photo will not be collected.

After completing the baseline assessment, participants will be randomized to receive either the behavioral intervention (n=150) or attention control (n=150). **Randomization** will be 1:1 using permuted blocks of randomly selected sizes. Randomization will be followed by initial counseling for the treatment group and attention control for the reference group. The next visit will be scheduled and participants will be compensated for their time.

Participants will be compensated $50 for the enrollment visit.

5.3.2. Interim Contact

Study staff will attempt to contact participants at two-month intervals between scheduled study visits (i.e. months 2, 6, 10, and 14) in order to update locator forms. This contact may be made by phone, other electronic means, or in person. Participants will be compensated $3 for updating contact information, either at the time of updating or at their next in-person visit.

Staff may attempt more frequent contact with participants at-risk to being lost-to-follow-up, however participants will not be compensated for these additional contacts.

5.4. Follow-up Visits (Month 4, 8, 12 and 16)

Participants will complete follow-up assessments every 4 months.

At months 4, 8 and 12, participants will provide a urine drug screen (for in-person visits only), complete the assessment, update their locator form, and receive counseling for the treatment group or attention control for the reference group.

At month 16, participants will provide a urine drug screen (for in-person visits only) and complete the assessment. REBOOT participants will not receive counseling at month 16, and attention control participants will not watch a video nor listen to a podcast at month 16. Participants will not update their locator forms at month 16.

If participants are in a facility at the time of the follow-up visit (i.e. hospital, substance use disorder treatment facility), every effort will be made to reach that participant to complete visit activities. These activities may be completed at the facility if feasible to staff and approved by the facility. Alternatively, assessments may be completed in-person or over the phone if intervention/control sessions are not feasible.

Subjects who have a phone will be compensated as follows: $60 for month 4 visit, $70 for month 8, $80 for month 12, and $100 for month 16. Payments are in the forms of cash or gift card.

As a retention strategy, participants who are not reliably reachable will be required to accept a study cell phone with unlimited minutes in lieu of the cash or gift card stipend. Participants will be informed of this requirement during the informed consent process. If at any visit a participant has their own phone, they will not be required to accept a study cell phone as payment.

5.5. Reliability Substudy Visit

REBOOT participants that complete the Month 16 visit may be invited to participate in one additional brief assessment (Timeline Follow Back re-test). Consent for this substudy visit will be obtained separately. In this visit, the participant will be administered the portion of the assessment for a time period already assessed during the study. The purpose of this re-test is to assess the reliability of the data captured in the assessment. We aim to re-test up to 100 participants. Participants will be compensated $50 for the additional visit.

5.6. Assessments

5.6.1. Labs

Urine drug screen (drugs of abuse screen/expanded opioids) will be done at all in-person visits.

5.6.2. Research Electronic Data Capture (REDCap)

Research staff will verbally administer assessments to participants using REDCap at enrollment and months 4, 8, 12, and 16. Assessments may be completed on paper and later entered into REDCap (e.g. if research staff are not permitted to bring electronic devices when conducting

interviews in a jail). The assessment will **always** be conducted by a staff person blinded to the participant's study arm and prior to administration of the REBOOT intervention or control arm procedures.

The assessment, which is administered at enrollment and months 4, 8, 12, and 16 includes items related to demographics (enrollment only), drug use history (enrollment only), opiate overdose, drug use, treatment, drug-related risk behaviors, incarceration, hopelessness, impulsivity, participant satisfaction with treatment, and questions related to COVID-19 and its impact on various aspects of participants' lives. As part of the assessment, we will record participants' COVID-19 vaccination status.

Primary and secondary outcome variables will be obtained from standardized scales or established approaches. We will utilize overdose measures developed in collaboration with other investigators (Drs Caleb Banta-Green, Traci Green, Amy Bohnert, and Alex Walley) to maximize comparability among overdose studies.

The following standardized scales will be administered and included in the assessment, regardless of study arm:

- **Severity of Dependence Scale:** This 5-item questionnaire measures severity of dependence on opioids (Gossop et al., 1995). It will be administered at all study visits.

- **Abbreviated Impulsiveness Scale (ABIS**): Derived from the Barratt Impulsiveness Scale version 11 (BIS-11), the ABIS is a 13-item measure of trait impulsivity (Coutlee et al., 2015). This scale will be administered at enrollment and month 16.

- **Brief-Neg-H & Brief-Pos-H**: This brief (4-item) measure of hopelessness contains two negatively-worded items and two positively-worded items, and has demonstrated concurrent validity with the Beck Hopelessness Scale (BHS) and the Center for Epidemiologic Studies Depression (CES-D) scale (Fraser, et al., 2014). It will be administered at all visits.

- **Addiction Severity Index (ASI)**: We will administer an adapted version of the ASI Drug Use Module at each study visit (McClellan et al., 1980).

5.6.3. Administrative data

If research staff learn that a participant has died during their participation in the study, date and cause of death will be ascertained from **Vital Records**, as well as from contacts listed on locator forms. Deaths will be reported as SAEs in accordance with IRB and GCP procedures.

Data from local emergency departments and hospitals may be obtained on some or all participants through signed ROIs during enrollment in order to assess for opioid overdose-related visits, as a means of validating self-report data.

5.6.4. Data Management

Data will be maintained in REDCap (tracking, administrative, and survey data). REDCap is more secure than Microsoft Excel or Access and can be accessed from any device with an internet connection and web browser. It is HIPAA-compliant, offers daily backups, and has an audit trail for increased security. Any paper forms will be stored with participant files in locked offices, separate from identifying information per GCP guidelines.

6. ADVERSE EVENTS MANAGEMENT

6.1. Definition of Adverse Events and Serious Adverse Events

Participants will be queried as to adverse events at the beginning of each visit. We will use the DAIDS Table for Grading the Severity of Adult and Pediatric Adverse Events Corrected Version 2.1, July 2017, available at: http://rsc.tech-res.com/safetyandpharmacovigilance/

We will record and report all AEs in accordance with these NIH guidelines. Safety monitoring will include the assessment, follow-up, and reporting of clinical AEs and serious AEs (SAEs). Each AE will be classified by the study clinician/principal investigator as serious or non-serious, and appropriate reporting procedures will be followed.

All AEs that are serious and meet the reporting criteria will be reported to NIDA and the DSMB within 72 business hours of learning of the SAE and to the UCSF IRB within 5 working days if they meet IRB reporting requirements. UCSF IRB is the primary IRB for both study sites.

A Serious Adverse Event (SAE) will be defined according to the guidelines set forth by the FDA (http://www.fda.gov/safety/medwatch/howtoreport/ucm053087.htm) with the modification for the primary outcome of overdose.

A ***serious AE*** is any untoward medical occurrence:

- results in death,
- is life-threatening (defined as an event in which the patient was at risk of death at the time of the event; it does not refer to an event which hypothetically might have caused death if it were more severe),
- requires inpatient hospitalization or causes prolongation of existing hospitalization,
- results in persistent or significant disability/incapacity,
- is a congenital anomaly/birth defect,
- is an important medical event (defined as a medical event(s) that may not be immediately life-threatening or result in death or hospitalization but, based upon appropriate medical and scientific judgment, may jeopardize the patient or may require intervention (e.g., medical, surgical) to prevent one of the other serious outcomes listed in the definition above).

Overdose events will be reported as SAEs if they result in hospitalization or death. Follow-up information which becomes available as the SAE evolves, as well as supporting documentation (e.g., hospital discharge summaries and autopsy reports), will be collected subsequent to reporting, if not available at the time of the initial report, and immediately sent using the same procedure as the initial SAE report.

SAE reporting will include a narrative that will provide details of relevant screening measures, medical history and physical, treatment compliance, participant reports of SAEs, and any other required information. The completed SAE form will contain the participant's ID#, gender, and age; the title and date of the SAE; and narrative explanation. The SAE form will track how the research staff was notified of the event; dates of consent, randomization, and study screening for inclusion/exclusion; study treatment received (visits attended, as staff will be blinded to

treatment arm); other relevant clinical information; dates and circumstances of the hospitalization/death; whether alcohol or drugs were known to be involved; and participant status at last clinical or research contact. The investigators will state whether the event was expected and assess its relatedness to the study intervention. A summary report of all AEs (including SAEs) will be submitted to the DSMB in the annual progress report.

For more information on protocol for AEs and SAEs, please refer to the DSMP protocol.

6.2. Management of SAEs and other study risks

We do not anticipate significant risks to the safety of participants due to study participation. An interim analysis will be conducted as described in section 7.1 of the DSMP to ensure that the study is not continued as designed if there is clear benefit or harm to the intervention or if there is no hope of demonstrating an effect of the intervention; this will be determined by analyzing the frequency of overdose events.

Should participants require acute medical care during study participation, they will be treated on-site by a clinician if available and, once stabilized, taken to the appropriate hospital for care; if a clinician is not available, emergency medical assistance will be sought and the participant transported to the appropriate hospital.

In the case of remote visits, staff will be able to reach the clinical psychologist, nurse practitioner or medical doctor by phone or text, if needed. At the beginning of remote visit calls, participants will be asked for their current location so that staff may provide that information to a 911 operator, if necessary.

6.3. Reporting of SAEs

All AEs that are serious and meet the reporting criteria will be reported to NIDA and the DSMB within 72 business hours of learning of the SAE and to the UCSF IRB within 5 working days if they meet IRB reporting requirements. UCSF IRB is the primary IRB for both study sites.

A Serious Adverse Event (SAE) will be defined according to the guidelines set forth by the FDA (http://www.fda.gov/safety/medwatch/howtoreport/ucm053087.htm) with the modification described in 6.2 of the DSMP for the primary outcome of overdose.

An expedited reporting of SAE will adhere to the following guidelines:

a) Apply regardless of the investigator's assessment of the relatedness of the SAE to the intervention under study.
b) Apply equally to trials requiring an IND and those not requiring an IND.
c) Apply to any SAE that occurs during the post-treatment observation period defined by the protocol.
d) Apply to suicidal or homicidal behavior that causes an SAE in the subject or someone else (*e.g.* hospitalization or death).

7. CHANGES TO STUDY PROTOCOL

7.1. Reporting of IRB actions and DSMB reports to NIDA

Through the study project officer, NIDA will be informed of IRB actions regarding the study and provided the annual DSMB report. When significant revisions to the protocol are planned, IRB and DSMB communications will be forwarded to the NIDA Project Officer (PO), Dr. Will Aklin, phone 310-827-5909, email: aklinwm@mail.nih.gov.

7.2. Report of changes or amendments to the protocol

All changes and amendments to the study protocol will require IRB approval prior to their implementation. When appropriate, the NIDA project officer will be informed of changes or amendments to the study protocol. Changes to the DSMP must also be approved by the DSMB and NIDA prior to implementation.

7.3. Trial stopping rules

Please see section 7.1 of the DSMP for details of interim analysis and stopping rules, including stopping for benefit, harm, or futility.

In addition, if it becomes clear that the trial puts undue safety risk on study participants or the trial will not achieve its enrollment goals, consideration will be given to stopping the trial, after consultation with the DSMB, IRB, and NIDA PO.

The overall safety risk to study participants will be determined through regular monitoring procedures. Study staff will consult with Drs. Coffin and/or Walley on these safety issues on a case-by-case basis as they are reported by participants. Non-urgent clinical issues that arise during the course of the study are discussed by the research staff at the next weekly meeting with Drs. Coffin or Walley. During weekly meetings, study staff will review all safety issues and incident adverse events for the study overall, by system category, and by possible relationship to the behavioral intervention. The PI will alert the DMSB and the NIDA P.O. immediately if at any point the team observes an unexpected frequency of serious AEs possibly related to the intervention. Of note, to maintain the partial blind, only interventionists will know the study arm of each participant.

7.4. Disclosure of conflicts of interest

Staff are required to disclose any financial conflicts of interest with the study. Signed documentation of conflicts of interest (or lack thereof) by study investigators will be provided to the IRB as required by the initial and continuing review process.

8. STATISTICAL CONSIDERATIONS

8.1. Analysis Objectives

8.1.1. Analysis Objectives

The primary objectives of this study are:

1. To adapt REBOOT intervention to ensure relevance in a setting heavily affected by fentanyl using the ADAPT-ITT process.
2. To determine if REBOOT, compared to attention control, reduces during 16 months of follow-up
    a. the number of opioid overdose events, or
    b. the occurrence of any opioid overdose
3. To determine if REBOOT, compared to attention control increases
    a. the number of days abstinent from opioid use, or
    b. days in substance use treatment.

The exploratory objectives of this study are:

1) To determine the efficacy of REBOOT first by site, then in affecting several secondary outcomes, such as modifiable risk behaviors and management of witnessed overdose.

8.2. Analysis Conventions

All individual subject data will be listed as measured. All statistical summaries and analyses will be performed using STATA® software.

8.3. Demographic Data and Baseline Characteristics

Demographic and baseline characteristics will be summarized using standard descriptive methods by treatment group and overall.

Demographic data will include sex, self-identified race/ethnicity, and age.

8.4. Data Analysis

8.4.1. Primary Analysis

1) Specific Aim 1: We will utilize ADAPT-ITT to ensure REBOOT's relevance in the context of fentanyl. We will produce a manuscript describing the process and outcomes, similar to that which we produced for a prior adaptation study of Personalized Cognitive Counseling that was accepted as a CDC Evidence-Based Intervention (https://tinyurl.com/ybx3oqep). While the manuscript will describe the process and outcomes from each ADAPT-ITT Phase, a major element of this analysis will be the theater test and focus group (Phase 3). Sessions will be audio-recorded and transcribed verbatim. Two independent analysts will develop a codebook and independently code the focus group transcript. The transcript will then be analyzed using standard thematic content analysis. The topical expert review (Phase 6) will also be a key element in

describing the adaptation process, as well as the final product of the adapted intervention manual.

2) Specific Aim 2a: Number of overdose events occurring during follow-up
    a. To determine if REBOOT, compared to attention control, reduces the occurrence of any opioid overdose event, we will use generalized estimating equations (GEE) models for the occurrence of any OD event in each reporting period, with robust standard errors to account for within-subject correlation of the repeated measures.

3) Specific Aim 2b: Occurrence of any opioid overdose event during follow-up
    a. To determine if REBOOT, compared to attention control, reduces the number of opioid overdose events, we will use GEE Poisson models for the number of OD events in each reporting period, set up in the same way as the model for Aim 2a.

4) Specific Aim 3: Number of days not using opioids and number of days engaged in treatment for opioid use disorder during follow-up
    a. To determine if REBOOT, compared to attention control, increases the number of days abstinent from opioid use and days in substance use treatment, we will use GEE Poisson models for each of these outcomes, both set up in the same way as the models for Aims 1 and 2.

8.4.2. Exploratory Analyses

Exploratory analyses will estimate the efficacy of REBOOT first by site, then in affecting several secondary outcomes. Some of these include modifiable risk behaviors and management of witnessed overdose. To estimate the effect of REBOOT, compared to attention control, on overdose risk behaviors, as measured by frequency of using opioids concomitant with alcohol or benzodiazepines (the most common modifiable overdose risk behavior), we will use GEE Poisson models with robust standard errors. We will also use GEE Poisson models with robust standard errors to assess evidence that the intervention increases the use of naloxone during overdose events witnessed by participants. We will also conduct descriptive analyses of overdose risk behaviors and events in the prospectively-followed and sizable control population.

COVID-19 Variables: Using the adapted REBOOT intake and follow up assessments we will assess whether COVID-19 infection status is associated with an increased risk of opioid overdose. First, we will estimate the proportion of the REBOOT cohort with a history of infection by COVID-19 based on combined TLFB and health record review, then assess trends in this proportion beginning in January 2020. The association of COVID-19 infection with overdose rates will be assessed using the Anderson-Gill extension of the Cox model for repeated failure events, with calendar date as the time scale.

We will also assess the changes during the COVID-19 pandemic in participant OUD treatment and overdose prevention service use (e.g. naloxone rescue kit access at syringe service programs) using GEE repeated measures models for these outcomes in each reporting period. Predictors of primary interest will include indicators for self-report of COVID-19 infection in the current or previous reporting period, the proportion of the current reporting period covered by a local shelter in place order, other COVID-19 public health mandates, and other policy factors. We will also assess trends in self-reported reduced service use due to the public health mandates. Overlap

of participant-specific 4-month reporting periods will be accommodated by including the reported outcomes in the assessment of included calendar month, with robust standard errors accounting for the repeated measures.

COVID-19 analyses: Sex, age, gender, race/ethnicity, OUD treatment status, medical and mental health comorbidities, incarceration, and homelessness may affect COVID-19 infection severity and overdose risk. Therefore, we will assess associations of overdose with indicators of any history of COVID-19 infection as well as time since the infection, controlling for these fixed and time-dependent confounders. These variables may also affect OUD service utilization and the impact of shelter in place orders. Therefore the GEE models will control for these fixed and time-dependent confounders. Results will also be analyzed by pre and post-COVID-19 pandemic and remote versus in-person visit status.

Biological Variables: Sex and age may affect the efficacy of REBOOT for primary as well as secondary outcomes. We will conduct additional analyses assessing modification of the REBOOT intervention by these factors.

Sample Size

Sample size justification: We estimate that the proposed sample of 300 participants, randomized 1:1 to REBOOT and attention control, will provide 80% power to detect net 59% reductions in the prevalence of any overdose by the final reporting period in the REBOOT group, conservatively accounting for net loss of 15% of participants by the end of the study. This is considerably smaller than the 83% net reduction observed in the pilot study. In making these calculations, we used data from the pilot to estimate baseline outcome rates by visit in the control condition, as well as the intra-class correlation of the repeated outcomes. Given the extremely high rates of overdose reported in fentanyl-affected areas, our power may exceed current estimates.

9. RESPONSIBILITIES

9.1. Investigator Responsibilities

9.1.1. Good Clinical Practice

The investigator will ensure that this study is conducted in accordance with the principles of the Declaration of Helsinki (as amended in Edinburgh, Tokyo, Venice, Hong Kong, and South Africa), International Conference on Harmonisation (ICH) guidelines, or with the laws and regulations of the country in which the research is conducted, whichever affords the greater protection to the study subject.

The investigator and all applicable sub-investigators will comply with 21 CFR, Part 54, 1998, providing documentation of their conflicts of interest. This documentation must be provided prior to the investigator's (and any sub-investigator's) participation in the study. Study completion is defined as the date when the last subject completes the protocol-defined activities.

9.1.2. Institutional Review Board (IRB) Approval

UCSF IRB is the primary IRB for both study sites. The investigator (or sponsor as appropriate according to local regulations) will submit this protocol, informed consent form, and any accompanying material to be provided to the subject (such as advertisements, subject information sheets, or descriptions of the study used to obtain informed consent) to the IRB. The investigator will not begin any study subject activities until approval from the IRB has been documented and provided as a letter to the investigator.

Before implementation, the investigator will submit to and receive documented approval from the IRB any modifications made to the protocol or any accompanying material to be provided to the subject after initial IRB approval, with the exception of those necessary to reduce immediate risk to study subjects.

9.1.3. Informed Consent

Study staff are responsible for obtaining written or verbal (for remote visits) informed consent from each individual participating in this study after adequate explanation of the aims, methods, objectives, and potential hazards of the study and before undertaking any study-related procedures. The investigator will use the most current IRB approved consent form for documenting written and verbal (for remote visits) informed consent. For in-person visits the informed consent will be appropriately signed and dated by the subject and the person conducting the consent discussion, and also by an impartial witness if required by IRB or by local requirements. If the informed consent process is done remotely, verbal consent will be obtained from the participant and appropriate documentation of the process will be completed by the staff person leading the consent discussion. The consent form will inform subjects about sample retention and use of retained samples.

9.1.4. Confidentiality

The investigator will assure that subjects' anonymity will be strictly maintained and that their identities are protected from unauthorized parties. Only subject initials, date of birth, and a unique identifier (as allowed by local law) will be recorded on any form or biological sample submitted to the Sponsor, IRB, or laboratory. Laboratory specimens will be labeled in such a way as to protect subject identity while allowing the results to be recorded to the proper subject. Refer to specific laboratory instructions. NOTE: If given signed or verbal permission by the subject, the investigators keep locator forms showing names, date of birth and addresses for all subjects screened and for all subjects enrolled in the trial. The information may be written on paper forms, recorded in REDCap, or both. Subject data will be processed in accordance with all applicable regulations.

9.1.5. Study Files and Retention of Records

The investigator will maintain adequate and accurate records to enable the conduct of the study to be fully documented and the study data to be subsequently verified. These documents should be classified into at least the following two categories: (1) investigator's study file, and (2) subject clinical source documents.

The investigator's study file will contain the protocol/amendments, CRF and query forms, IRB and governmental approval with correspondence, informed consent, drug records, staff curriculum vitae and authorization forms, and other appropriate documents and correspondence.

The required source data should include sequential notes containing at least the following information for each subject:

- Subject identification (name, date of birth, gender);
- Documentation that subject meets eligibility criteria;
- Documentation of the reason(s) a consented subject is not enrolled
- Participation in study (including study number);
- Study discussed and date of informed consent;
- Dates of all visits;
- Documentation that protocol specific procedures were performed;
- Results of efficacy parameters, as required by the protocol;
- Participant study start and end date, including treatment arm;
- Record of all adverse events and other safety parameters (start and end date, and including causality and severity);
- Date of study completion and reason for early discontinuation, if it occurs.

9.1.6. Case Report Forms (CRFs)

For each subject consented, a CRF will be completed by an authorized study staff member whose training for this function is documented according to study procedures. CRFs should be completed on the day of the subject visit to enable the sponsor to perform central monitoring of safety data. Prior to database lock (or any interim time points as described in the clinical data management plan), study staff will use his/her log in credentials to confirm that the forms have been reviewed, and that the entries accurately reflect the information in the source documents. The CRFs capture the data required per the protocol schedule of events and procedures.

9.1.7. Protocol Compliance

The investigator is responsible for ensuring the study is conducted in accordance with the procedures and evaluations described in this protocol.

9.1.8. Study Discontinuation

The investigator reserves the right to terminate the study at any time. Should this be necessary, the investigator will arrange discontinuation procedures and notify the appropriate regulatory authority(ies) and IRB.

10. APPENDICES

Appendix 1. Study Procedures Table
Appendix 2. REBOOT 2.0 Counseling Manual

10.1. Appendix 1. Study Procedures Table

Screening, Enrollment, Monthly Visits

Procedure	Screening visits	Enrollment	Visit identified by study month				Post-study Visit
			4	8	12	16	
Informed consent	X						
Locator form		X	X	X	X		
Urine drug screen (expanded opioids and other drugs of abuse)*	X	X	X	X	X	X	
Opioid use disorder, DSM-5	X					X	
Suicide plan/attempt (past year)	X						
Randomization		X					
Intervention		X	X	X	X		
REDCap assessment		X	X	X	X	X	X**

* Urine drug screens will not be completed for remote or other visits in which urine cannot be collected.

****Partial assessment**

10.2. Appendix 2. REBOOT 2.0 Counseling Manual

REBOOT 2.0
Intervention Guide

v. 1.3 (04/25/19)

Introduction (3 minutes)

Key Objectives

- ☐ Provide time frame for today's conversation as well as future sessions
- ☐ Explain purpose of today's conversation (intervention)
- ☐ Engage participant and build rapport
- ☐ Review definitions (if needed)
- ☐ Assess opioid use

Outline and Sample Prompts

1. **Introduce yourself and explain the purpose of the intervention.**
   - *Thank you for participating in REBOOT. We really appreciate it.*
   - *This portion of the study visit will take about 45 minutes.*
   - *Today we'll be discussing your experience with witnessing an overdose and your own most recent overdose.*
   - *We will also talk about what increases risk for an overdose and what can reduce overdose risk*
   - *Then we will discuss what all you might want to do to reduce your risk for another overdose.*
   - *Before we dive in, do you have any questions for me? Do you need something more to drink or eat?*

2. **Review definitions.**
   - *For this session, we will be using the same definition of opioids provided during the survey you completed. Do you have any questions about that?*
   - *For an opioid overdose, please think of something that happens when a person uses more opioids than their body can handle at that time.*
   - *A person who is experiencing an overdose is not responsive, lost consciousness after using drugs, is turning blue, or is not breathing normally.*

Interventionist Note:
You do not need to review the definitions unless the participant would like a refresher.

Opioids: Common drugs like heroin, fentanyl, and morphine. Also includes many prescription drugs like oxycodone, hydrocodone, hydromorphone, OxyContin, Vicodin, Dilaudid, MSContin, Percocet, methadone and Suboxone.
Naloxone: Also known as Narcan, the medication that pulls people out of an opioid overdose.

3. **Briefly Assess Participant's Opioid Use.**
    - *Just so I have an idea of your opioid use, please share a little with me about your use, for example, how frequently you use, where and with whom (if anyone) you use, and how you typically use (route).*
    - *Thank you for providing me with that brief summary. That helps me get a good picture of your use.*

Witnessed Overdose History (4 minutes)

Key Objectives

- ☐ Discuss most recent witnessed overdose experience
- ☐ Assess participant's knowledge of how to recognize and define an overdose
- ☐ Begin to identify risk factors for overdose

Now I would like to ask you some personal questions about overdose experiences. These experiences may be difficult to share. Please let me know if at any point you need to take a moment.

Outline and Sample Prompts

1. **Explore participant's experience of witnessing an overdose.**
    - *Please think back to the last time you saw someone overdose and walk me through what happened.*

Example prompts to establish narrative:

- *Where did the overdose occur?*
- *What substances was the person using?*

2. **Assess participant's knowledge of how to recognize and define and overdose.**
    - *How did you know it was an overdose? What are some other signs that someone may be overdosing?*

Interventionist Note:
1) Check in to see how participant is doing and if they need support around this event. If appropriate, provide referrals for mental health/trauma resources at the end of session.

Example responses:

- *I'm sorry to hear that happened, it's a good thing you were there to help.*

- *That sounds like that was a hard/upsetting/traumatic experience.*

2) If participant reports never witnessing an overdose, inquire about an overdose they've heard about.

3. **Explore risk factors for witnessed overdose.**
   - *Looking back on that event, what do you think contributed to this person's overdose?*
     - [If participant doesn't know, use prompt]:
       In general, what things do you think can contribute to overdose?

Personal Overdose History (6-10 minutes)

Key Objectives

- ☐ Discuss participant's most recent, or most significant, personal overdose
- ☐ Assess participant's view of own overdose risk
- ☐ Identify participant's risk factors for overdose
- ☐ Begin to elicit motivation for behavior change

Outline and Sample Prompts

1. **Explore participant's own experience of overdosing.**
   - *Now let's discuss the last time you experienced an overdose. Thinking back to that time, please tell me the story of your most recent (or most significant) overdose.*

Example prompts to establish narrative:

- *When and where did it occur?*
- *Who all, if anyone, was with you?*
- *What, if any, other drugs or alcohol had you used that day?*
- *What, if anything, was different about your use this time?*

2. **Elicit potential risk factors for this overdose.**
   - *Looking back on that event, what things (factors) do you think contributed to your overdose?*

Example prompts to probe for additional risk factors:

- *You mentioned that _____ [see prompts below]_____, how might this have contributed to your overdose?*
  - *You had just gotten out of jail/treatment/detox/the hospital*
  - *You had bought from a new dealer / used a new batch*
  - *You didn't know how strong the batch was*

- *You had used other drugs or medications that day*

If not described in narrative: *Do you think that _____ contributed to your overdose this time?*

3. **Explore participant's experience after the overdose and motivation for change.**
    - *What happened next?*

Example prompts to establish narrative:

- *Who was with you when you were using?*
    - *Were they using also?*
    - *Did you use at the same time, or take turns?*
- *Did someone give you naloxone to wake you up?*
- *Did someone call 911? If not, did someone stay with you until you were okay?*
    - *What happened when they came?*
    - *Did you go to the hospital?*
- *Since this overdose, what thoughts (if any) have you had about your use?*

Example response:

- *I'm sorry to hear that this happened and am glad you're here today.*

Provide Information on Risk Behaviors and Prevention (10 minutes)

Key Objectives

Using **Handout A**, first discuss **overdose risk factors**:

- ☐ Using more or stronger opioids
- ☐ Using fentanyl
- ☐ Mixing opioids with other drugs
- ☐ Injecting
- ☐ Using after a break
- ☐ Using alone and/or in a place where nobody will find you
- ☐ Not having naloxone nearby
- ☐ Having overdosed before

Using **Handout B**, then discuss **overdose prevention strategies**:

- ☐ Test drug w/ fentanyl test strips
- ☐ Tester shot/go slow
- ☐ Changing route of administration (from injection to less risky)
- ☐ Using with others/taking turns
- ☐ Making injection spaces safer (e.g. better lighting, not rushing, etc.)
- ☐ Carrying naloxone/using with someone who has naloxone
- ☐ Medications like methadone and buprenorphine

Interventionist Notes:

Counselor should use open-ended questions to elicit participant's own knowledge around overdose risks. Counselor should affirm participant knowledge and fill in any gaps in knowledge. Refer to Handouts A & B during the discussion.

Outline and Sample Prompts

2) Review overdose risks with participant

- *Statistically, people who have overdosed before are more likely to overdose again. So just by having overdosed in the past, you are at a greater risk for having an overdose in the future.*
- *It is also true that people who practice certain harm reduction strategies can greatly reduce their risk of overdose, no matter what their overdose history is.*
- *Let's talk about other things that increase a person's risk of having an overdose and the things people do that reduce their chances of an overdose.*

Example prompts to promote discussion:

- *In general, what things do people do that can lead to an overdose?*

Example responses:

- *You're right, _____ are things that we know can lead to an overdose. May I share some additional information about overdose risk?*

Provide participant with Handout A: Behaviors that Contribute to Overdose Risk.

- *Here is a handout that lists things that have been proven to increase the chances of a person overdosing, some of which you already mentioned.*

Counselor and ppt take turns reading Handout A out loud, if possible, while the other follows along.

Example scripts to promote discussion and provide information:

- *Which of these, if any, are new to you?*
- *Which of these, if any, are relevant to you (i.e. potentially contribute to your risk of an overdose)?*

If participant is uncertain, counselor may offer some factors potentially relevant to the participant based on their earlier description of use patterns and overdose experience.

3) Review overdose harm reduction with participant.

Example prompts to promote discussion:

- *Now let's review some of the practices that have been proven to reduce a person's chance of having an overdose.*

Provide participant with Handout B: Behaviors/Activities that Can Reduce Risk of Overdose.

Counselor and participant take turns reading Handout B out loud, if possible, while the other follows along.

Example prompts to promote discussion:

- *Thinking about the things you mentioned earlier that increase your chance of having an overdose, which of these, if any, do you already do to protect yourself?*
- *Which of these things, if any, are you willing or interested in doing to further protect yourself and further reduce your chance of overdosing again?*

Interventionist Note: Participants may report non-evidence-based strategies to reduce their overdose risk. You should acknowledge that this method may have worked for them or for others in the past, and encourage them to incorporate evidence-based methods into their plan.

Interventionist Note: If at any time during the session the participant expresses a desire for substance use disorder treatment, provide referrals for treatment options at the end of the session. Methadone and buprenorphine are opioid agonists that help to maintain the body's ability to tolerate opioids and help to control other opioid use by reducing craving and avoiding withdrawal – both effects that reduce the risk of overdose.

Motivation and Change Plan (10 minutes)

Key Objectives

- ☐ Reinforce that overdose can be avoided
- ☐ Reinforce principles of harm reduction
- ☐ Elicit motivation for behavior change
- ☐ Assist participant in developing realistic overdose prevention plan
- ☐ Work with participant to create harm reduction pocket card

Outline and Sample Prompts

1. **Reinforce that overdose can be avoided.**
   - *Just in the same way that going to a needle exchange and using sterile equipment allows people to avoid getting HIV or Hep C, there are ways to prevent overdose.*

     OR
   - *As mentioned before, people who practice certain harm reduction strategies can greatly reduce their risk of overdose, regardless of the number of overdoses experienced.*

2. **Reinforce Principles of Harm Reduction.**
   - *What does the term "harm reduction" mean to you?*
   - *Yes, those are good points you mention. May I add a little more to what you shared?*

- *Harm reduction is a set of practical strategies used to reduce the negative consequences associated with drug use.*
- *Harm reduction is also built on a belief in, and respect for, the rights of people who use drugs.*
- *Harm reduction affirms that drugs users themselves are the primary agents of reducing the harms of their drug use, and seeks to empower users to share information and support each other in strategies that meet their actual conditions of use.*

3. Elicit motivation for behavior change, and address ambivalence and barriers.

Example prompts to elicit motivation:

- *Based on our conversation thus far, it sounds like _____ are things that you might realistically be ready to do to avoid overdoses in the future. Do I understand correctly?*
- *On a scale from 0-10, how ready are you to make that change?*
    - If a "0", discuss barriers:
        - *What would have to happen to move to a "4" or "5"?*
    - If a "1"-"9", elicit change talk:
        - *Please tell me why you are a "2" or __ and not a "0"?*
        - *What would have to happen for you to move from a "2" or _ to "6" or a"7"?*
        - Then reflect change talk back:
            - *What if anything, are you willing to do starting this week or next to reduce your risk of overdose?*
    - If a "10", discuss plan to implement.
- *What are the reasons you want to make this change?*

Example responses to reflect change talk and address barriers:

- If ready to make a change:
    - *It sounds like _____ is really important to you. Making these changes can help you protect yourself and the people you care for.*
- If not ready to make a change:
    - *What, if anything, might you consider changing down the road?*
    - *What would have to happen for you to be more prepared to make a change?*

4. Discuss details of participant's plan to implement these changes.

Example prompts:

- *Let's walk through a typical day for you. What would happen and how would you incorporate these strategies?*
    - *What things could interfere with your plan? How might you overcome these?*

- *Who might support you in making these changes who you could share the plan with?*
    - *When do you want to make these changes?*

5. **Create harm reduction pocket card with participant.**
    - *Some people like having a reminder card with their plan to hold on to (and possibly share with others). Once we write down the plan, you can decide where to keep it and whether to share it.*
    - *You can keep it to help you remember your plan. When I see you again in 4 months, we can review it together and see if there are any changes that you might want to make.*

If possible, encourage participant to fill out the harm reduction card. Otherwise, encourage the participant to "dictate" what should be written down on the card. Whenever possible, use participant's own language and direct quotes.

Review Overdose Response (5 minutes)

Key Objectives

- ☐ Recognize overdose signs
- ☐ Understand how to respond to overdose
    - ☐ Assess responsiveness (sternal rub)
    - ☐ Administer naloxone
    - ☐ Call 911
    - ☐ Do rescue breathing/chest compressions/follow 911 dispatch instructions
- ☐ Know after-care best practices
    - ☐ Recovery position
    - ☐ Stay with the person

Interventionist Notes:
SKOOP ("Skills and Knowledge on Overdose Prevention") is a program designed by the Harm Reduction Coalition.
Refer to Handouts C & D during this discussion.

Outline and Sample Prompts

- *Let's review the steps that you can take if you see someone else experiencing an overdose and want to help.*

1. **Review SKOOP curriculum (outlined below).**

Provide participant with **Handout C: 3 Steps in the Management of Witnessed Overdose**

- *Step 1: Recognize an overdose*
    - *As we've discussed, someone might be having an overdose if they lose consciousness after using drugs, if their skin color looks bluish or grey, or they are not breathing normally.*
    - *Use a sternal rub to attempt to waken the individual.* [Counselor to provide brief demonstration on self].
- *Step 2: Respond to the overdose*
    - *Administer naloxone as soon as possible.*
    - *Call 911. Tell the dispatcher that the person is unresponsive (or not breathing).*
    - *Provide rescue breathing and/or chest compressions. Also, 911 dispatchers can walk you through these procedures.*

Interventionist Note: If unknown, ask participant if they have ever administered naloxone before (or if they know how to administer naloxone), and if they have ever performed rescue breathing or chest compressions. If not, offer to perform naloxone, rescue breathing, and/or chest compression demonstration at the next session (unless participant asks for it to be done during current session).

- *Here are a few things to keep in mind about naloxone:*
    - *Always carry naloxone with you or know where it is so you can act quickly!*
    - *Naloxone can be used on anyone, so if you suspect an overdose, use it.*
    - *If they don't respond after about 3 minutes, give another dose.*
    - *Naloxone expires. Be sure to replace your kit every 2 years if you have not used it. But if expired naloxone is all you have in an emergency, use it!*
    - *Fentanyl may cause a faster overdose – where the person stops breathing or their heart stops right away, so:*
        - *You may need to do rescue breathing and/or chest compressions right away.*
        - *An ambulance may be needed sooner.*
        - *Naloxone might need to be given several times.*

- *Step 3: Provide after-care*
    - *Place person in the recovery position.*

      [Provide participant with **Handout D: Diagram of recovery position**].
    - *Stay with the person until help arrives or they are awake for at least 2-3 hours (longer if using prescription opioids). Naloxone only lasts about an hour, so the effects of the opioid may come back and they may overdose again.*
    - *If you are not comfortable staying with them, make sure that someone (either a friend of theirs or a medical professional) is available to help.*

Interventionist Note: In Boston, if a participant expresses concern about staying with someone who has overdosed, you can provide them with information about the SPOT at Healthcare for the Homeless, where a nurse will monitor patients to make sure they are ok.
In SF and Boston, harm reduction programs are also a safe space to go when participants are extremely high.

Wrap Up (4 minutes)

Key Objectives

- ☐ Remind participant of follow-up appointments
- ☐ Provide harm reduction card and review plan
- ☐ Allow participant to reflect on any final thoughts
- ☐ Offer referrals, if applicable

Outline and Sample Prompts

1. **Ensure participant has scheduled a follow-up appointment.**
    - *After today, your participation in the study will involve 4 more in-person visits (every 4 months). At the first 3 of those, you will complete a survey and we will meet for another counseling session. The last visit (16 months from today) will just be for a survey.*
    - *Have you been scheduled for your next visit in 4 months?*

2. **Review harm reduction plan and provide participant with harm reduction card.**
    - *Here is the plan that you made to help reduce your risk of having another opioid overdose.*

3. **Reinforce participant's interest in self-care.**
    - Acknowledge steps participant has taken toward self-care in both receiving naloxone and participating in this study/counseling.
    - Point out and reinforce participant's strengths that may help them reach their goals around substance use, and overdose prevention.
    - Thank participant for visit and express enthusiasm in working together during the next 16 months.

4. **Close out the session.**
    - *Do you have any last questions before we wrap up for today?*
    - *During our session you mentioned _____. Would you like any additional information/support about this?*
        - Refer to resource guide and provide appropriate referrals to participant.

Additional Sections (To be Completed by Session 4)

Naloxone Practice Session (5-10 minutes)

1. **Assess participant's knowledge of naloxone.**

Example prompt:

- *Please tell me what you already know about naloxone (or Narcan) - what it is, what it does, how to get it - just anything you know or have heard about it.*
    - With participant's permission, fill any gaps in their knowledge, if needed, so that they have a basic understanding of naloxone.

Example prompts:

- *It seems like you have [quite a bit of/some] knowledge about Naloxone (Narcan).*
- *May I share some other important things to know about naloxone?*
    - Based on participant's knowledge and interest, more or less of the following information may be shared:
        - *Naloxone acts to reverse an opioid overdose, and does nothing more than that.*
        - *Naloxone is safe to give to anyone, even if you're not sure if the person is overdosing, or overdosing on opioids.*
        - *The effects of naloxone are short-acting and will wear off in 30 -90 minutes (a half hour to an hour and a half). If there is still a large dose of opioids in a person's system, the person may fall back into an overdose when the naloxone wears off.*
        - *Naloxone may cause a person to feel sick from withdrawal, but they will feel better again once the naloxone wears off. Encourage the person to ride out the withdrawal symptoms and let them know that to avoid another overdose, it is very important that they not use more opioids for a couple hours.*
        - *Naloxone will not reverse other kinds of overdoses, but there is no harm in trying, and it may still work if someone is overdosing on opioids in combination with other drugs.*
        - *Naloxone expires every 2 years, BUT if all you have on you is expired naloxone, use it!*

2. **Assess participant's experience administering naloxone (if not already known)**.

Example prompt:

- *Tell me about your experiences, if any, giving naloxone to someone who was overdosing.*

Interventionist Note: Many participants will have had previous experience administering naloxone, some will have done so several times. Counselors should be mindful of participants' past experiences and expertise.

3. **Provide information and naloxone demonstration.**

If a participant has extensive experience administering naloxone:

- *This next portion of our conversation will be review for you and maybe a chance to fine-tune your knowledge around naloxone administration.*
- Invite participant to practice naloxone administration while you coach them through the process.

Example prompt:

- *Please walk me through what you do to administer naloxone.*

If a participant has never administered naloxone and is unfamiliar with the process:

- Ask permission to share the steps of the process:
  Is it okay if I share with you the steps to administering naloxone?

Intranasal administration (Boston site/SF site optional):

1. Depending on participant's knowledge/experience, the counselor may ask them to describe the steps to administering naloxone, filling in any information gaps, or the counselor may describe the steps while the participant goes through the motions with the demo kit. *Peel back the package to remove the device. Hold the device with your thumb on the bottom of the plunger and two fingers on the nozzle.*
2. *Place and hold the tip of the nozzle in either nostril until your fingers touch the bottom of the person's nose.*
3. *Press the plunger firmly to release the dose into the person's nose.*
4. *Administer naloxone as many times as needed, 2-3 minutes between doses.*

Intramuscular administration (SF site/Boston site optional):

Depending on participant's knowledge/experience, the counselor may ask them to describe the steps to administering naloxone, filling in any information gaps, or the counselor may describe the steps while the participant goes through the motions with the demo kit.

1. *Determine where naloxone will be injected: shoulder, buttock, or thigh.*
2. *Naloxone can be injected through clothing, including denim, but if necessary, remove any especially heavy clothing covering injection site (leather, puffy coats, multiple layers of thick clothing).*

3. *Unwrap 25g syringe (in blue wrapper) or any syringe with a larger needle, like 23g, 21g, or 18g.*
4. *Remove orange cap from naloxone vial.*
5. *Plunge the needle of the syringe into the soft center of the top of the vial.*
6. *Turn the vial upside-down so that the point of the needle is submerged in the naloxone, draw up 1ml (most likely the entire vial).*
7. *With one fluid and assertive motion, stick the needle into injection site, deep enough to enter the muscle, probably the entire length of the needle. (It's best to inject the naloxone into the muscle of the upper arm or thigh, but naloxone is still effective below the skin).*
8. *Depress plunger completely, administering full dose of naloxone. Withdraw needle.*
9. *If no reaction in 2-3 minutes, repeat the entire process, administering another 1ml of naloxone.*
10. *Administer naloxone as many times as needed, 2-3 minutes between doses.*

Review after care:

1. *Wait 2-3 minutes before giving a second dose, if necessary.*
2. *Perform rescue breathing/or chest compressions until person is responsive or help arrives.*
3. *If you can't stay with the person until help arrives, put them in the recovery position before leaving.*

Example prompts:

- *How long should you wait for the person to wake up before administering another dose of naloxone? (2-3 minutes)*
- *It's best to stay with the person to wait for help and ensure they don't use again before the naloxone wears off.*
- *You can put the person in the rescue position – which is on their side as if they were sleeping.*

4. **Address any questions about the demonstration.**
    - *What questions or concerns, if any, are coming up for you?*

5. **Evoke optimism about overdose prevention and health promotion.**

Example prompts:

- *With all the naloxone available, many lives are saved from overdoses.*
- *You are one of the people able to pull others out of an overdose.*
- *How does it feel that you may be able to save someone's life?*

Rescue Breathing and Chest Compressions (5-10 minutes)

Outline and Sample Prompts

- *In the event of an overdose where no naloxone is available, or when naloxone has been administered but it has not yet taken effect, knowing how to do rescue breathing and chest compressions can save someone's life and prevent or limit any long-term damage they might otherwise suffer.*

1. **Assess participant's knowledge and comfort around rescue breathing and chest compressions.**

Example prompts:

- *How familiar are you, or what is your experience, with rescue breathing and chest compressions?*
- *How likely is it that, if you knew what the steps were, you would perform rescue breathing on a friend who was overdosing? How about a stranger? And how likely is it that, if you knew what the steps were, you would perform chest compressions?*

Interventionist Note: Participant may opt-out of learning rescue breathing (and combined rescue breathing and chest compressions). For example, if they report that they would never do rescue breathing, do not demonstrate.

2. **Briefly coach participant through chest compressions with rescue dummy.**
   1. *Position victim on back.*
   2. *Push down in the center of the chest about 2 inches, 2 times per second.*
   3. *Make sure to let the chest bounce back between pushes.*

3. **Briefly coach participant through rescue breathing with rescue dummy.**
   1. *Position victim on back.*
   2. *Tilt head back and pinch nose.*
   3. *Cover the mouth with your mouth and blow until you see the chest rise.*
   4. *Give 2 breaths, 1 second each.*

5. *Continue with 1 breath every 5 seconds.*
6. *If something is obviously in the victim's mouth, ok to take it out, but don't fish around looking for something because that can drive it further into their airway.*

- *You can do rescue breathing, chest compressions, or both, depending on which you're more comfortable doing. If you do both, do cycles of 30 compressions followed by 2 breaths.*
- *If you call 911, we recommend doing whatever the dispatcher recommends.*
- *Whatever you end up doing, chest compressions, rescue breathing, or both, keep doing it until the person show signs of being stable (regular breathing and pulse) or help arrives.*

Interventionist Note: We do not know if recommending rescue breathing or chest compressions is superior. While opioid overdose is due to reduced breathing, rescue breathing is difficult to teach, people often don't want to perform rescue breathing, and when people do rescue breathing they may do it poorly. Some experts believe that much of the benefit from rescue breathing in opioid overdose might actually be from stimulation rather than oxygen transfer, and chest compressions can provide both stimulation and some air transfer by moving the chest. Furthermore, if an overdose is not observed, it is possible that the person has progressed to cardiac arrest and will require chest compressions. Finally, 911 dispatchers generally recommend chest compressions so we want to avoid recommending people to go against dispatcher instructions.

Evaluate readiness to change substance use (5 min)

Outline and Sample Prompts

- *We've spent a good amount of time talking about overdose prevention. Let's spend some time today talking about overall substance use.*

Example prompts:

- *What are the drugs you currently use?*
- *What benefits do you get out of your drug use?*
- *What are the drawbacks (or costs) of using those drugs?*
- *How, if at all, does using get in the way of you taking care of yourself or others who depend on you?*
- *How do you feel about your current drug use?*

1. **Discuss interest, expectations, and concerns about treatment for substance use.**
   - *What, if anything, do you want to change about your substance use?*
   - *On a scale of 0-10, 0 being not at all important and 10 being extremely important, how important is it for you to make that change?*
     - If a "0", discuss barriers:
       - *What would have to happen to move from a "0" or "1" to a "4" or "5"?*
     - If a "1"-"9", elicit change talk:
       - *Please tell me why you are a "2" or __ and not a "0"?*
       - *What would have to happen for you to move from a "2" or _ to "6" or a"7"?*
       - Then reflect change talk back:
         - *What if anything, are you willing to do starting this week or next to change your substance use?*

   If not ready to make changes:
   - *What would have to happen for you to be more interested in making some changes around your substance use?*
   - *If you choose to make **no** changes in your use, where do you see yourself in the next 3-5 years?*
   - *If you were to make some changes in your substance use, where might you see yourself in the next 3-5 years?*

2. **Discuss substance use disorder treatment options, based upon above discussion.**

   Example prompts:

   - *What is your experience, if any, of receiving substance use treatment services?*
   - *What kind?*
     - *How did/does it help you?*

    - *How, if at all, might treatment lower your overdose risk?*
- *If you were to seek treatment, of all the treatments available, what treatment would appeal to you most?*
- *If and when you were to seek treatment services in the future, what steps would you take or how would you find a treatment agency?*
- *At this time, what if anything, would you like from me regarding treatment services?*

3. **Keep the substance use treatment "door" open.**

Example prompts:

- *Thank you for being upfront about your thoughts/feeling about substance use treatment right now in your life.*
- *Please let me know if you ever want to discuss substance use treatment options again.*
- If additional study visits remain:
    - *Would it be okay if I check in with you about your substance use in general during future visits?*

Discuss HIV/HCV Risk Reduction (5 min)

Outline and Sample Prompts

- *We've talked a lot about overdose and overdose risk. But we haven't yet talked about HIV/HCV, other possible, and preventable, risks of drug use.*

1. Assess HIV/HCV status and knowledge.

Example prompts:

- *How do you think preventing HIV/HCV is similar to preventing overdose?*
- *Tell me about your experience with HIV/HCV testing? When was the last time you were tested and what were the results?*
- *What do you already know about Hep C? What do you already know about HIV?*

2. Share information.

- *Do you mind if I share some additional information with you?*
    - *Hep C is a virus that causes inflammation of the liver. HIV is a virus that attacks the immune system.*
    - *Both Hep C and HIV can be acquired through sharing needles, but a person can also get Hep C through sharing other drug equipment with someone else who has Hep C and whose blood has contaminated a cooker, cotton, and even a preparation surface. Sometimes this can happen when people divide drugs in one syringe.*
    - *A person can get HIV from vaginal and anal sex (receptive is higher risk than insertive), but Hep C is not typically transmitted through anal, vaginal or oral sex, unless prolonged or rough sex causes tears and there is blood to blood contact.*
    - *Hep C is curable; HIV is treatable; and both are preventable, even when engaging in "higher risk" activities.*

Interventionist Note: The counselor can use motivational interviewing to "meet participant where they're at" and explore motivation/interest around whatever changes, if any, they'd like to make in relation to HIV/HCV prevention and care.
Examples might be maintaining a negative status; starting or continuing treatment, starting PrEP, getting tested or increasing frequency of tests, talking to partners/friends they use with/have sex with about their status'; washing their hands before/after using, or sharing equipment with one person only.

3. Discuss harm reduction around HIV/HCV.

Example prompts:

- *What do you already do to prevent HCV/HIV? What do you already do to care for yourself in regards to your HIV/HCV?*

- *How easy or difficult is it for you to use a new needle each time you inject drugs [for vein health]? How easy or difficult is for you to use your own equipment each time you use [HCV prevention]? Do you use the needle exchange?*
- *How often do you share equipment? In what situations have you either decided to share or felt that there was no choice but to share injection equipment?*
- *How do you protect yourself from getting HIV and other sexually transmitted infections?*
- *Have you heard of PrEP for preventing HIV? What is your experience with PrEP? What have you heard about it?*

If HIV-positive:

- *What is your experience of taking HIV medications?*
- *How long has it been since your viral load was last checked?*
- *What all do you know or understand about U=U (undetectable VL=untransmissible)?*
- *What kind of care do you receive for your HIV? What is your relationship like with your doctor?*

If HCV-positive:

- *What do you know or what have you heard about HCV treatment?*
- *What, if any, thoughts have you had about getting treated for HCV (if you get treated, you can't pass it on to anyone else)?*
- *What, if anything else, are you ready to do to reduce your risk for HIV/HCV (or manage your HIV/HCV)?*

If participant reports doing all they can to stay negative, reports keeping up with their treatment, and is not interested in making any other changes, they may be more open to a conversation around maintaining their health program.

Example prompts:

- *It sounds like your health is very important to you, you're doing all you can to stay healthy, and it sounds like there are no changes at this time that you're interested in making. Do I understand correctly?*
- *Are there any situations, events or even people in your life that could compromise the stability of your health routine?*
- *What do you do, or can you do, to avoid those situations/events/people? If you can't or don't want to avoid them, what can you do to ensure that your health regimen is not jeopardized?*

Some participants may express ambivalence, or apathy around HIV/HCV transmission.

Example prompt:

- *What would have to happen for you to want to protect your health and maintain your negative status?*

  OR
- *What would have to happen for you to want to receive care/treatment?*

4. Validate participant's concerns for their health and conclude conversation.

Example prompts:

- *Good for you taking care of yourself in this/these ways.*
- *You care a lot about your health and you're willing to do what it takes to protect it. Thanks for talking about this with me and for sharing your experiences.*
- *It sounds like you have some mixed feelings about making changes to reduce your risk of HIV/HCV infection (or starting treatment) and you know what changes you could make to reduce your risk. Thank you for being so engaged in this conversation, I really appreciate you sharing your thoughts.*

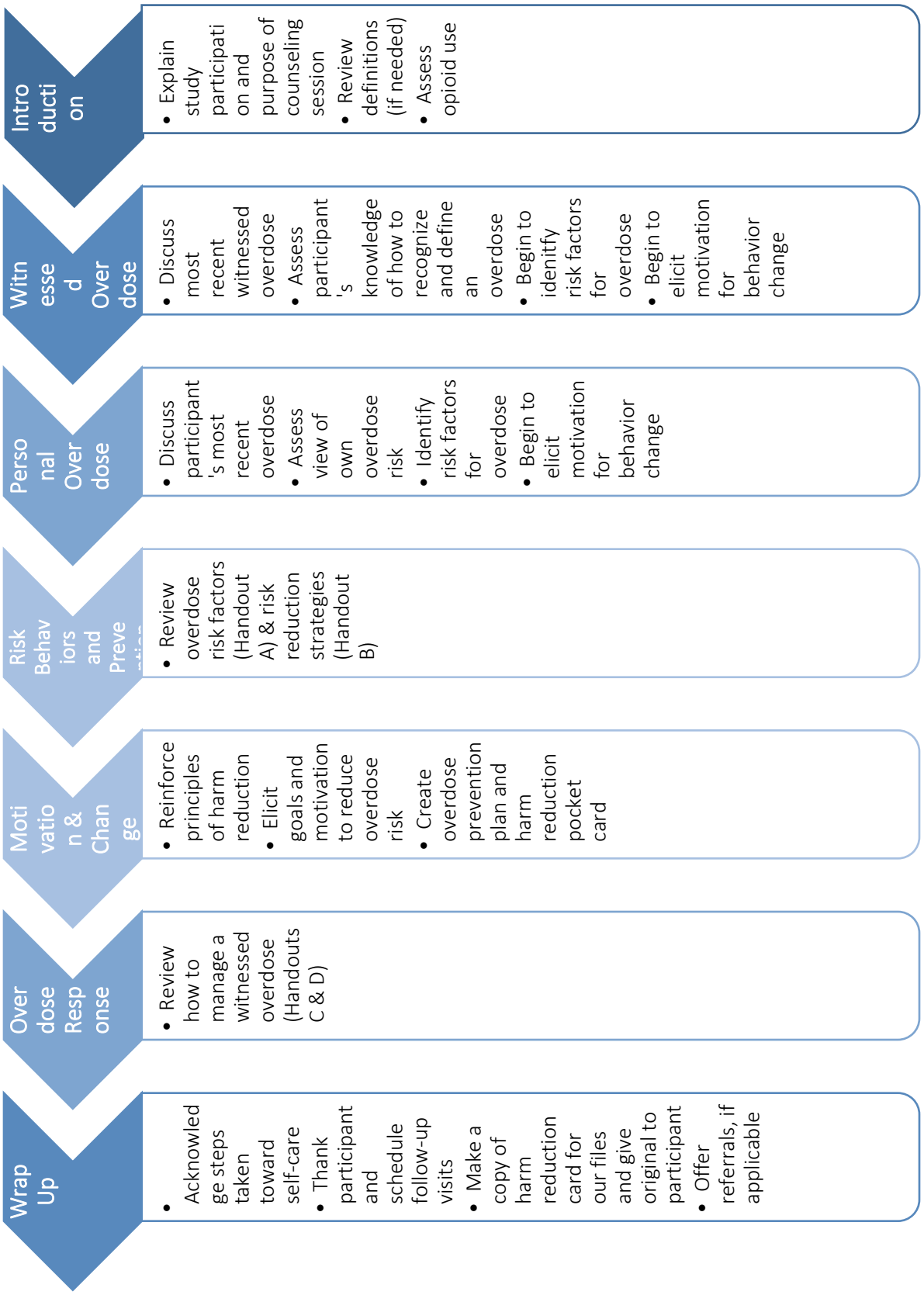
For participants who don't want to talk about HIV/HCV:

- *It sounds like you have had a lot of people talk with you about HIV/HCV and you feel confident in knowing what things you can do to protect your health.*
- *Please let me know if there are any concerns you have around this that have not already been addressed in past discussions.*
- *Please also let me know if you want additional information (flyers/handouts) about HIV/HCV that I can provide you.*

Intervention Overview

Introduction
• Explain study participation and purpose of counseling session
• Review definitions (if needed)
• Assess opioid use
Witnessed Overdose
• Discuss most recent witnessed overdose
• Assess participant's knowledge of how to recognize and define an overdose
• Begin to identify risk factors for overdose
Personal Overdose
• Discuss participant's most recent overdose
• Assess view of own overdose risk
• Identify risk factors for overdose
• Begin to elicit motivation for behavior change
Risk Behaviors and Preve
• Review overdose risk factors (Handout A) & risk reduction strategies (Handout B)
Motivation & Change
• Reinforce principles of harm reduction
• Elicit goals and motivation to reduce overdose risk
• Create overdose prevention plan and harm reduction pocket card
Overdose Response
• Review how to manage a witnessed overdose (Handouts C & D)
Wrap Up
• Acknowledge steps taken toward self-care
• Thank participant and schedule follow-up visits
• Make a copy of harm reduction card for our files and give original to participant
• Offer referrals, if applicable

Intervention Overview



10.3. Appendix 3. Descriptions and Dates of Amendments

Amendment: 08/06/2020

1. Adjusted eligibility criterion regarding urine drug screen results. Because of COVID-19 precautions, one site may be in a new space that may not permit checking of urines. This amendment involves a "trusted source verification" protocol in which study staff contact professionals referred by the participant to confirm the participant's recent use of opioids. The process includes a detailed SOP for determining the result of the inquiry.

2. Clarified that eligibility criterion allowing potential participants currently treated with methadone or buprenorphine for opioid use disorder who report illicit opioid use but test negative for illicit opioids on urine drug screen to be enrolled if they test positive for cocaine or methamphetamine does not apply for eligibility assessments that do not include a urine drug screen.

3. Allow verbal consent and redcap consent collection in some situations due to COVID-19 precautions.

4. Added COVID-19 related questions and analyses, as well as remote versus in-person visit analysis plan, include adjustment to compensation for relevant visits.

5. Provide phone with plan in lieu of other compensation for visits when participant does not have personal phone.

Amendment: 12/28/2020

1. Increased screening payment from $10 to $20.

Amendment: 08/16/2021

1. Added snowball referrals from participants to recruitment methods. Active study participants will be compensated $40 for up to five successful referrals to the study.

2. Added to procedures a one-time visit consisting of a brief assessment at the end of study participation. The purpose is to validate study activities in the assessment (specifically the time-line follow-back). Up to 40 participants will be compensated $50 for this assessment. Consent for this visit will be obtained separately.

3. Specify that we will begin to collect COVID-19 vaccination status during the assessment at follow-up visits.

Amendment: 05/09/2023

1. Updated the number of participants who will be asked to participate in one-time visit consisting of a brief assessment at the end of study participation from 40 to 100.