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APPENDICES

1.0 BACKGROUND AND HYPOTHESES

There are an estimated 1.2 million people who inject drugs (PWID) in the US.[29,30] Injection drug use dramatically increases risk for blood borne infectious diseases, endocarditis, soft tissue infections, drug overdose, psychiatric disorders, and mortality.[31-38] Despite this, there are few interventions to prevent drug injection initiation, and we are not aware of any that have been proven to be efficacious in a rigorous, large randomized controlled trial (RCT).[39-43]

To address this critical public health need, we propose to conduct a large-scale RCT of "Change the Cycle" (CTC),[7,44] an hour long, single-session, one-on-one intervention that aims to reduce injection initiation by encouraging active PWID to not promote drug injection, model injection behavior, describe how to inject, or assist in injection initiations of non-injectors. This approach is informed by social learning theory, which postulates that people learn behaviors through interaction, observation, behavioral experimentation, and reinforcement.[1,2] These constructs are all highly relevant to the prevention of injection initiation; existing research convincingly demonstrates that *interactions* with active PWID who describe injection, observations of injection drug use, and *reinforcing* conversations that promote the advantages of drug injection (e.g., the better "high" to be gained from injecting) contribute to injection initiation.[45-56] Further, retrospective accounts of injection initiation episodes have found that between 68% and 88% of non-injectors were assisted in their first injection by an active PWID.[48,57] Therefore, intervening on active PWID to reduce describing how to inject to non-injectors (*interaction*), injecting in front of non-injectors (observation), speaking positively about injection drug use (*reinforcement*), and assisting in first injection (*experimentation*) could be a promising approach for reducing uptake of injection drug use.

CTC uses the Information-Motivation-Behavioral skills (IMB) model[3,4] to achieve changes among active PWID through seven short modules. Information and motivational domains are addressed in guided conversations about (1) their own first injection episode and consequences, (2) past experiences initiating injection-naive people and consequences, (3) health, legal, and social risks related to injection drugs, (4) health, legal, social risks of initiating people, and (5) identifying their own behaviors that might promote injection among others. The behavioral skills domain is addressed through a (6) skill-building discussion and rehearsal of responses to possible initiation scenarios, and (7) safer injection education. CTC pilot study results found significant reductions in injection initiation episodes; however, the study did not have a control group.[7] Our specific aims are:

Aim 1: To test the efficacy of CTC on reducing the number of non-injectors initiated into injection (counts) by PWID. *Hypothesis 1:* PWID who receive CTC will report initiating fewer non-injectors into drug injection at 6 and 12 months as compared with PWID in the equal attention control condition.

Aim 2: To test the efficacy of CTC on reducing the number of times PWID are asked to initiate (counts) someone into injection. *Hypothesis 2:* PWID who receive CTC will report having been asked fewer times to initiate someone into drug injection at 6 and 12 months as compared with PWID in the equal attention control condition.

Aim 3: To test whether injection initiation social learning risks (injecting in front of, describing injection to, and speaking positively about injection to non-injectors) act as mediational mechanisms for the efficacy of the CTC intervention on initiation and request-to-initiate outcomes. *Hypothesis 3:* Social learning variables will significantly mediate the association between the CTC intervention and episodes of initiating and being requested to initiate someone into drug injection at 6 and 12 months.

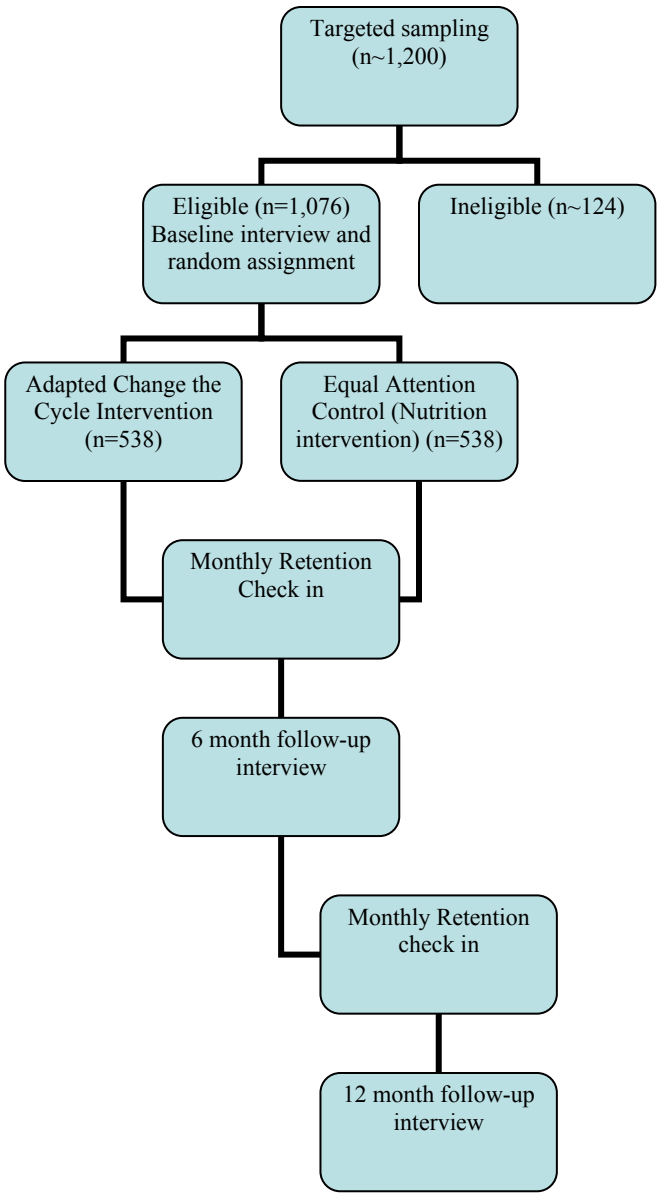
Following completion of 12-month follow-up interviews, we will collect elucidation interviews with up to 100 PWID for purposes of providing preliminary data on key issues related to 1) Hepatitis A and C risk, needs, and services collected through a quantitative survey, and 2) experiences with drug effects and withdrawal and symptoms management in a qualitative audio-recorded interview.

The elucidation interview topics were selected to investigate key issues related to health promotion among PWID. A brief justification for each topic is provided below. 1) HCV/HAV module: A recent outbreak of HAV in Los Angeles highlighted the inadequacy of both sanitation services (toilets and showers) for homeless populations in Los Angeles and HAV vaccination interventions (http://publichealth.lacounty.gov/eprp/Health%20Alerts/DPH%20HAN%20Hep%20A%20Outbreak%20091917.pdf). Items related to the HAV will include access to toilets and showers, HAV vaccination, and preferences for sanitation services for homeless PWID. New direct-acting HCV treatments are now available, but inducing and completing treatment for PWID has proven to be difficult. Items on knowledge, attitudes, beliefs, and

preferences for HCV treatment will be asked of participants. 2) Drug effects and withdrawal module: Anaylses of our prior study data (2011-13) indicated that polyroute (injection and non-injection -71%) and polysubstance (use of two or more illicit substance – 70%) use was common in our sample, yet little is known about reasons for specific drug use combination and/or sequences. To begin to understand these common phenomena, we will ask open-ended items on common drug use combinations and sequences and elicit reasons for using substances in these combinations or sequences. Lastly, preliminary data from the baseline interviews indicate that withdrawal symptoms in the last 6 months were reported by 85% of eligible heroin users and 54% of methamphetamine users. Management of withdrawal symptoms by PWID has not been extensively studied and may related to polyroute and polysubstance use behaviors. We will ask open-ended (i.e., qualitative) questions about how PWID handle withdrawal symptoms when they occur. Study resuls will contribute to efforts to address HAV and HCV infections and to inform substance use treatment approaches. Participants will be offered the opportunity to complete the Hepatitis survey and the qualitative interview separately. We have developed separate consent forms for each. Participants will be selected by convenience and data collect for the separate modules will not be linked together or linked to the parent study. Participants will be given $10 to complete each module.

2.0 OBJECTIVES AND PURPOSE

To achieve these aims, people who inject drugs (PWID) who report having initiated someone or having injection initiation social learning risks in the past 6 months (N=1,076) will be randomly assigned to receive CTC or an equal attention control condition in Los Angeles (LA) and San Francisco (SF), CA. Injection initiation and injection initiation social learning variables will be collected at baseline, 6 months, and 12 months. CTC is brief, easy to implement, and novel in its focus on active PWID as a conduit for preventing injection initiation. If proven efficacious, CTC will be a much-needed, practical approach to preventing drug injection initiation.[39-43]



The main outcomes by Aim are as follows: 1) Counts of non-injectors initiated into drug injection at 6 and 12 months; 2) Counts of request to initiate a non-injector into drug injection at 6 and 12 months; and 3) Counts of non-injectors initiated into drug injection and request to initiate non-injectors at 6 and 12 months. The study will be implemented in 2 phases. Phase 1 involves adaptation and training of intervention personnel and Phase 2 involves implementing the full study.

Elucidation goals are to better understand issues related to 1) HAV/HCV effects and 2) drug effects and withdrawal and symptoms management PWID.

3.0 STUDY DESIGN

3.1. CTC training and piloting. Intervention staff from LA and SF will participate in a week-long CTC training led by Co-I Strike and consultant Hunt. The goal of the training is to develop the knowledge and skills necessary to faithfully and effectively deliver the CTC intervention. Training modules include information about active listening, safer injection practices, overdose prevention, and risk associated with injection initiation. The peer handbook training manual is provided in ***Appendix A***. Training will be completed by the four interventionists (2 from each site), study coordinator/directors at each site, and the MPIs.

Following training, each interventionist will pilot the CTC intervention with four PWID at each site (2 interventionists per site, 4 PWID per interventionist, 16 PWID total). The CTC information Guide (***Appendix B***) was developed by Drs. Strike and Hunt. Participants will be recruited for community settings and undergo informed consent prior to undergoing the intervention session (see **Appendix C for informed consent form**). Each practice session will be audio-recorded and reviewed by the MPIs and project directors for fidelity to intervention protocols. A brief semi-structured exit interview will be conducted with the PWID participants to solicit their input on feasibility, acceptability, and satisfaction with the intervention session (**Appendix D**). PWID will receive $30 for completing the pilot CTC session and exit interview. Modifications to terminology used in the intervention and other minor changes will be considered based on this feedback. Following completion of training and piloting, a cross-site meeting with staff from each site and Drs. Strike and Hunt will be held to finalize any changes to the CTC curriculum.

Interventionists will also devote a week to learning and practicing the equal attention control intervention (see ***Section* 7.0***)*. To prevent interventionist contamination, one interventionist from each site will conduct the CTC intervention for the first half of data accrual while the other interventionist will implement the equal attention control. Interventionists will then switch for the second half of data collection.

We will also conduct up to 20 pilot interviews (10 in each site) of the baseline questionnaire (Appendix H). Pilot interview participants will be self-identified persons who inject drugs and are 18 years of age or older. The pilot interview will occur in a private one-on-one session with a trained research interviewer. Participants will receive $15 USD for completing the interview. Information from these interviews will be used to revise specific questionnaire items for comprehension and clarity.

3.2. Sampling. We will use targeted sampling methods developed by Watters and Biernacki to recruit PWID into the screening component of this study (N~1,200).[75-78] This method is a systematic approach to sampling hidden and uncounted populations when true random sampling is not feasible and has been widely used in epidemiological studies of drug users including our own.[58-60] We chose targeted sampling for four reasons: (1) in San Francisco, targeted sampling has been found to reach a more diverse population of PWID than RDS;[79] (2) several unresolved methodological issues regarding the analysis of RDS data could potentially obfuscate findings;[80-82] (3) in cohort studies, RDS referral chains can get easily broken through loss to follow-up, thus requiring a large amount of data imputation; and (4) it is not possible to analyze data across two cities because the referral chains cannot extend between cities.

3.3. Field sites and interview setting. Data collection will occur at community-based field sites conveniently located for PWID to access and conducive to private confidential interviews and intervention sessions. In the past, we have rented space in community-based agencies and single-room occupancy hotels.

3.4. Recruitment and screening for eligibility. Subjects will be recruited into the study by community outreach workers with extensive experience working in LA and SF PWID communities. The outreach workers will walk through specified recruitment areas delineated in the targeted sampling plan, engage potential study participants in conversation, and distribute socks, water, other supplies and referral information when necessary. The outreach workers will briefly describe the study procedures to potentially eligible subjects. Individuals interested in participating will be given a card with the hours and location of the local community field site. Upon arrival at the community field site, potential study participants will be taken to a private space to meet briefly with the Study Coordinator, who will ask a series of questions evaluating age and ability to provide informed consent to determine eligibility for the study. Eligible study participants will be given a same-day appointment, either immediately or very shortly thereafter for the screening interview. ***Figure 1*** describes the participant flow through the study.

Recruitment for the elucidation sub-study will be from the parent study. Participants returning for follow-up interview or check-ins will be told about the sub-studies and offered an opportunity to participant in one or both of the sub-studies. Eligibility for the parent study will be the same for the sub-studies. However, we will not re-screen potential participants for recent drug use.

3.5. Eligibility and inclusion/exclusion criteria: To be eligible to participate in the study potential subjects must report: (1) Recent injection of illicit drugs (past 30 days) as verified by checking for signs of venipuncture ("tracks");[84] (2) age 18 years or older; (3) ability to speak English, and (4) ability to provide informed consent. Exclusion criteria less than 18 years of age, no physical evidence of recent injection drug use, insufficient English language comprehension, and intoxication. Intoxicated potential participants will be invited to return for eligibility screening once they are sober. Eligibility screening will be conducted by Project Coordinators.

3.6. Biometrics data collection to prevent duplicate participation. To prevent duplicate participation, all screening-eligible participants will provide the following biometric information: race/ethnicity, age, eye color, height, circumference of wrist and length of forearms, and the location of notable scars and tattoos (Appendix F). Use of these measures has been found to be acceptable to PWID and provide sufficient information to deter, detect, and prevent duplicate enrollment of participants.[85] These same procedures were successfully implemented in the pilot study conducted by Dr. Strike.[7]

No biometric data will be collected as part of the elucidation study.

3.7. Informed consent. Informed consent will be obtained in a confidential space prior to the baseline interview (**Appendix E**). The Study Coordinator or research interviewer will read the consent form aloud individually to each participant. Questions and concerns will be addressed throughout the consent process. All study procedures will be approved by the Institutional Review Boards at the University of Southern California. Elucidation information consent forms are provided in Appendix L (HAV/HCV) and M (Drug effects and withdrawal).

3.8. Locator form. For retention purposes, participants will be asked to provide contact information (phone number, e-mail address, day-time hangouts), the names and phone numbers of up to three contact persons, and the names and locations of social service agencies they utilize (**Appendix B)**. Participants will be requested to sign releases authorizing the staff to contact these agencies to locate them if they miss an appointment (see **Appendix J)**. They can refuse to provide this information and still participate in the study. We have regularly asked and obtained this information in studies with PWID in LA and SF. No identifying information will be collected from elucidation sub-study participants.

3.9. Baseline interviewing. Baseline interviews will be conducted in English using computer assisted personal interview. The interview will occur in an one-on-one session with a trained research interviewer. Participants will receive $15 for completing the screening interview. We will conduct approximately 48 baseline interviews per month (24 interviews at each site per month) until 538 participants have completed the CTC intervention and 538 participants have completed the equal attention control intervention (***Timeline, Table 1*** see below).

The elucidation study interviews will be offered to current study participants. Study 1 (HAV/HCV) is a quantitative survey that covers topics related to HAV risk (sanitation issues) and HCV treatment (Appendix N). Study 2 is qualitative in nature and addresses effects and withdrawal symptoms (Appendix O). Procedures in section 3.10 to 4.0 do not apply to the elucidation study.

3.10. Randomization. Following completion of the interview each participant will be randomly assigned (using urn,[89] see ***Section 6.0***) to receive either the CTC intervention or the equal attention control nutrition intervention session, according to a computer-generated random numbers program. *3.11. Intervention fidelity and quality control.* All intervention trainings will be audio-recorded. To ensure intervention fidelity, the Study Coordinator will listen to all recorded trainings for the first month and then a 10% random sample thereafter. The Study Coordinator will score intervention fidelity on a standardized form that will include a list of all intervention manual components. Interventionists will receive reports from these sessions. If interventionists score less than 95% fidelity on any session, they will be retrained by the Study Coordinator and tape recordings of their next sessions will be reviewed until a 95% fidelity rate is obtained. Given our past experience, training plan and oversight, we expect fidelity to rarely fall below 95%. Participants will also complete a short questionnaire on their satisfaction with the intervention session to which they were exposed (see **Appendix K**).

3.12. Cohort maintenance and recapture strategies. We will use multiple proven strategies to retain cohort members at the 6-month and 12-month follow-up interviews. First, during enrollment for the proposed study, we will collect detailed tracking information, as described in ***Section 3.8***. The Study Coordinator will enter tracking information into a Microsoft Access database on a password-protected laptop computer. We will use this information to locate participants who miss appointments. Second, participants will have a monthly check-in appointment with study staff, which will be held at field sites in the recruitment communities, and will receive a $10 incentive for attending. At check-in, tracking information will be verified and updated. Dr. Kral has conducted two NIDA-funded cohort studies that compared the effectiveness of incentivized check-in appointments with that of standard tracking by outreach workers[67,90] and found that paying each cohort member $10 monthly yields much higher return rates and is less costly than relying on staff outreach alone. Third, we will use graduated incentives for the interviews: $15 for the screener/baseline and $20 for each of the 6-month and 12-month follow-up interviews. We will also allow the participants to return for up to one month past their study appointments. Study participants will continue to be eligible for the study throughout the follow-

up period even if they miss their check-in appointments. To minimize any potential participation biases during check-ins, research staff will only update contact information and not discuss any substantive topics.

3.13. Follow-up interviews at 6 and 12 months. Similar to baseline/screening interviews, 6- and 12- month follow-up interviews will be conducted using CAPI in a one-on-one session with a trained research interviewer. Participants will be remunerated $20 for each follow-up interview they complete.

3.14. Timeline: As described in **Table 1**, below, following training and piloting, baseline data collection will commence in May 2016 and continue until December 2018.

Table 1. Project Timeline

	Year 01				Year 02				Year 03				Year 04			
Activity	Q3	Q4	Q1	Q2	Q3	Q4	Q1	Q2	Q3	Q4	Q1	Q2	Q3	Q4	Q1	Q2
Calendar year	'15	'15	'16	'16	'16	'16	'17	'17	'17	'17	'18	'18	'18	'18	'19	'19
RCT Baseline				X	X	X	X	X	X	X						
6-month follow-up						X	X	X	X	X	X	X				
12-month follow-up								X	X	X	X	X	X	X		

3.15. Data collection measures. Data collection measures were selected based on their relevance to evaluating CTC, applicability to social learning theory and IMB model, and potential as confounders. Items from each area are described below and a draft of the baseline questionnaire is included in ***Appendix H***.

3.16. Main outcome measures for **Aims 1 & 3** will be the number of people initiated in the past 6 months. This item will be assessed by asking the following questions: "In the past 6 months, have you helped someone get their first hit (the first time they ever injected)?" If participants respond Yes, they will be asked the following question: "How many people (total) have you helped get their first hit (inject for the first time) in the past 6 months?" Not applicable responses (or No on the first item) will be recoded as zeros for data analysis purposes. For **Aims 2 & 3** we will ask the following items: "In the past 6 months, have you been asked to help someone inject an illicit drug for the first time?" Participants responding 'yes', were then asked how many people had asked them to provide their first injection. The time frame of 6 months allows us to assess changes in the outcome at 6 months (as was done in the pilot) and 12 months. The use of a count approach for outcome variables enables us to account for changes even if they only occur among high volume initiators and those with multiple injection initiation social learning risk. We will also collect data on sex risk, specifically, unprotected sex, multiple sex partners, and sex risk by partner type[91,92] for purposes of determining the efficacy of the attention control condition although this is not an aim of the proposed study.

3.17. Main independent measures will be intervention condition: CTC or equal attention control group for Aims 1 & 2. For Aim 3, we will also evaluate three injection initiation social learning risks as mediating variables. These items are intended to capture social learning constructs (i.e., observation of behavior, supportive interactions, and reinforcement) within the social processes of injection initiation. To capture observing, we will ask current PWID the following item: "In the past 6 months, have you injected drugs in front of someone who has never injected an illicit drug?" To capture interaction, we will ask "In the past 6 months have you explained or described how to inject to someone who has never injected an illicit drug (i.e., a non-injector)?" To measure reinforcement we will ask, "In the past 6 months, have you spoken positively about injecting with someone who has never injected an illicit drug?" Each item is a binary variable (Yes/No) where Yes denotes endorsing the injection initiation social learning risk assessed.

We will also collect IMB constructs related to injection initiation and sex risk. For the information construct, we will collect true or false knowledge items on sex-related HIV prevention provided by Kalichman, Simbayi and others[5,6] and develop similar items for injection initiation risks. To develop injection initiation risk motivation and behavioral skill items we will follow procedures outlined by Kalichman, Simbayi and others.[5,6] For sex-risk related motivation and behavioral skill items we will draw from existing studies.[5,6] All injection initiation risk and sex-related IMB skill items will all be pilot tested. Psychometric properties of existing measures are known and acceptable, however, we will test both existing and new measures for their applicability to this study population. Drafts of all items are provided in the baseline survey (**Appendix H**).

3.18. Potential confounding variables or covariates will be selected from the following domains: socio-demographics/economics, current drug use patterns, blood borne infectious disease risks, experimental condition contamination, and social desirable responding. *Socio-demographic and socioeconomic characteristics* will be collected from each participant, including race/ethnicity (with options for multiple racial/ethnic identification), age, education, income/income sources, living arrangements (including homelessness), and relationship status. *Drug use history and current use patterns* have previously been

shown to be associated with initiation of injection-naive people.[59] In the proposed study, we will assess frequency of injection and non-injection in the past 30 days for the following drugs: crack cocaine, cocaine, heroin, methamphetamines, speedball (admixture of heroin/cocaine), goofball (admixture of heroin/methamphetamines), prescription drug misuse (e.g., opiates, tranquilizers, stimulants, sedatives, methadone, and buprenorphine), and marijuana. The drug use items have been found to be valid and reliable.[16,17] *Injection-related HIV and HBV/HCV risk* will be captured using modified items from NIDA's cooperative agreement study of the 1990s (the "RBA").[96] These items have been found to be valid and reliable.[15,17] *Socially desirable response set measure* (SDRS-5) contains five items adapted from the Marlowe-Crowne Form A measure of social desirability. Respondents rank each item on a 4-point scale ranging from 1 (strongly disagree) to 4 (strongly agree).[97]

3.19. Six-month and 12-month follow-up measures will include all main outcome (***Section 3.16.)*** and independent variables (***Section 3.17****)* as well as socio-demographic and economic variables that could change during the 6-month follow-up periods (e.g., relationship status, homelessness, income). We will also assess *contamination* at 6-month follow-up interview. It is possible that skills learned by the CTC participants may be shared with participants in the equal attention control group. This type of contamination cannot be prevented, but it can be measured. At 6-month interview, participants in both conditions will be asked if they have had conversations with other PWID on a variety of health issues, including injection initiation, initiation injection social learning risk, sex risk, and other items to mask the intent of the question. We will also ask them about intervention phrases such as "Change the Cycle" to assess whether control group participants are familiar with them. A similar approach has been used in other intervention studies among PWID to identify exposure to an intervention.[98] We will ask questions about satisfaction with and usefulness of the CTC intervention or the equal attention control intervention at 6 month follow-up interview. Lastly, we will ask questions from several other domains on either the 6 month or 12 month survey. The domain lists for items to be included in the 6 and 12 month survey are provided in **Appendix I.**

4.0 DRUG/DEVICE INFORMATION

4.1 Not applicable.

5.0 SELECTION AND WITHDRAWAL OF SUBJECTS

5.1 Inclusion Criteria: Inclusion criteria for the baseline/screening interview are (1) recent injection of illicit drugs (past 30 days), as verified by checking for venipuncture marks,[84] (2) age 18 years or older, and (3) ability to provide informed consent.

5.2 Exclusion Criteria: Less than 18 years of age, no evidence of recent drug injection, inability to provide informed consent, and non-English speaking.

5.3 Withdrawal Criteria: Participants who unable to complete either the experimental or control condition intervention may be asked to withdraw from the study. Each participant will be given at least 2 opportunities to complete the one-hour educational session to which they were assigned.

6.0 STRATIFICATION/DESCRIPTIVE FACTORS/RANDOMIZATION SCHEME

6.1 Stratification factors. Not applicable.

6.2 Descriptive factors. Based on prior studies with PWID, we anticipate the following characteristics: The majority will be over the age of 50, roughly a third will be white, a third will be African American, and 25% will be Latino. About 25% will be female. The vast majority will be heroin injectors although a third will also report methamphetamine use, and 10% will report cocaine and opiate prescription injection in the last 30 days.

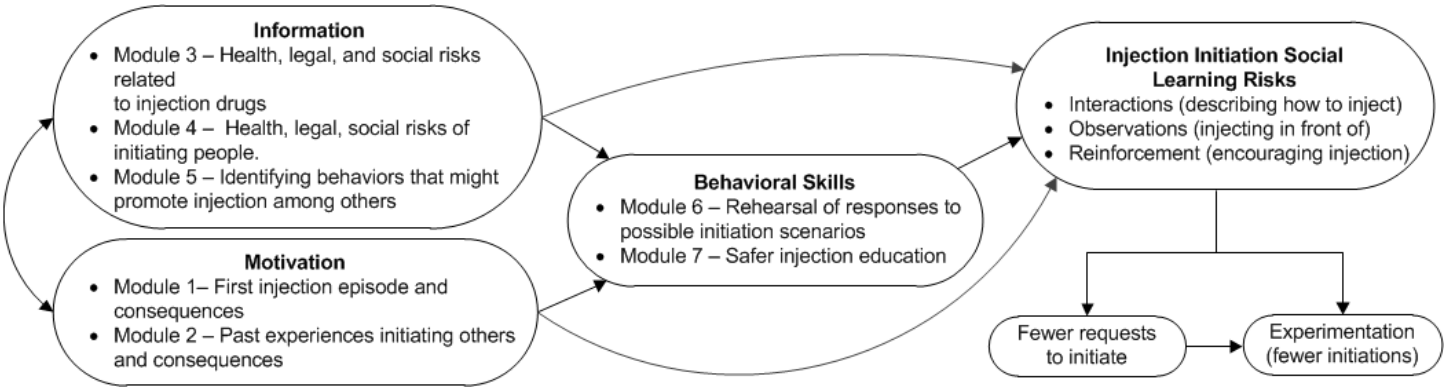
6.3 For participants in the RCT, randomization will be accomplished using urn. Urn randomization is an adaptive biased-coin randomization method.[89] In brief, it means you not only replace the ball that is chosen out of a hat (for example: blue for experimental and red for control condition), but you add a ball from the opposite color as well. The urn design forces balance for studies

with a large number of confounders as it approaches complete randomization and full balance as the size of the trial increases. Consequently, the urn design is not as vulnerable to experimental bias as are other restricted randomization procedures.

7.0 STUDY AGENT ADMINISTRATION OR INTERVENTION AND TOXICITY MANAGEMENT PLAN

7.1. CTC can be viewed as integration of social learning theory and the Information-Motivation-Behavioral skill model (IMB). CTC uses social learning theory to explain how active PWID might influence directly (by assisting in first injection) and indirectly (through promoting and exposing non-injectors to injection) injection initiation among non-injectors.[1,2] It uses IMB to *promote* behavior change among active PWID by providing them with information, motivation and behavioral skills related to direct and indirect influences of injection initiation.[3,4] **Figure 2**, graphically illustrates these theories are integrated within CTC.

Figure 2. Integration of IMB skill model with social learning theory for purposes of reducing injection initiation as operationalized in CTC.



In the figure, the IMB model constructs of information and motivation (the 2 left-most bubbles) reinforce each other; enhance behavioral skills acquisition; and contribute to reductions in injection initiation social learning risk (top bubble on the right), requests for injection initiation, and actual injection initiation episodes (bubbles below social learning risk bubble). CTC modules are listed within IMB construct bubbles. We expect IMB-related changes to influence social learning risk, including interactions with (describing how to inject), observations/exposure to injection (injecting in front of non-injectors), and reinforcement (encouraging injection drug use). Reductions in social learning risk should lead to lower incidence of both requests to initiate and actual injection initiation episodes (behavioral experimentation). The integrated model targets the injection initiation social learning risks documented in the literature to be involved in the transition to injection drug use, by providing information, motivation, and behavioral skills to reduce injecting in front of, describing injection to, and speaking positively about injecting to non-injectors.[45-56] **Aim 1** will test the impact of CTC on counts of injection episodes, while **Aim 2** tests CTC effect on injection initiation request. **Aim 3** will explore the theoretically and empirically supported mediational mechanism between CTC, social learning risk, and request for and episodes of injection initiation.

7.1.1. The Change the Cycle intervention

The CTC intervention is an hour-long, guided conversation with a trained interventionist. Copies of the Peer Educator Handbook and Intervention Guide that were developed by Drs. Strike and Hunt and adapted for this study are included in ***Appendices A*** and ***B***, respectively. Using the Intervention Guide, the interventionist introduces and summarizes CTC goals and then delivers the following seven modules in one session:

1. Discussion of the participant's own experience the first time they injected, including when it occurred, motivations for initiation, who was present, and feelings about initiation (~5 minutes).
2. Discussion of the participant's experiences of initiating others, focusing on the participant's thoughts about the experience, the relationship to the person they initiated, the context of initiation, and descriptions of those times they refused to initiate someone (~5 minutes).
3. The participant's perceptions of the health, legal, and social risks of initiating non-injectors (~5 minutes).
4. The participant's perceptions of the health, legal, and social risks of initiation for themselves (~5 minutes).
5. Identification of aspects of the participant's own behavior and the behaviors of other PWID that may promote injecting to non-injectors and linking those behaviors back to the participant's own initiation experience (~10 min). Includes discussion of: (A) Talking about the physical benefits of injecting in front of

injection-naive people; (B) Talking about the economic benefits of injecting compared with using drugs other ways (e.g., snorting, smoking); and (C) Describing how preparing drugs for injection in front of non-injectors might inadvertently promote injection initiation.

6. Skill-building session to prevent future initiation events. We have developed 9 different scenarios covering a range of possible events based on the relationship and drug use characteristics of the participant.
7. A safer injection education session focusing on topics such as hygiene, risks of sharing needles and other injection equipment, rotating veins to avoid abscesses, etc. (~5 min).

7.1.2 *The equal attention control intervention.* To ensure that the participants in the intervention and control groups are having the same study-related experiences, control participants will receive an intervention that mimics the experience but differs in content. The equal attention control intervention will focus on improving health eating among PWID. We have developed a single-session, 60- minute Information-Motivation-Behavioral (IMB) skills-based intervention addressing healthy eating (**Appendix J**). Similar to the CTC, the healthy eating intervention uses a one-on-one guided conversation between the interventionist and the participant. The intervention addresses (1) information about current eating patterns and recommendations for healthy alternatives (20 minutes), (2) motivations for improving healthy eating by providing feedback to participants on personal responsibility, a menu of alternative change options, a decision balance exercise, and eating goal setting (10 minutes), and (3) Behavioral Self-Management Component (30 minutes) that covers eating scenarios, participant responses, and healthy alternatives to the scenario and the participants feedback. The participant is also remunerated $15 for completing the session.

7.2. *Elucidation studies:* The elucidation studies are pilot interviews. We anticipate interviewing 60 PWID for study 1 and 40 PWID for study 2.

8.0 ASSESSMENT OF EFFICACY AND SAFETY

8.1 Side effects/Toxicities to be monitored. NOT APPLICABLE

8.2 Dosage change based on toxicity. NOT APPLICABLE

8.3 Adverse Event Reporting: Although the occurrence of adverse events as a direct result of the research is unlikely, such events may occur because the research population includes people who are current drug users, involved in illegal activities that make them vulnerable. Any serious adverse event will be reported verbally within 24 hours and a written report will follow within 72 hours of an adverse event. Reports will be made to the IRB at USC and RTI international. The program official at NIDA will also be notified.

8.4 Data Monitoring Committee:

The Data Safety and Monitoring Board (DSMB) for this study consists of the following members.

Name	Affiliation	Areas of expertise
Keith Heinzerling, MD, MPH	**UCLA**	Dr. Heinzerling is a graduate of Stanford University School of Medicine, the NYU/Bellevue Internal Medicine Primary Care Program, where he was a Medicine Chief Resident, and the Robert Wood Johnson Clinical Scholars Program at UCLA. Dr. Heinzerling is currently an Associate Professor in Residence in the UCLA Department of Family Medicine and Medical Director of the UCLA Center for Behavioral and Addiction Medicine. His research and clinical practice focus on the development and dissemination of anti-addiction medications.
Mary Howe	**Homeless Youth Alliance**	Ms. Howe is a formerly homeless youth who has dedicated her career to developing and implementing interventions that empower young people to improve their own lives and those of their peers, and to addressing the structural causes of poverty and homelessness. Mary

		assumed leadership of HYA in 2006 when two longstanding grassroots programs—Haight Ashbury Youth Outreach Team and San Francisco Needle Exchange—ended their affiliation with Haight Ashbury Free Clinics, Inc. and merged to form a single organization under the name "Homeless Youth Alliance." Prior to serving as Executive Director of HYA, Mary was an outreach worker and later the Center Manager for Haight Ashbury Youth Outreach Team, Program Coordinator for San Francisco Needle Exchange, and Trainer for the Drug Overdose Prevention and Education Project of the City and County of San Francisco. She is the recipient of a 2009 Bay Area Unsung Hero Award from KQED Northern California.
Paula Lum, MD, MPH	**UCSF**	Dr. Paula J. Lum graduated from the Case Western Reserve University School of Medicine in 1993. She works in San Francisco, CA and specializes in Internal Medicine. Dr. Lum is affiliated with San Francisco General Hospital Medical Center and UCSF Medical Center Parnassus.
Cathy Reback	**Friends Research Institute, Inc**	Dr. Reback is executive Director of Friends Community Center and a Senior Research Scientist with Friends Research Institute, Inc. Her work focuses on the intersection of HIV risk behaviors, substance use, sexual identity and gender identity. Dr. Reback is also a Research Sociologist with UCLA Integrated Substance Abuse Programs (UCLA ISAP) and a Core Scientist with the UCLA Center for HIV Identification, Prevention and Treatment Services (UCLA CHIPTS).
Shoshanna Scholar	**Los Angeles Community Health Outreach Project**	Ms. Scholar is the executive director of LA Community Health Project. LACHP reaches some of Los Angeles' most vulnerable populations through three specific, evidence-based public health interventions: LA's oldest syringe exchange program, which operates in Hollywood, downtown LA/ Skid Row, Pico Union and Watts; the Overdose Outreach Project, which trains doctors, medical workers, people who use drugs and their communities in overdose prevention and response; and Transition Partners, a pilot project seeking to integrate drug users and homeless clients into the emerging community clinic health system. Since 2003, Scholar has developed, tested and adapted innovative public health strategies for drug-using populations. She is especially focused on activating peer networks to reach hard-to-find populations, working with government to implement better public health policies and raising public awareness around overdose prevention. She currently serves as a Los Angeles County HIV Commissioner.
Steve Shoptaw	**UCLA**	Dr. Shoptaw is a licensed psychologist and Director of the Center for Behavioral and Addiction Medicine at UCLA. I am a Professor in the UCLA Departments of Family Medicine and Psychiatry and Biobehavioral Sciences and Vice Chair of Research in Family Medicine. He is also a member of the DAIDS-funded, HIV Prevention Trials Network (HPTN) Executive Committee, and site Principal Investigator for HPTN-073, a feasibility

		study of Pre-Exposure Prophylaxis (Truvada) in Black men who have sex with men. Lastly, Dr. Shoptaw is Co-Director for the UCLA Center for HIV Identification Prevention and Treatment Services (CHIPTS; Rotheram-Borus PI) where he works with a team of colleagues to develop funded research on application of the next generation of technological advances and biomedical approaches to prevent HIV transmission.

The charge of the DSMB includes advising the multi-PIs on study procedures related to risk to subjects, consideration of the interim results from the study, and providing reports to the IRBs at USC and RTI International as requested from this bodies. No members of the board have any conflicts of interest with the study or its key personnel. Members will meet at least annually. In the event that a serious adverse event occurs, the DSMB will be notified of the event within 10 days and convened within a month to review the case. The multiple PIs acknowledge the requirement to provide a report on DSMB activities in the annual progress report to NIDA.

9.0 CLINICAL AND LABORATORY EVALUATIONS AND STUDY CALENDAR

Not applicable

10.0 CRITERIA FOR EVALUATION AND ENDPOINT DEFINITIONS

NOT APPLICABLE

11.0 SPECIAL INSTRUCTIONS:

NOT APPLICALBE.

12.0 DATA COLLECTION AND MONITORING

Data Security. On all data records, participants will be identified by unique ID numbers rather than names. Forms containing participants' names (release of information, and consent form) will be kept in separate and locked file cabinets. The tracking database, containing participants' names and contact information will be kept in a password protected database on an encrypted laptop that is backed up nightly to a server at each of the study sites (USC and RTI). Both the forms and the database will be, accessible only to the Study Coordinators, Project Director and Principal Investigators.

Data Storage. The data will be stored as follows:

Informed consent	Locked file cabinet (Study Coordinator, Project Director and Principal Investigators will have access).
Release forms	Locked file cabinet with informed consent. (Study Coordinator, Project Director and Principal Investigators will have access)
Tracking database (computerized)	Locked file cabinet (Study Coordinator, Project Director and Principal Investigator will have access).
Biometric Information database (computerized)	On Study Coordinator's laptop, used in office and at field site. Laptop will be encrypted and files will be password protected and backed up to an FTP secure server at RTI at the end of each day.
Interview data – Screener, 6 and 12 month follow-up (computerized)	On field laptops. Encrypted and password protected. Data will be uploaded to an FTP site at RTI at the end of each day and automatically deleted from laptops.

Paper forms and databases containing identifying information will be destroyed within 30 days of the completion of the study.

Data transfer will occur through the use of password protected USB jump drives. Completed interviews will be copied and pasted into the USB storage device. These devices will then be immediately transported to USC or RTI where they will be downloaded onto a secure computer. Data files on field site computers will be deleted and the recycling bin emptied. One advantage of using the Questionnaire Development System for data collection and transfer is that in the unlikely event that interview computers are stolen or the USB storage device is misplaced, the actual data files cannot be viewed without a data warehouse module. The data warehouse module will not be installed on computers used for the collection of data or on the USB device. Once data is stored on USC/RTI computers, these computers will be maintained in secured, password-protected folders, accessible only to designated staff through the USC file server. The surveys will be securely downloaded and maintained in the database of Dr. Bluthenthal. Drs. Bluthenthal and Kral have successfully used similar methods for data management in other multisite NIDA-funded studies.

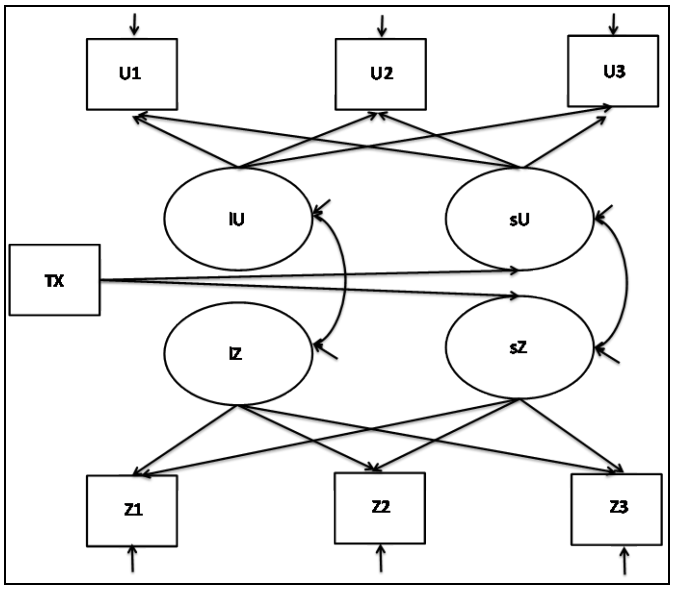
Elucidation data will consist of pen and paper survey forms for Study 1 and digitally recorded, qualitative interviews for Study 2. Study 1 forms will contain no identifying information and limited demographic information (sex, race, age). After data has been entered into a data entry form, paper versions of the survey will be destroyed. Study 2 will only include identification number on recording. Participants will be asked to use a fake name to refer to themselves and others in the recording. This has worked well in the past. No information will be collected that connects an individual by name to the audio recording. Following transcription, audio files will be deleted for audio-recorders and study computers.

13.0 STATISTICAL CONSIDERATIONS

13.1. Data analysis will involve (a) understanding the structure of all of the variables, (b) assessing whether randomization worked, (c) assessing and addressing intervention fidelity, and (d) testing the three hypotheses proposed in Aims 1, 2, and 3. First, we will employ exploratory data analytic techniques using the survey data collected at baseline and the 6- and 12-month follow-up. Dispersion and central tendency measures (e.g., means, standard deviations, medians, proportions) will be calculated for all items. The distributional properties and reliability of continuously scaled variables will be examined. We will also create longitudinal plots to identify trends in the key variables. We will also assess whether there is any statistically significant differential loss to follow-up between the two conditions. Any variable that is statistically significantly associated with loss to follow-up between conditions will also be included as a covariate in the hypothesis testing analyses. Next, we will examine fidelity to ensure compliance to the intervention based on observed intervention check lists that document the receipt of the intervention as manualized, compared with any changes that may occur. We can treat fidelity in the model as parameterized as a covariate in the observed model. Finally, we will test the three hypotheses. Similar procedures will be used to determine if the sex risk reduction intervention was efficacious.

Aim 1: **To test the efficacy of CTC on reducing the number of non-injectors initiated into injection (counts) by PWID.** *Hypothesis 1*(H1): PWID who receive CTC will report initiating fewer non-injectors into drug injection at 6 and 12 months as compared with PWID in the equal attention control condition. To test H1, we will conduct structural equation modeling (SEM) using Mplus (release 7.11).[99] Our primary outcome analysis is based on an outcome that is distributed as counts of the number of episodes initiating someone into drug injection. This is a standard Poisson count variable with a potential inflation of the number of zeros as there will likely be many who do not initiate others (e.g., zero-inflation). This Poisson count outcome can essentially be thought of as consisting of two separate, yet interrelated, processes—one in which the participant engaged in the behavior of initiating someone else at all (i.e., binary yes/no) and another in which we assess the number of times the participant initiated someone (ranging from 1 to j, where j=the number of episodes initiating someone. In SEM literature, this is referred to as a two-part process for zero inflated Poisson, as SEM models these two processes separately as unique latent processes.[100] As this outcome is collected as part of an intervention with a baseline (T0) and two follow-ups (T1, T2), the model is parameterized to accommodate three time points, following Olsen and Schafer (2001).[100] Note that with three time points, the implied model is mis-identified given the number of measured variables in the variance-covariance from the observed data in an SEM measurement model with an intercept (i) and slope (s) for 3 observations.[101-103] However, joint modeling the ZIP as a two-part process redresses the identification problem, and results in 6 measured variables, one for the process in which the participant actually initiated another person (0 for no, 1 for yes) and another for the

Figure 3. Two-Part Zero-Inflated Poisson SEM



change/reduction in the number of initiations over the 3 observation times (1 to j). The first part of the analysis will involve characterization of the measurement model for the change over time from T0 to T1 and from T1 to T2. As shown in ***Figure 3***, the model will include a treatment covariate representing the effect of the CTC intervention on changes over time for the binary (sU) and count (sZ) latent variables, and it may contain other covariates identified as having been distributed differentially by condition at baseline or associated with loss to follow-up. Note that if there are no differences at baseline in preliminary bivariate analyses, there is no need to include a treatment effect on the intercept for the SEM because with no differences at baseline, the intercept test for difference is likely to be non-significant so there is no value in risking the extra degrees of freedom. Through model constraints, we will also examine specific differences between conditions within time points (e.g., T1 or T2) and between time points (e.g., change over time from T0 to T1). There will be little need for additional covariates to control for potential inflation of the correlations due to recruitment sites, as the targeted sampling will ensure full coverage across the locations where PWID congregate in LA and SF. We will, however, explore differences between the two sites, and may introduce a control variable to account for large-scale environmental differences between the two sites. To avoid any analytic decisions being driven by a desire for a certain result, the statistician and data analysis team will be blinded as to whether 0 or 1 denotes the treatment or control condition until the analyses are completed. There is also potential for contamination, which we will assess by asking the respondents in the control condition their level of exposure to intervention components, as described in ***Section 3.5.17.3***. We will follow procedures outlined by Keogh-Brown et al. (2007) using complier average causal models (CACE),[104] in which the bias associated with contamination is significantly reduced by averaging the estimated causal effect over classes of participants that differ in the level of exposure to contamination. Each person in the control group will be assigned to a class, depending on their level of exposure and type of exposure, using latent classification techniques utilized by Dr. Novak in previous publications.[105] Lastly, we will compare differences in examining the rate of change versus the standardized difference at each follow-up point (e.g., compare counts of injection initiation at 6m and 12m) and test for differences by condition. The latent change model has more power than the raw difference approach, and we will present differences in our published work if the outcome is sensitive to model estimation.

Aim 2: **To test the efficacy of CTC on reducing the number of times PWID are asked to initiate (counts) someone into injection.** *H2:* PWID who receive CTC will report having been asked fewer times to initiate someone into drug injection at 6 and 12 months as compared with PWID in the equal attention control condition. This model will be estimated in the same manner as the model for the outcome of the actual number of reported counts, save that this one will estimated using the self-reported counts by the respondent regarding being asked to initiate another person.

Aim 3: To test whether injection initiation social learning risks (injecting in front of, describing injection to, and speaking positively about injection to non-injectors) act as mediational mechanisms for the efficacy of the CTC intervention on initiation and request-to-initiate outcomes. *H3:* Social learning variables will significantly mediate the association between the CTC intervention and episodes of initiating and being requested to initiate someone into drug injection at 6 and 12 months. The outcome variable will remain counts of the number of episodes initiating someone into drug injection (Aim 1) and the counts of request to initiate another person (Aim 2). The mediational models will be specified following the work of Baron and Kenny and newer generalizations.[106-108] With only three time points, we can examine the effect of baseline randomization to treatment status on 12-month counts of injection initiation as the outcome and 6-month injection-risk behavior variables as the mediators. The lagged approach can be used as static measures at 6 months and 12 months, or changes in injection initiation social learning risks and IMB skills constructs that precede changes in the number of counts of initiation as outcome. This latter approach is strong in that the change in a variable, created by difference scores, is isolated so that it precedes the subsequent outcome.

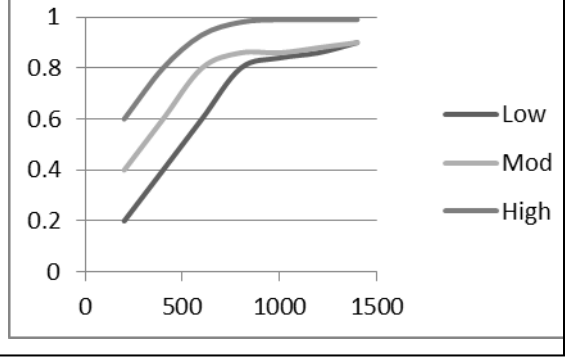
There are also techniques for estimating mediational models with only 2 time-points;[109] consequently, we will examine mediation from randomization to 6-month follow-up with the mediator and outcome measured concurrently. We can estimate separate mediational models for each injection initiation social learning risk and IMB skills construct, or enter the mediation mechanisms together into a single model, while examining overfit due to multiple mediational paths.[110] Omnibus measures of model fit (chi-square, root mean square error of approximation, Tucker Lewis Index [TLI]), and specific path coefficients will be used to assess the treatment effect and test for the mediational pathways. The null hypothesis will be rejected if the p value for the variable that denotes treatment condition is below 0.05. Proposed Co-I Dr. Novak has extensive experience with these techniques as part of longitudinal community-based interventions.[105,111,112]

13.2. Sample size/ power analyses

Power calculations were estimated using Mplus by creating a Monte Carlo Simulation by generating a synthetic data set based on the expected parameter values, such as slopes, standard errors, and correlations among measured variables, for the anticipated treatment effect.[113,114] Power was estimated assuming an intracluster correlation of 0.5, which is similar to our previous NIDA-funded studies.[105,112,115] Statistical tests were two-sided, allowing detection of effects in either direction, and an alpha of .05 and power at 80%, corresponding to moderate effect sizes. Because the outcome is a count (i.e., Poisson), standard errors were estimated as non-normal via a sandwich estimator in Mplus.[116] Co-Is Strike and Hunt found that the number of participants who initiated people into injection was halved at follow-up.[7] Preliminary data from MPIs Bluthenthal and Kral's study in LA and SF indicated that 809 active PWID were found to have initiated 431 people in the past year. Using the same proportion, we expect that 573 people would be initiated by our proposed sample size of 1,076 participants at baseline (286 in each arm). If the number of people initiated by intervention group participants is halved, as suggested by Strike and Hunt's pilot data, that would represent a reduction of 143 people not being initiated into injection.

We also calculated the effect under different assumptions of attrition, subgroups (e.g., 25% Latino), sex, and age. For brevity, we illustrate power for primary outcome and most conservative—changes in the number of injection initiation events. We also account for 25% attrition—our worst-case scenario. To test the three hypotheses given our alpha and power specifications, we would need a baseline recruitment of 1,076 (n=538 per condition). We will recruit 1,076 participants to achieve the final sample of approximately 800 at the 12-month data point. The sample power for Cohen's effect sizes for small (2 percentage point difference), medium (5% difference) and large (10%–15% difference) effect sizes are plotted in **Figure 4**, revealing that after accounting for attrition, a final study of 800 participants at the 12-month follow-up, evenly randomized, will have excellent power to detect small (0.82), moderate (0.88), and large (0.99) effect sizes. We also examined power for our mediational analyses in which the injection initiation risk variables will be differentially associated with treatment assignment. Following data from Co-I Strike for the mediational models, we expect that there was a 37% change in transition from initiation to non-initiation, and a 38% reduction in the participants injecting in front of injection-naive people. These parameter estimates were converted to a Monte-Carlo simulation in Mplus, and we will have power to detect a mediational effect of for moderate to large pathways (Tx→Mediator→Outcome). Note that we will not have sufficient power for small mediational effects with our proposed sample, which may be clinically insignificant anyway.

Figure 4. Statistical Power (Y axis) for Sample Size (Total N) for Small, Medium, and Large Effect Sizes



13.3 Missing data

The likelihood of missing data at the item level will be reduced by using CAPI. Therefore, much of the missing data will likely be due to participant-attrition. We will attempt to gather detailed tracking information to mitigate the likelihood of dropout, which has been approximately 25% at 12 months in our prior NIDA-funded studies of this population in LA and SF. We will censor data at the point of loss to follow-up. Other options, such as last-observation carried forward, will also be explored. As the team has done in previous studies, separate intent to treat (ITT) analyses will be conducted by treating the dropouts as the unfavorable outcome. We will explore mechanism of attrition, and can explore model-based extrapolations, such as pattern mixture modeling to account for data that are non-missing at random and the selection mechanism cannot be explained by observed covariates.[103,117-119] Regardless of the method used to redress missing data, we will

conduct sensitivity analyses by comparing results using these procedures to those that exclude missing data altogether so that reviewers may incorporate any differences in the evaluation of our work.

13.4. Elucidation Study 1

We will use descriptive statistics to characterize participants responses to these items.

13.5. Elucidation Study 2

Interviews and data analysis will be conducted by experienced qualitative interviewers (Drs. Bluthenthal, Karina Dominguez-Gonzalez, Johnathan Zhao). We anticipate qualitative interviews taking no more than 60 minutes. All interviews will be audio-recorded. Participants will receive $10 for completing the interview. The interviews will be digitally recorded and later transcribed verbatim by a professional transcription service that the investigative team has worked with successfully for four years. Transfer of audio files is accomplished through Hightail website. Audio files on digital recorders are erased after been transferred to Dr. Bluthenthal's password protected computer. Thematic analysis of transciptions will be conducted in an iterative fashion. After the completion of sets of 5 to 7 interviews, transcribed interviews will be coded and read to determine if new questions need to be added to explore emerging themes. This iterative analytic meeting will occur every other week until all 40 interviews are completed or therotical saturation has been achieved. Coding of interviews involves reading transcripts in their entirety, coding them and meeting with the research team to refine codes and check for inter-coder reliability. Coding will be conducted using Atlas-Ti qualitative data analysis software.

14.0 REGISTRATION GUIDELINE

Not applicable.

15.0 BIOHAZARD COMTAINMENT

Not applicable

16.0 ETHICAL AND REGULATORY CONSIDERATIONS

All institutional and Federal regulations concerning the Informed Consent form will be fulfilled. The study will be conducted in adherence to ICH Good Clinical Practice.

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APPENDICES (Include any desired tables, scales, questionnaires, etc.)

Appendix A: Peer Handbook Training Manual
Appendix B: Change the Cycle (CTC) Information Guide
Appendix C: Pilot informed consent
Appendix D: Assessment of pilot intervention
Appendix E: Screening interview informed consent
Appendix F: Randomized controlled trial informed consent
Appendix G: Contact form
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Appendix J: Releases of information forms for USC and RTI International
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