Official Title of the study:

Intermittent Oral Naltrexone Enhanced With an Ecological Momentary Intervention for Methamphetamine-using MSM

NCT number:

NCT04791969

Document Type:

Study Protocol

Date of the document:

09/30/2024

Study Application (Version 1.21)

1.0 General Information

***Enter the full title of your study:**

The ION+EMI Study: Intermittent Oral Naltrexone enhanced with an Ecological Momentary Intervention for Methamphetamine-using MSM

***Enter the study alias:**

HiNT Study
* This field allows you to enter an abbreviated version of the Study Title to quickly identify this study.

2.0 Add departments

2.1 and Specify Research Location:

Is Primary?	Department Name
◆	**UCSF** - *318006* - N_CHS-Administration
○	**UCSF** - *469026* - E_Human Rsch Protection Prog

3.0 List the key study personnel: (Note: external and affiliated collaborators who are not in the UCSF directory can be identified later in the Qualifications of Key Study Personnel section at the end of the form)

3.1 *Please add a Principal Investigator for the study:

Santos, Glenn-Milo

Select if applicable

☐ Department Chair ☐ Resident

☐ Fellow

If the Principal Investigator is a Fellow, the name of the Faculty Advisor must be supplied below.

3.2 If applicable, please select the Research Staff personnel

A) Additional Investigators

Coffin, Phillip O, MD
Other Investigator
Matheson, Tim
Other Investigator
Vittinghoff, Eric PhD
Other Investigator

B) Research Support Staff

Balcazar, Andrew L
Study Recruiter
Dunham, Alexandrea
Clinical Research Associate
Farley, John
Study Recruiter
Hoffmann, Thomas, PhD
Biostatistician
Ikeda, Janet
Study Coordinator
Jan, Fareshta
Clinical Research Associate
Parker, Ella
Clinical Research Associate
POPE, EMILY R
Clinical Research Associate
Tavasieff, Sophia R
Study Recruiter
Walker, John
Study Nurse
Yuhas, Trent W
Clinical Research Associate

3.3 *Please add a Study Contact

Ikeda, Janet
Santos, Glenn-Milo

The Study Contact(s) will receive all important system notifications along with the Principal Investigator. (e.g. The project contact(s) are typically either the Study Coordinator or the Principal Investigator themselves).

3.4 If applicable, please add a Faculty Advisor/Mentor:

3.5 If applicable, please select the Designated Department Approval(s)

Add the name of the individual authorized to approve and sign off on this protocol from your Department (e.g. the Department Chair or Dean).

4.0 Initial Screening Questions

Updated April 2020 - Revised Common Rule (January 2018) Compliant / COVID-19 - v94

4.1 * PROJECT SUMMARY: (REQUIRED) Give a brief overview of this project (250 words or less). Tell us what this study is about, who is being studied, and what it aims to achieve. If you have an NIH Abstract, paste it here (Click on the orange question mark to the right for more detailed instructions):

Methamphetamine (meth) use is very common among men who have sex with men (MSM), particularly MSM living with HIV. Meth use among HIV-negative and HIV-positive MSM is up to 13 and 34 times more prevalent than in the general U.S. adult population, respectively. Meth use is independently associated with HIV-related sexual risk behaviors among MSM and can function as a barrier to antiretroviral therapy (ART) and pre-exposure prophylaxis (PrEP) adherence. Thus, effective interventions to reduce meth use may also function as an important HIV prevention and care intervention by reducing meth-related HIV risk behavior, and optimizing ART and PrEP adherence. MSM comprise two-thirds of the new infections in the United States. Despite this continued domestic HIV epidemic and the high prevalence of meth use among MSM, few interventions have proven efficacious for MSM who use meth. We seek to address this gap by evaluating the efficacy of intermittent oral naltrexone enhanced with an ecological momentary intervention (ION+EMI) for meth use treatment. Naltrexone, a μ-opioid receptor antagonist, is a promising agent for MSM who use meth. Meth is rapidly metabolized to amphetamine in the bloodstream and daily naltrexone has shown efficacy in reducing amphetamine *urine-positivity and relapse*. Oral naltrexone is inexpensive and has few toxicities, but the standard daily regimen for naltrexone hampers compliance as patients frequently neglect to take the medication. Alternate regimen schedules have been proposed to increase efficacy and expand the population that may benefit from this pharmacologic agent. One alternative approach is the targeted administration of intermittent oral naltrexone (ION), whereby individuals are instructed to take the medication *as needed* in anticipation of substance use, after exposure to triggers of substance use, or during periods of craving. Administration of naltrexone prior to exposure to amphetamines significantly attenuated amphetamine craving in 4 trials. Additionally, emerging evidence suggests that ecological momentary interventions (EMI) that respond to in-the-moment contexts can lead to positive health behaviors, such as increasing medication dosing. EMI are particularly well-suited to enhancing as-needed dosing of naltrexone because anticipation of meth use and meth craving in a natural setting changes within a person from moment to moment, and the detection of these momentary fluctuations can support the delivery of just-in-time messages to encourage medication use to prevent participants from proceeding from craving to meth use. A pilot study led by our research team on ION found that meth-using MSM who use at least 1 day per week had significantly greater reductions in meth-using days when treated with as-needed naltrexone, compared to placebo. Moreover, naltrexone participants had greater reductions in serodiscordant receptive anal intercourse and serodiscordant condomless receptive anal intercourse, compared to placebo. In the pilot, participants reported taking study drug 64% of the days that they craved or anticipated meth use. Participants also completed ecological momentary assessments (EMA) with a 74% response rate, indicating that real-time assessments are feasible and acceptable. To build on the results of this study and 4 other naltrexone trials, we propose to evaluate intermittent naltrexone to treat meth in a phase 2b efficacy trial supplemented by an EMA-informed EMI that responds to a participant's real-time craving levels or anticipated meth use to provide in-the-moment medication reminders when participants would most benefit from naltrexone. We hypothesize that pairing ION with EMI will further amplify reductions in meth use by providing just-in-time reminders for naltrexone to optimize adherence, thereby interrupting the progression from craving to meth use.

4.2 * HUD DEVICE: (REQUIRED) Does this application involve a Humanitarian Use Device (HUD):

- (•) No
- ( ) Yes, and it includes a research component
- ( ) Yes, and it involves clinical care ONLY

4.3 * TYPE OF RESEARCH: (REQUIRED) Select the option that best fits your project (Click the orange question mark to the right for definitions and guidance):

- (•) Biomedical research (including medical records review, biospecimen collection and/or use, other healthcare or health outcomes related activities, research database, biospecimen bank, or recruitment registry)
- ( ) Social, behavioral, educational, and/or public policy research
- ( ) Hybrid - includes aspects of BOTH types of research (check this option if your research is mainly social/behavioral but also involves specimen collection or blood draws to look at biological measures)

4.4 * SUBJECT CONTACT: (REQUIRED) Does this study involve ANY contact or interactions with participants:

- (•) Yes (including phone, email or web contact)

○ No (limited to medical records review, biological specimen analysis, and/or data analysis)

4.5 * RISK LEVEL: (REQUIRED) What is your estimation of the risk level, including all screening procedures and study activities:

○ Minimal risk
◉ Greater than minimal risk

4.6 * REVIEW LEVEL: (REQUIRED) Requested review level (Click on the orange question mark to the right for definitions and guidance):

◉ Full Committee
○ Expedited
○ Exempt

4.9 * DATA/SPECIMEN ANALYSIS ONLY: (REQUIRED) Does this study ONLY involve records review and /or biospecimen analysis (do not check 'Yes' if this is a registry, research or recruitment database, or biospecimen repository):

○ Yes ◉ No

4.10 * CLINICAL TRIAL: (REQUIRED)
Is this a clinical trial:

According to The World Health Organization (WHO) and the International Committee of Medical Journal Editors (ICMJE) a clinical trial is:

- Any research study that prospectively assigns human participants or groups of humans to one or more health-related interventions to evaluate the effects on health outcomes.

ICMJE requires registration of a clinical trial in a public database (such as ClinicalTrials.gov) prior to enrollment, for eventual publication of results in member biomedical journals.
Guidance: Public Law 110-85 requires that all investigators who perform an *applicable clinical trial* must ensure that the trial is registered on a government web site called **ClinicalTrials.gov**.

The FDA requires registration for 'applicable clinical trials,' defined as follows:

- For any trials of drugs and biologics: controlled clinical investigations, other than Phase 1 investigations, of a product subject to FDA regulation.
- For trials of biomedical devices: controlled trials with health outcomes of devices subject to FDA regulation, other than small feasibility studies, and pediatric post-market surveillance.

For additional information on the **ClinicalTrials.gov** registration process at UCSF and the definition of a clinical trial for purposes of registration, visit the **ClinicalTrials.gov section of the UCSF Clinical Research Resource HUB**.

(•) Yes ( ) No

Clinical Trial Registration - 'NCT' number for this trial:

NCT04791969

4.11 * CLINICAL TRIAL PHASE: (REQUIRED) Check the applicable phase(s):

- [ ] Phase 0
- [ ] Phase 1
- [ ] Phase 1/2
- [x] Phase 2
- [ ] Phase 2/3
- [ ] Phase 3
- [ ] Phase 4
- [ ] Not Applicable

4.12 * INVESTIGATOR-INITIATED: (REQUIRED) Is this an investigator-initiated study:

(•) Yes ( ) No

The UCSF IRB recommends use of the Virtual Regulatory Binder to manage your study.

4.13 * CORONAVIRUS RESEARCH: (REQUIRED) Does this study involve research on coronaviruses (COVID-19, SARS, MERS or other):

( ) Yes (•) No

4.15 * CANCER: (REQUIRED) Does this study involve cancer (e.g., the study involves patients with cancer or at risk for cancer, including behavioral research, epidemiological research, public policy research, specimen analysis, and chart reviews):

( ) Yes (•) No

4.16 * RADIATION EXPOSURE: (REQUIRED) Does your protocol involve any radiation exposure to patients /subjects EITHER from standard care OR for research purposes (e.g., x-rays, CT-scans, DEXA, CT-guided biopsy, radiation therapy, or nuclear medicine including PET, MUGA or bone scans):

( ) Yes (•) No

4.17 SCIENTIFIC REVIEW: If this study has undergone scientific or scholarly review, please indicate which entity performed the review (check all that apply):

- [ ] Cancer Center Protocol Review Committee (PRC) (Full approval is required prior to final IRB approval for cancer-related protocols.)
- [ ] CTSI Clinical Research Services (CRS) Advisory Committee
- [ ] CTSI Consultation Services
- [ ] Departmental scientific review
- [x] Other:

* Specify **Other: (REQUIRED)**

NIDA

4.18 * STEM CELLS: (REQUIRED) Does this study involve human stem cells (including iPS cells and adult stem cells), gametes or embryos:

- (•) No
- ( ) Yes, and requires IRB and GESCR review
- ( ) Yes, and requires GESCR review, but NOT IRB review

4.19 * FINANCIAL INTERESTS: (REQUIRED) Do you or any other responsible personnel (or the spouse, registered domestic partner and/or dependent children thereof) have financial interests related to this study:

( ) Yes (•) No

5.0 Funding

5.1 * FEDERAL FUNDING: (REQUIRED) Is this study currently supported in whole or in part by Federal funding, *even by a subcontract*, OR has it received ANY Federal funding in the past:

(•) Yes ( ) No

5.2 * DoD INVOLVEMENT: Is this project linked in any way to the Department of Defense (DoD): (REQUIRED)

( ) Yes (•) No

5.3 SPONSORS: Identify all sponsors and provide the funding details. If funding comes from a Subcontract, please list only the Prime Sponsor:

External Sponsors:

View Details	Sponsor Name	Sponsor Type	Awardee Institution:	Contract Type:	Project Number	UCSF RAS System Award Number ("A" + 6 digits)
⊟	NIH Natl Institute on Drug Abuse	01	UCSF	Grant	PO549101	

Sponsor Name:	NIH Natl Institute on Drug Abuse
Sponsor Type:	01
Sponsor Role:	Funding
CFDA Number:	
Grant/Contract Number:	DA053171-01A1
Awardee Institution::	UCSF
Is Institution the Primary Grant Holder:	Yes
Contract Type:	Grant
Project Number:	PO549101

UCSF RAS System Award Number ("A" + 6 digits):	
Grant Number for Studies Not Funded thru UCSF:	
Grant Title:	The ION+EMI Study: Intermittent Oral Naltrexone enhanced with an Ecological Momentary Intervention for Methamphetamine-using MSM
PI Name: (If PI is not the same as identified on the study.)	Glenn-Milo Santos
Explain Any Significant Discrepancy:	

Other Funding Sources and Unfunded Research - Gift, Program, Departmental or other Internal Funding (check all that apply):

- ☐ Funded by gift (specify source below)
- ☐ Funded by UCSF or UC-wide program (specify source below)
- ☐ Specific departmental funding (specify source below)
- ☐ Unfunded (miscellaneous departmental funding)
- ☐ Unfunded student project

6.0 Sites, Programs, Resources, and External IRB Review

6.1 * UCSF AND AFFILIATED SITES (check all that apply): (REQUIRED)

- ☐ UCSF Benioff Children's Hospital Oakland (BCHO)
- ☐ UCSF Cancer Center Berkeley
- ☐ UCSF Cancer Center San Mateo
- ☐ UCSF China Basin clinics and facilities
- ☐ UCSF Helen Diller Family Comprehensive Cancer Center
- ☐ UCSF Langley Porter Psychiatric Institute (LPPI)
- ☐ UCSF Medical Center at Mission Bay (Benioff Children's Hospital, the Betty Irene Moore Women's Hospital, Bakar Cancer Hospital, or outpatient clinics)
- ☐ UCSF Mount Zion
- ☐ UCSF Parnassus (Moffitt-Long hospital, dental clinics or other outpatient clinics)
- ☑ UCSF Other Sites (including Laurel Heights and all the other sites outside the main hospitals and clinics)
- ☐ Fresno - UCSF Fresno OR Community Medical Center (CMC)
- ☐ Gladstone Institutes
- ☐ Institute on Aging (IOA)
- ☐ Jewish Home
- ☑ SF Dept of Public Health (DPH)
- ☐ SF VA Medical Center (SF VAMC)
- ☐ Vitalant (formerly Blood Centers of the Pacific and Blood Systems Research Institute)
- ☐ Zuckerberg San Francisco General (ZSFG)

Research involving the SFDPH: SFDPH sites and clinics has some special requirements, including adherence to the SFDPH HIPAA Policy, involvement of an SFDPH-approved investigator, and inclusion of a signed SFDPH Research Proposal Approval. Your submission will be returned to you if it does not include this form.

6.2 LOCATIONS: At what locations will study visits and activities occur:

Study visits will occur at 25 Van Ness Ave., Suite #500, San Francisco, CA. 94102

6.3 OFF-SITE PROCEDURES: Will any study procedures or tests be conducted off-site by non-UCSF personnel:

(•) Yes ( ) No

Please identify which procedures may be done off-site:

Study activities will take place at 25 Van Ness Ave., Suite #500. These activities include screening, enrollment, and follow-up visits that include survey administration, urine tests, safety labs, sweat patches and HIV tests.

6.4 RESEARCH PROGRAMS: Check any UCSF research programs this study is associated with:

- [ ] Cancer Center
- [ ] Center for AIDS Prevention Sciences (CAPS)
- [ ] Global Health Sciences
- [ ] Immune Tolerance Network (ITN)
- [ ] Neurosciences Clinical Research Unit (NCRU)
- [ ] Osher Center
- [ ] Positive Health Program

6.5 * CTSI CRS SERVICES: (REQUIRED) Will this study be carried out at one of the UCSF Clinical Research Services (CRS) units or utilize CRS services:

( ) Yes (•) No

6.6 * MULTI-CENTER TRIAL: (REQUIRED) Is this a multi-center or multi-site research trial:

By **'multi-center trial'** we mean a study where the protocol is developed by an lead investigator, an industry sponsor, consortium, a disease-group, etc.,and multiple sites across the nation or in different countries participate in the trial. The local sites do not have any control over the design of the protocol.

( ) Yes (•) No

6.8 OTHER SITE TYPES: Check all the other types of sites not affiliated with UCSF with which you are cooperating or collaborating on this project:

Do NOT check any boxes below if this is a multi-center clinical trial, UCSF is just one of the sites, and neither UCSF nor one of its faculty-linked affiliates (SF VAMC, Gladstone, ZSFG) are the coordinating center.

- [ ] Other UC Campus
- [x] Other institution
- [ ] Other community-based site
- [ ] Foreign Country
- [ ] Sovereign Native American nation (e.g. Navajo Nation, Oglala Sioux Tribe, Havasupai, etc.)

6.11 * OUTSIDE RELIANCES: (REQUIRED) Are any of the collaborating sites requesting to rely on UCSF's IRB:

○ Yes ◉ No

6.14 * RELYING ON AN EXTERNAL IRB: (REQUIRED) Does this application include a request to rely on an external IRB (a central IRB (other than the NCI CIRB) or an external IRB (other UC campus, commercial, or institutional):

○ Yes ◉ No

7.0 Outside Site Information

7.1 Outside Site Information

If you have more than 10 sites to add, list the outside sites in the Outside Sites List document and upload it in the Other Study Documents section of the Initial Review Submission Packet form. Any sites requesting to rely on UCSF's IRB must be listed below.

Click "Add a new row" to enter information for a site. Click it again to add a second site again to add a third site, a fourth site, etc.

Outside Site Information

Non-UCSF affiliated site information:

Site name:

University of Texas, Health Science Center

Contact name:

Diane Santa Maria

Email:

Diane.M.Santa Maria@uth.tmc.edu

Phone:

713.500.2002

For Federally-funded studies only, corresponding FWA#:

#00000667

*** The research at this site will be reviewed by:**

○ The non-affiliated site's IRB or a private IRB
○ The non-affiliated site is requesting UCSF to be the IRB of

record for this study

- ( ) The non-affiliated site is not engaged in the human subjects research and has provided a letter of support

If the other site's IRB approval letter is available now, attach it to the application. If the IRB approval letter is not yet available, submit it once you receive it.

Or, if the other site is **not engaged** in human subjects research, attach the letter of support to your application.

Outside Site Information

Non-UCSF affiliated site information:

Site name:

University of Oklahoma, Health Science Center

Contact name:

Michael Businelle

Email:

Michael-Businelle@OUHSC.edu

Phone:

405-271-8001 x50460

For Federally-funded studies only, corresponding FWA#:

#00007961

*** The research at this site will be reviewed by:**

- ( ) The non-affiliated site's IRB or a private IRB
- ( ) The non-affiliated site is requesting UCSF to be the IRB of record for this study
- (•) The non-affiliated site is not engaged in the human subjects research and has provided a letter of support

If the other site's IRB approval letter is available now, attach it to the application. If the IRB approval letter is not yet available, submit it once you receive it.

Or, if the other site is **not engaged** in human subjects research, attach the letter of support to your application.

8.0 Research Plan and Procedures

8.1 HYPOTHESIS: Describe the hypothesis or what the study hopes to prove:

Our Hypotheses are:

1. *Targeted Intermittent Oral Naltrexone (ION) will significantly reduce meth use, as determined by the proportion of meth-positive urine tests, compared to placebo.*
2. *Targeted ION will significantly reduce meth-associated sexual risk behavior, as determined by the audio computer assisted self-interview (ACASI) data and sexual risk behavior data, compared to placebo.*
3. *Targeted ION will significantly increase PrEP adherence among HIV-negative participants and ART adherence among participants living with HIV, as determined by drug levels and viral load testing; and sexual risk behavior data accounting for PrEP use and viral suppression, compared to placebo.*

8.2 AIMS: List the specific aims:

Our Aims are:

1. *To determine the efficacy of ION vs. placebo in reducing meth use, as determined by the proportion of meth-positive urine tests*
2. *To determine the efficacy of ION vs. placebo in reducing meth-associated sexual risk behaviors*
3. *To determine the efficacy of ION vs. placebo in increasing PrEP adherence among HIV-negative participants and ART adherence among participants living with HIV*

8.3 DESIGN: Briefly describe the study design (e.g., observational, interventional, randomized, placebo-controlled, blinded, cross-over, cross-sectional, longitudinal, pharmacokinetic, etc.):

Research Design: *This is a double-blind, placebo-controlled phase 2b trial in which 60 MSM who use meth will be randomly assigned (2:1) to receive 12 weeks of as-needed intermittent oral naltrexone 50 mg enhanced with an EMA-informed EMI platform, or receive as-needed placebo with EMA-informed EMI. The 12-week treatment period is consistent with other pharmacotherapy*

trials for substance use disorders.[66,85,124,125,142,143] The proposed sample size is also consistent with other phase 2b trials for substance use treatment.[66,125,144] Upon enrollment, participants will complete daily EMA assessments and weekly visits for behavioral surveys and urine testing for meth metabolites, study drug dispensing and counseling for substance use. Safety laboratory assessments and vital signs will be completed monthly. Efficacy (Specific Aims 1-3) will be assessed upon trial completion as measured by proportion meth-positive urine samples; PrEP and ART adherence by drug levels and viral load testing; and sexual risk behavior data accounting for PrEP use and viral suppression.

8.4 BACKGROUND AND SIGNIFICANCE: Briefly provide the background and significance of this study (e.g. why is this study needed) (space limit: one half page):

If this is a first in humans study, please summarize the safety data from the animal studies. For pediatric drug or device studies, please identify if this is the first study in pediatric populations.

Meth use is a major public health issue among cisgender men who have sex with men (MSM). National HIV Behavioral Surveillance (NHBS) data indicate that among HIV-negative and HIV-positive MSM, meth use is up to 13 and 34 times more prevalent than in the general adult population.[1,2] Meth use is associated with significant morbidity and mortality.[3,4] Meth is a highly addictive drug with serious medical, societal, and economic consequences.[5-16] In San Francisco, there has been a steady increase across all meth indicators (treatment admissions, emergency department visits, inpatient hospitalizations, and deaths) since 2009.[17]

Cisgender MSM are disproportionately impacted by HIV, accounting for 66% and 74% of new infections in the US and San Francisco, respectively.[18,19] The rate of new infections in cisgender MSM in San Francisco is estimated at 369 infections per 100,000, compared to 36 per 100,000 overall.[19] It is imperative to develop more evidence-based HIV-prevention interventions for MSM, including MSM who use meth.

Meth use is independently associated with HIV risk behaviors. NHBS data show that meth use before or during sex are common for MSM. In NHBS, 66% of meth users reported having sex while under the influence of meth.[20] The acute effects of meth (e.g., altered cognition, impairment of judgment, and increased sexual desire and confidence) are postulated to contribute to risk-taking behaviors.[21-23] A myriad of psychosocial factors (e.g., cognitive escape, impulsivity, expectancies) are believed to mediate the association between meth use and sexual risk behaviors.[24,25] Additionally, for racial and ethnic minority MSM, co-occurring psychosocial and clinical morbidities, as well as the intersection of stigmas, are also associated with greater meth use and sexual risk.[26-29] Furthermore, the late-night bar, club, and circuit-party (weekend-long dance events) settings frequented by MSM are environments conducive to both meth use and meeting sex partners.[30-32]

In systematic reviews of studies among MSM, *event-level* analyses of meth use immediately before or during sexual episodes consistently indicate that it is independently associated with increased likelihood of having condomless sex in that event.[33,34] *Event-level* assessments of meth use provide a precise temporal link between these substances and HIV risk, and provide stronger evidence for causality.[33,34] Meth use is independently associated with condomless anal intercourse, multiple partners, increased duration of sex, anonymous partners, sex in a public sex venue, and exchanging money or drugs for sex.[35-40]

Meth use has been independently associated with new HIV infections.[40-42] In a longitudinal study of 4,295 HIV-negative MSM from six metropolitan areas, 16% of incident HIV infections were attributable to meth use.[43] Moreover, meth use is associated with syphilis infection and other sexually transmitted diseases, which in turn increase HIV risk.[44-46] Injection of meth has been documented across 60 countries globally and people who inject meth may be at heightened risk for HIV because of the potential for HIV transmission from sexual and injecting risk behaviors.[47] **Among people living with HIV, meth use is associated with poor health outcomes due to lower antiretroviral therapy adherence**.[48,49 50] Meth may function as a barrier to the ability of HIV-positive MSM to adhere to ART by increasing their forgetfulness, or reducing their ability to maintain routine.[46] Frequent meth use is also associated with two-fold increased odds for primary drug resistance to any class of HIV drugs.[51] **Among HIV-negative**

individuals using pre-exposure prophylaxis (PrEP) to prevent HIV infection, meth use has also been reported as a barrier to PrEP adherence.[52] Moreover, meth use was associated with sub-optimal (less than 4 doses per week) PrEP adherence based on drug level testing data.[53] Because meth use is associated with high-risk sexual behavior, lower PrEP and ART use, HIV seroconversion, STD incidence, and drug-resistant HIV, data strongly support that meth use plays an important role in perpetuating the U.S. HIV epidemic. ADDIN EN.CITE.DATA [5,32,40,44,46,51,54-63] Therefore, effective interventions that reduce meth use will also likely have profound effects in reducing HIV risk via reductions of meth-associated sexual risk behaviors.

Pharmacotherapy for substance use disorders treatment can play an important role in addressing HIV. For example, efficacious, FDA-approved pharmacologic interventions that treat opioid use disorders have also been demonstrated to reduce HIV transmission.[64,65] Research conducted by our group among MSM with severe meth use disorders has also demonstrated that reductions in meth use from pharmacologic treatment can lead to successful reductions in meth-associated sexual behaviors.[66]

There are no FDA-approved medications for meth use disorders. Furthermore, there are no effective pharmacologic strategies for meth-using MSM without severe use disorders.[67,68] Although a sizable proportion of meth users are episodic users who do not have severe use disorders,[69,70] pharmacologic studies have focused on individuals with severe use disorders.[70,71] While some behavioral interventions for MSM reduce substance use and HIV risk behaviors,[68,72,73] they may benefit from adjuvant pharmacologic agents.[74,75]

Naltrexone is a promising agent for meth use that blocks the rewarding effects of meth. Administration of meth enhances release of mRNA precursors for endogenous opioids that bind to μ-opioid receptors and increase extracellular dopamine levels.[76-78] Naltrexone competitively blocks endogenous opioids from activating μ-opioid receptors[79] in the nucleus accumbens and ventral tegmental area, which mediate dopamine release. Thus, the opioid antagonism by naltrexone decreases the activity of the dopamine reward pathways, tempering the positive neurobiological effects of meth.[78-81]

Naltrexone is effective in attenuating the positive subjective effects of meth intoxication—including quality of "high", craving, and euphoria, supporting efficacy among current meth users.[82-87] ***Meth is rapidly metabolized to amphetamine*** *in the bloodstream* and administration of oral naltrexone prior to amphetamine exposure significantly reduced both the subjective effects of amphetamine and craving for amphetamine among healthy and amphetamine-dependent humans in laboratory studies.[87,88] Additionally, oral naltrexone was associated with reductions in both craving and subjective response to meth, and also significantly reduced the association *between* craving and subjective response to meth after meth administration.[89,90] Four double-blind, placebo-controlled naltrexone trials have observed efficacy on subjective effects and craving.[87-89,91]

Daily oral naltrexone has significantly reduced amphetamine-positive urine samples and craving in a randomized controlled trial with a 12 week follow-up. Naltrexone significantly reduced relapse measured via urinalyses for amphetamine use and resulted in a "reasonably strong" to "strong" effect size (d=0.5) in a trial among 80 amphetamine-dependent heterosexual adults.[91] The study reported that naltrexone produced reductions in both craving and reward sufficient to counteract the reinforcing effect of amphetamine, even in the setting of modest adherence (63% had naltrexone adherence of at least 66% during follow-up).[91] Given naltrexone's efficacy in blocking the rewarding effects of meth/amphetamine and relapse to use,[92] naltrexone may be a promising option to attenuate craving and reduce episodic meth use on an "as-needed" basis. Naltrexone is well-tolerated and has no known significant drug interactions with meth.[79,91,93-96] Naltrexone has few serious side effects and no known abuse potential or sexual side effects.[94,95,97-100]

Oral naltrexone's pharmacokinetic properties support its promise for intermittent targeted administration (i.e., during craving). Naltrexone's activity is believed to be due to both the parent compound and the 6-β-naltrexol metabolite.[97] Naltrexone reaches peak plasma levels within 1 hour of oral administration. The mean elimination half-life for naltrexone and 6-β-naltrexol are 5 and 13 hours, respectively.[97,101,102] Naltrexone also has high affinity for the μ-opioid receptor (Ki = 2.5 ± 0.21 nM) and a single 50mg dose can block μ-opioid receptors for up to 72 hours,[103] raising the possibility that dosing 1-2 days prior to anticipated meth use may be effective. With its rapid onset and long duration of action, naltrexone is well-suited for intermittent dosing.

Targeted administration of intermittent oral naltrexone (ION) on an "as-needed" basis has shown promise in treating substance use and reducing sexual risk behaviors.[104-108] A pilot study of targeted ION conducted by our group found that meth-using MSM who used at least 1 day per week had significantly greater reductions in meth-using days when treated with as-needed naltrexone, compared to placebo (RR = 0.78).[109] In the same study, we found that targeted ION participants had greater reductions in serodiscordant receptive anal intercourse (RR = 0.15) and serodiscordant condomless receptive anal intercourse (RR = 0.11), compared to placebo.[109] In other substance using populations, ION dosing has also been shown to be feasible, acceptable and efficacious.[106,110] For example, ION administered after a period of daily dosing significantly reduced heavy-drinking relapse.[108] In another trial by Kranzler, et al. (n=163), men assigned to *ION* showed significantly greater reductions in mean drinks per day, and in number of drinks during drinking days, compared to those assigned to *daily* naltrexone administration, *daily* placebo, or intermittent placebo.[106] Therefore, there is mounting evidence that ION is a promising dosing strategy to treat substance use and sexual risk behaviors.

Meth use is associated with factors that fluctuate from day to day—such as craving, stress, and mood—antecedents which have all been shown to have high predictive validity for meth use.[111] Day-level antecedent fluctuations detected in ecological momentary assessments (EMA) strongly predict subsequent drug use. Santa Maria (Co-I) and Santos (PI) observed that days with high drug craving were significantly associated with a 47.2 increased odds of using drugs within the same day.[112] Meta-analysis of EMA data on drug craving also observed consistent linkages between drug craving and drug use.[113] Furthermore, using EMA to monitor these antecedents is ideal because the predictive validity of these antecedents on meth use decreases as the time of assessment becomes more distant (i.e., as the assessments of antecedents happen further away from real-time).[111] Therefore, monitoring these antecedents with EMA in real time would enable more precise identification of moments when the risk of meth use is high. Monitoring daily variations of these antecedents in EMA decreases recall bias and increases data validity because the measurements occur near real-time, and in natural settings (i.e., environments outside research laboratories or clinics).[112,114-116] Furthermore, we have demonstrated the feasibility, acceptability and validity of EMA approaches among MSM who use meth in pharmacotherapy,[116,117] diverse samples of substance-using MSM[118] and other marginalized populations.[112,115]

Targeted administration of ION could be enhanced by just-in-time reminders that leverage EMA monitoring for craving or perceived likelihood of using meth. Ecological momentary approaches can be extended to dynamically send ("push") information based on EMA responses that indicate heightened risk for meth use, with what is referred to as EMA-informed ecological momentary interventions (EMI). Specifically, EMA detection of meth use antecedents such as craving can be used to trigger just-in-time EMI adherence reminders to encourage naltrexone use during these moments when individuals are at heightened risk for meth use and when they could most benefit from the effect of this pharmacologic intervention via its effects on reducing meth craving. The use of EMA-informed EMI to increase adherence is supported by the Health Belief Model (HBM), which posits that individuals are more likely to engage behavior change when they are made aware of their perceived susceptibility to a health issue (e.g., high susceptibility for meth use when antecedents identified by EMA), perceive benefit from a behavior (e.g., efficacy of taking ION during moments when antecedents are identified); and when they receive prompts or cues to act/engage in behaviors (e.g., prompts from EMI to take ION cued at moments of susceptibility).[119,120] In systematic reviews, the majority of adherence interventions (78%) informed by HBM have significantly increased medication adherence across multiple health conditions.[121]

EMA-informed EMI procedures are feasible and acceptable among marginalized populations. Dr. Santa Maria (Co-I) and Dr. Businelle (consultant) have successfully enrolled and completed EMA-informed EMI studies, with high EMA completion rates and high EMI receipt rates (>80% across the MY-RID and Smart-T studies), among homeless youth and socioeconomically disadvantaged adults from urban safety-net hospitals. [122,123] Furthermore, participants in Drs. Santa Maria and Businelle's studies consistently report liking EMA-informed EMI and report high study satisfaction rates, indicating high acceptability.[122,123]

MSM who use meth in pharmacotherapy trials will likely benefit from just-in-time adherence reminders because this population often cite forgetfulness as a primary reason they have difficulty taking their medications for meth treatment. The most common reason for non-adherence reported by participants in three pharmacologic studies of oral medications among MSM who use meth conducted by our group (cumulative sample n=180) was forgetfulness.[66,124,125] People living with HIV also cite forgetfulness because of their meth use as

a barrier to HIV treatment.[50] Adherence text reminders are efficacious in increasing medication adherence; data from the EPIC study by Vittinghoff (Co-I) and colleagues, for example, observed that text message reminders on PrEP adherence significantly increase PrEP use.[126] Similarly, a meta-analysis of text messaging adherence reminders demonstrated efficacy in increasing medication adherence across chronic diseases.[127] Given the fact that antecedents that predict meth use such as craving vary daily and can be reduced by naltrexone, but meth users often forget to take their oral medications, utilizing EMA-informed EMI adherence reminders is a promising approach to enhance naltrexone treatment of meth use. EMI can provide just-in-time reminders to facilitate adherence during moments when individuals would most benefit from the pharmacologic intervention. *Despite the potential of EMI to support adherence to targeted pharmacotherapy, to our knowledge, there have been no trials that have evaluated the efficacy of treating meth use with targeted intermittent oral naltrexone enhanced with EMI adherence reminders.*

8.5 PRELIMINARY STUDIES: Briefly summarize any preliminary studies relevant to your proposed research (space limit: one half page):

Preliminary Studies: Numerous studies published by Dr. Santos and the collaborating research team involving MSM have informed the proposed research.[58,66,70,71,124,149-156] The study team has successfully enrolled multiple cohorts of non-treatment seeking MSM in non-abstinence–based pharmacologic and behavioral trials with excellent participation in study visits, procedures, and retention rates.[66,124,125,150] Our previous research has also demonstrated that reductions in substance use can result in parallel reductions in HIV sexual risk behaviors.[66,71] **Table 1** lists relevant studies conducted by our group. **Project iN (intermittent naltrexone) study:** The current proposal logically builds on this pilot study establishing the feasibility, acceptability and tolerability of ION among 30 meth-using MSM without severe use disorders *(*ClinicalTrials.gov Identifier: NCT01723384). Preliminary data were extremely promising with a 61% screen to enroll rate, 95% retention rate and 93% study completion rate, suggesting that conducting a larger efficacy study on ION is feasible among meth-using MSM without severe use disorders. In addition, MSM in the trial reported high acceptability for the study procedures: most were satisfied /highly satisfied with the study (76%), were very likely to participate in a future study (71%), and were very likely to recommend the study to a friend (71%). No one in the study had stopped medications because of adverse events, suggesting that this intervention is tolerable in this population. This pilot was not powered to detect efficacy. We recognize the need for caution when interpreting results of pilot studies for hypothesis testing, as well as the controversy on estimating treatment effects from pilot studies.[157,158] Nevertheless, specifying and testing analyses on meth use and sexual behaviors in the context of our pilot work is an important step in determining the applicability of our measures and analyses for a larger formal efficacy trial. In *e xploratory, intention-to-treat (ITT) analyses*, we noted a point estimate consistent with a protective *signal* in favor of naltrexone, compared to placebo, on meth use (RR = 0.82).[109] While this was not statistically significant, we recognize that in small trials such as ours, type II error (i. e., false negatives) is a bigger concern due to small samples sizes, as opposed to type I error (i. e., false positives).[158] Hence, we interpret this result with caution. The study also found that meth-using MSM who used at least 1 day per week had significantly greater reductions in meth-using days when treated with ION, compared to placebo in a sub-group analysis (RR = 0.78).[109] Finally, we also found that ION participants had greater reductions in serodiscordant receptive anal intercourse (RR = 0.15) and serodiscordant condomless receptive anal intercourse (RR = 0.11), compared to placebo.[109] Participants also reported taking study drug 64% of the days that they craved meth or anticipated meth use. While this study drug compliance rate is better relative to our other pharmacotherapy trials with daily dosing, it still indicates a gap in compliance that can be enhanced with an adherence intervention, such as EMI. Hence, these findings support the *f easibility, acceptability, tolerability, and potential utility* of ION to treat MSM who use meth and reduce HIV-related risks.

TABLE 1: RELEVANT STUDIES BY RESEARCH TEAM

PHARMACOTHERAPY FOR MSM WHO USE SUBSTANCES	(n)	Duration	Retention	# Screened (Enroll. ratio)
Harness Study (Intermittent Oral Kudzu)	120	12 weeks	Ongoing	Ongoing

Curb the Line (Lorcaserin)	22	12 weeks	86%	56 (40%)
Say When (Intermittent Oral Naltrexone)	120	12 weeks	89%	269 (45%)
Trex Study (Intramuscular Naltrexone) [144]	100	12 weeks	90%	194 (52%)
Project iN (Intermittent Oral Naltrexone[109])	30	8 weeks	95%	49 (61%)*
BUMP Study 1 (Bupropion[124])	30	12 weeks	90%	54 (56%)
BUMP Study 2 (Mirtazapine[66])	60	12 weeks	95%	212 (56%)
BUMP Study 3 (Aripiprazole[125])	90	12 weeks	83%	375 (24%)
M 2.0 Study (Mirtazapine)	120	48 weeks	94%	241 (50%)

Observational/Ecologic Momentary Studies on Substance Use	**(n)**	**Duration**
SUPreMe Study (Substance Use and PrEP among MSM)	250	1 year
Digital Divide Ecological Momentary Study[118]	45	7 days
SAMBA: Stimulants Alcohol Momentary Behavioral Assessments	263	14 days
Project Youth HIV Risk Estimator Development	66	21 days
Smart-T EMI Study	59	3 weeks

8.6 * TREATMENT PROTOCOL: Is this a treatment study, i.e. does this study intend to provide treatment to individuals with a medical or psychological condition: (REQUIRED)

(•) Yes ( ) No

8.7 * BILLABLE PROCEDURES: Does this study involve any procedures, lab tests or imaging studies that have a CPT code and could be billable to patients, their insurance, Medi-Cal, Medicare, or any other entity (answer 'Yes' even if the study is going to pay for all the procedures): (REQUIRED)

( ) Yes (•) No

If you are not sure if your study involves billable procedures, send an email to the UCSF Office of Clinical Research (OCR) for help answering this question.

8.8 * COMMON RESEARCH ACTIVITIES: Types of research activities that will be carried out. Check all that apply and describe in more detail in the 'Procedures / Methods' section: (REQUIRED)

- [x] Interviews, questionnaires, surveys
- [ ] Educational or cognitive tests
- [ ] Focus groups
- [ ] Social media-based research activities
- [ ] Observation
- [ ] Fitness tests or other exertion activities
- [x] Use of mobile health apps or other apps
- [ ] Collection of data from wearable tech such as Fitbit, Apple Watch, Garmin, motion actigraphs, etc.)
- [ ] Non-invasive imaging or testing (MRI, EEG, pulse oximetry, etc.)
- [ ] Imaging procedures or treatment procedures that involve radiation (x-rays, CT scans, CT-guided biopsies, DEXA scans, MUGA or PET scan)
- [ ] Administration of contrast agent
- [ ] Randomization to one intervention versus another
- [x] Use of placebo
- [ ] Biopsy conducted solely for research purposes
- [ ] Sham surgical procedure
- [ ] None of the above

8.9 * PROCEDURES / METHODS: (REQUIRED)

For clinical research, list all study procedures, tests and treatments required for this study, including when and how often they will be performed. If there are no clinical procedures, describe the research activities.

If some of the activities would occur even if the person were not in the study, as in the case of treatment or tests performed for diagnostic purposes, **clearly differentiate between those activities that will be done solely for research purposes and those that are happening as part of routine care.**

Examples may include:

- additional scans outside standard clinical diagnosis or monitoring
- additional biopsies to collect tissue for research
- extra clinic visits
- extra lab tests not required for clinical care

If you have a procedure table, attach it to the submission with your other study documents.

Study Procedures: Potential participants will be asked brief eligibility screening questions in person or over the phone after providing verbal consent. Potential participants will provide informed consent and be screened for eligibility during the pre-enrollment screening visit. The schedule for the study procedures is shown in **Table 3**.

Participants will be compensated for their time at each visit and in responding to daily ecological momentary messages (up to a total of $421). Participants will receive $50 for the 2 in-office screening visits ($20 at Screen 1 and $30 at Screen 2), $15 each for in-office run-in visits 1 and 2, $40 for in-office enrollment, $15 for remote weekly visits (1-3, 5-7, and 9-11), $15 for in-office weekly visits (4, 8, 12), $40 for in-office week 4 (month 1) and week 8 (month 2) visits, and $50 for week 12 (month 3). In addition, they will receive $0.40 for each day that they complete the daily EMA series throughout the 12-week treatment period (up to $36). Participants will be paid by cash, visa gift cards, or by paypal.

Participants could receive a gift card ($10) for partial screening visits. For any snowball referral that has completed a screening visit, the participant who referred the new participant will receive

$10. If the new participant enrolls in the study, the participant who referred the new participant will receive $40.

COVID-19 Precautions: We will follow the UCSF's COVID-19 policy for clinical research, which prioritizes the health and safety of UCSF's patients, participants, staff, trainees, and community. It also aligns with State of California laws, local public health directives, NIH policies, and other institutional guidance on COVID-19.[163] Additionally, as a precaution prior to each study visit, participants will be asked whether they have any of the current symptoms indicated by the Centers for Disease Control and Prevention for COVID-19 in the past two weeks for screening visits, or since the last visit for active participants.[164] Those experiencing symptoms regardless of severity will be referred to free public testing sites by staff[165] and visits will be rescheduled as appropriate (i.e., until receipt of COVID-19 test result to rule out infection). Temperature checks to screen for fevers will also be used among participants upon arrival at our research site. Additionally, we will require staff and patients to wear personal protective equipment (PPE) during study visits and promote six-feet social distancing. The Center on Substance Use and Health (CSUH) at 25 Van Ness Ave is implementing a COVID-19 safety standard operating procedures (SOP) that includes infection control such as using EPA List N: Disinfectants for Use Against SARS-CoV-2 and 30-minutes of fluorescent lights to kill air-borne viruses. We will also conduct the following weekly visits remotely (1-3, 5- 7 and 9-11) for the safety of our participants and staff. We will incorporate additional guidelines as policies and precautions for COVID-19 evolves or COVID-19 diminishes.

Recruitment Procedures: Potential participants will be recruited through multiple sources. Our recruitment team has a long record of successful recruitment of individuals with meth use. We will recruit from bars and clubs, needle exchanges, street corners, HIV and other clinics, and social service programs. We will post advertisements, including website (www. hintstudy.org), local newspapers, billboards, and public transit posters. We will also recruit participants that screen ineligible for our other ongoing studies.

Study Site: Study activities will take place at the Center on Substance Use and Health (CSUH) of the San Francisco Department of Public Health (SFDPH), a well-established clinical trial site located at 25 Van Ness Avenue. Dr. Santos has a joint appointment as a Senior Research Scientist at SFDPH. He has conducted research at this field site since 2008. The site is centrally located near multiple transit lines with convenient access for residents of multiple neighborhoods with high rates of alcohol use. As noted above, we have had remarkable success recruiting and retaining meth users at this location. Study staff have access to both SFDPH resources (see LOS from SFDPH Director Colfax) and UCSF resources as described in the Facilities section. The paired effort of these institutions has proven highly effective in both research and clinical care in San Francisco.

Randomization: Randomization (2:1 for ION versus placebo) will occur using double-blind, block randomization. *Assignment of two-thirds of participants to the ION arm was chosen to improve our ability to 1) examine whether EMI leads to greater ION adherence, and reductions in meth use, and 2) enhance our ability to detect adverse events in the active treatment arm.* Thi s ratio was also selected with the knowledge that it has a negligible impact on the study's minimum detectable treatment effects, compared to a 1:1 allocation (i.e., the difference in the detectable treatment effects between the 1:1 and 2:1 allocation ratios were minor across all primary outcomes), while retaining a stable size for placebo, in the event that some participants are lost to follow-up. The study biostatistician will generate a random allocation sequence list with treatment assignments associated with order of enrollment, using randomly permuted blocks with randomly selected block sizes 3 and 6. To ensure balance by HIV-status, allocation will also be stratified by HIV serostatus. To mask the randomized allocation sequence, the statistician will provide this stratified list to the study pharmacist.

Study medication: The Safeway Compounding Pharmacy, which currently prepares our study drug for our ongoing clinical trials, will provide the study drug kits for the proposed trial. Drugs are over-capsuled in a locking capsule to ensure the same appearance across all study arms and maintain double-blind. Study medications will be dispensed by the study clinician in MEMS® capped bottles with dosing instructions, date of dispensing, prescribing clinician, a 24-hour telephone study phone number for medical emergencies (415-356-8980), and advisements against drug combinations. Training on targeted dosing: Participants will be trained on targeted medication dosing during enrollment and be provided an instructional leaflet for reference. They will be instructed to take 1 tablet when they believe that meth use risk is high or when meth use is imminent.[109] Participants will be given seven 50mg tablets per week and will be instructed to not exceed 1 tablet every 24 hours.[109] Based on concordance in adherence measures (self-report, pill count, and electronic monitoring) in our *double-blind* trials, we are confident that very little, if any, sharing of study medications is occurring between *blinded* participants.[168,169] As a precaution, participants will be briefed about the importance of not sharing medications.

EMA and EMI Cognitive Interviewing Methodology: The study team will *beta test* the EMI and then conduct cognitive interviews with 10 MSM who use meth in individual sessions using a semi-structured interview guide with open-ended questions to explore their perceived understanding of EMA questions and EMI prompts and explore problems with wording and language. Consistent with prior studies, we will read the content of EMA and EMI messages and ask participants to paraphrase the meaning to the messages. Interviews will also ask participants to reflect, comment, and elaborate on the meaning and relevance of, and discuss potential sources of confusion from the messages and prompts. We will also include explicit probes about relevant HBM constructs being conveyed in EMI prompts. Specifically, we will ask participants whether the EMI prompt successfully inform them of their perceived susceptibility to meth use, the benefits of taking the medication at this moment of susceptibility, and whether the EMI prompt provides a clear cue to action to take their medication. Using Framework analysis, the study team will synthesize concerns and make modifications to address problems identified related to the following areas: vague language, confusing questions and response options, variable interpretation of terms, and misinterpretation of EMI recommendations. Framework analysis is well-suited for analyzing the specific questions posed in the cognitive interviews.[170,171]

EMA and EMI procedures: The EMA and EMI platform with be programmed and administered using the HIPAA-compliant platform of PiLR Health (MEI Research), which is capable of deploying text messaging prompts that pull and push content to participants that are timed, randomized, and triggered by specific logic and skip programs based on real-time data. Hence, this platform can be tailored to suit the needs of the study to collect EMA data and administer EMA-informed EMI adherence reminders. We already utilize PiLR Health' platform to develop and implement automated surveys and dynamic prompts on our ongoing studies. For this study, participants in both arms will receive EMA surveys for data collection using established methods consistent with EMA protocols that involve daily assessments at set and random time periods.[112,114,115] Consistent with our other studies, EMA surveys will capture data on the drug use antecedents (craving, mood, and stress) previously shown to predict drug use in the literature and our prior research[116,118,172-176]; data on recent meth use[112,116,118]; and data on study drug use[116] **(Table 3).** Each day, participants will receive a series of up to five EMA surveys that monitor these constructs near real-time (note: the number of random surveys may be adjusted based on the findings on the number of questions threshold of acceptability from the cognitive interviews). One survey will be consistently deployed during the time when the participant begins their day; up to four additional surveys will be deployed at random times throughout the same day.[112,114,115] Participants will also receive additional prompts to take their medication during days when they have not yet taken their study medication, but have reported high levels of craving, stress, or bad mood (i.e., EMA-informed EMI adherence reminders). Participants will receive stipends for completing the EMA surveys and the stipends will be escalated over follow-up to maintain engagement and response rate. In final ACASI surveys, we will assess the acceptability of lowered or no stipends for the EMA surveys, as well as alternative incentives that have been deemed acceptable in other clinical settings (e.g., raffle drawings[177], ultra-low magnitude reinforcers[178]).

HIV testing and counseling: All participants will receive standard HIV risk reduction counseling at enrollment and month 3 with HIV rapid antibody test and pooled viral load (HIV-negative participants) and CD4 and viral load testing (participants living with HIV).[179] Participants with positive rapid tests will have confirmatory HIV Ab/Ag and HIV viral load testing conducted, and will receive HIV counseling and referrals to HIV service providers. Participants newly diagnosed with HIV at screen will be referred to community resources and will be contacted for rescreening in the subsequent month, consistent with our prior studies among MSM who use meth.[66,124,125]

Computer based counseling for substance use: This study's aim is to determine the efficacy of pharmacologic interventions to reduce meth use, thus we will utilize a background of relatively brief counseling that would be feasible in a clinical setting with limited resources: a computerized version of cognitive behavioral therapy, CBT4CBT, previously demonstrated to efficaciously reduce substance use. CBT4CBT may be less likely to mask a clinically significant effect, in keeping with the "Lessons Learned" paper from the NIDA-sponsored Cocaine Rapid Evaluation Screening Trials (CREST), in which it was recommended that clinical trials of pharmacologic agents for substance use utilize less intensive, but standardized, psychosocial counseling interventions.[176] In addition, intensive interventions among people who use meth have had low completion rates,[68] suggesting that multiple lengthy counseling sessions may be unacceptable to many who may otherwise enroll in the trial. While intensive counseling

interventions (e.g., 1.5 hours of group counseling thrice weekly) have been associated with reduced substance use, these results have not been validated outside of research, and interventions have not been adopted widely in clinical practice.[68,177]

Medical safety measures: Blood specimens will be collected for monthly safety lab assessments via venipuncture by clinicians or research associates with phlebotomy training. Medications taken 30 days prior to enrollment and while enrolled in the study will be documented on a concomitant medications form. Adverse events (AE) detection: AEs and concomitant medications will be elicited from participants verbally and documented weekly. As previously noted, participants will be given the 24-hour phone number to reach the study clinician in emergencies. Clinicians will follow the "Division of AIDS Table for Grading the Severity of Adult and Pediatric Adverse Events" and UCSF IRB reporting guidelines.168 Safety monitoring will include the assessment, follow-up, and reporting of clinical/serious AEs.

Opioid and Fentanyl testing: During screen 1 and 2, run- in 1 and run- in 2 visits and enrollment visit, and follow-up monthly visits at Month 1, 2, and 3. We will be testing participants for opiates through urine samples using the 11 panel Reditest from Redwood Toxicology (Abbott). We will also use the rapid response single drug Fentanyl strip in urine from BTNX to make sure that substances purchased on the streets were not cut with fentanyl which also interacts with the study drug naltrexone. Participants will be provided with a Study guide that includes a list of drugs that contain opioids and reminded during the weekly visits that the study drug naltrexone interacts with opioids and can cause withdrawl symptoms. Participants will be tested for opioid and fentanyl at Screen 1 & 2, Enrollment, week 4 (month 1), week 8 (month 2) and week 12 (month 3) visits.

Sweat Testing: We will utilize tamper evident sweat patches (PharmChem, Inc., Fort Worth, Texas) that absorb perspiration 24 hours a day, for up to 10 days of continuous wear.[187] These patches will be tested for the presence of meth and meth metabolites, using testing procedures approved by the FDA since 1995.[187] PharmChek patch enzyme immunoassays to detect meth in sweat have been found to have 85% sensitivity and a 93% specificity rates, compared to gas chromatography-mass spectrometry.[188] At screening visits, we will affix patches on all participants. These patches have a semi-permeable membrane to allow oxygen, carbon dioxide and water vapor to pass through the patch, keeping the skin underneath sterile and healthy. We will replace the used patch worn since the prior visit and send those used patches for meth testing to PharmChem's laboratories. These patches will retain meth and meth metabolites for any use during the period it was worn. Hence, we anticipate no gaps in the window of detection for meth use.

PrEP and ART adherence: Among HIV-negative participants on PrEP and HIV-positive participants on ART, we will collect 20 ml. urine samples and test drug levels using a Urine Tenofovir immunoassay and RNA viral load from blood samples collected at baseline and monthly follow-up visits. For PrEP, good adherence will be defined as having tenofovir-diphosphate (TFV-DP) concentration of 1500 ng/ml, which has been classified as evidence of consistent dosing.[182,183,184] Good ART adherence among participants living with HIV will be defined as having undetectable HIV viral load below 50 copies/ml.

Study drug adherence: The study will collect self-reported adherence via weekly modified TLFB assessments, similar to prior targeted naltrexone studies[106,209] and via EMA for all participants.[109] Pill counts at weekly visits will also assess adherence. *MEMS caps* will be used to track medication adherence daily for as-treated analyses; each cap opening is recorded as an event in real time. MEMS have been shown to be reliable for adherence monitoring and have been used in our studies.[66,124,109]

Behavioral survey measurements: **Table 4** summarizes the data source and collection schedule for the study measures. Standardized and validated behavioral measures[42,201,202,210-213] will be assessed using audio computer administered surveys (ACASI) and EMA to minimize underreporting of risk activities and standardize data collection.[201,202] To minimize potential social desirability bias, staff will not access to data during the trial.

Retention and Termination: We will remind participants of their upcoming visits in advance by phone. Missed visits will be rescheduled. Participants will not be provided with ION after study completion. Participants will be provided with referrals for primary care providers, including providers who accept uninsured patients.

Community Input: CPHR's Community Consulting Group (CCG) is a panel of community stakeholders, treatment advocates, and service providers from a range of community-based organizations. Members of the CCG includes individuals with expertise on meth, and other individuals familiar with the unique needs of MSM who use meth. The CCG meets quarterly and

has a long history of partnership with our unit, providing input on community perceptions, preferences and priorities and is modelled after other research community advisory boards (e.g., the Community Advisory Board in the Center for AIDS Prevention Studies at UCSF).[214] Additionally, CCG members play an important advisory function in protocol design to maximize enrollment (e.g., identify outreach venues, clarify study risks) and retention (e.g., problem-solve barriers to engagement), help identify resources for participants, and help disseminate findings. *Fi nally, we will work with the CCG to develop additional COVID-19 safety precautions and incorporate guidelines in ways that also meet the needs of study participants.*

TABLE 3. Study Procedures	**Visit:**	**S**	**E**	**W**	**M 1, 2**	**M 3**
Informed consent		**X**				
Safety lab assessment		**X**			**X**	**X**
Rapid HIV test* or CD4		**X**				**X**
HIV risk reduction counseling		**X**				**X**
Complete medical history, physical exam, SCID		**X**				
Vital signs, weight		**X**	**X**		**X**	**X**
Symptom-driven physical exam			**X**			**X**
Intermittent Medication Training			**X**			
Training for EMA			**X**			
Randomization			**X**			
11-panel Urine testing for opiates, substance use and fentanyl		**X**	**X**		**x**	**x**
Urine testing for meth metabolites				x		
Audio Computer Assisted Survey Instrument (ACASI)			**X**	**X**	**X**	**X**
Adverse event assessment				**X**	**X**	**X**
Medical Management Counseling			**X**	**X**		
PrEP ART adherence by drug levels (HIV-), viral load (HIV+)			**X**		**X**	x
Study drug MEMS adherence monitoring			**X**	**X**	**X**	**X**

*Confirmatory tests will be performed for reactive tests. S=Screening, E=Enrollment visit /Baseline, W=weekly, M = Month (M 3 = Final visit),

8.10 STANDARD CLINICAL PRACTICE: To what extent, if any, do the planned research procedures differ from the care that people would otherwise receive at this institution or the study site if not being done locally:

All participants will receive substance use counseling and psychotherapy for reducing methamphetamine use disorder. There is no FDA approval to use oral Naltrexone for reducing meth use disorder. This differs from the care that people would otherwise receive at the institution.

8.11 INSTRUMENTS: List all questionnaires, surveys, interview, or focus group guides that will be used for this study:

Table #4 provides a summary of the study measures:

TABLE 4: SUMMARY OF MEASURES	**Data Source**	**Schedule**
PRIMARY PREDICTOR VARIABLE		
Trial arm (ION+EMI, placebo+EMI)	Randomization	En
OUTCOME VARIABLES		
Primary biologic outcome		
Urine samples: negative vs. positive for meth	Urine samples	En, Wkly
PrEP* and ART adherence	Lab specimens	En, M 1-3,
Behavioral outcomes[201,202]		
Total # of sexual partners, by partner HIV status; number of partners using Pre-Exposure Prophylaxis (PrEP); # of partners with undetectable viral load	ACASI	En, M 1-3,
Total # of condomless sex acts on/off PrEP/ART, by partner HIV status, PrEP status and viral load status	ACASI	En, M 1-3,
Reported days/episodes meth use[116] timeline follow-back	ACASI; EMA	En, W, M 1-3,
Other substance use (opioids, alcohol, cocaine, marijuana, ecstasy, gamma-hydroxybutyrate, etc.)	ACASI;	En, M 1-3
Injecting behaviors: needle-sharing, sharing works	ACASI	En, M 1-3

Substance use treatment (outside study)	ACASI	En, M 1-3
Barratt's Impulsivity Scale [186]	ACASI	En, M 1-3
Substance use antecedences: Brief Substance Use Craving[172]; Visual Analog Scale Craving Scores[173]; Daily Craving[174]; Affect, Mood [175]; Sexual Excitation Scale/Sexual Inhibition short form [187], Perceived Stress Scale [176], EMA Risk Antecedents [197]	ACASI; EMA	En, W, M 1-3, Daily
Additional covariates		
Demographics (age, race, education, income)	ACASI	En
Brief Symptom Inventory[204], Severity of Dependence[205]	ACASI	En, M 1-3,
Study Drug, MEMs and EMA adherence		
Timing of pill via MEMs cap openings	MEMS Caps	Daily
Adherence, AIDS Clinical Trials Group measure[206]; SR[109]	ACASI; EMA	Mon 1-3; Daily
Completion rate of EMA, receipt of EMI prompts	EMA data	Daily
Safety outcomes		
Adverse events (including symptoms & exam findings)[207]	SR; Clinician	En, M 1-3
Safety laboratory assessments[207]	Lab specimens	Scr, M 1-3
Trial process measures		
Number persons pre-screened, screened, enrolled, retained	Visit database	Ongoing
Perception of EMI effects on HBM constructs[119,120]	ACASI	M 3

Notes: Scr= screening; En=enrollment/baseline; Wk=Weekly; M=Month; SR=Self Report;

Attach any unpublished instruments in the 'Other Study Documents' section of the Initial Review Submission Packet form after completing the study application. Published instruments should NOT be attached.

8.12 * BIOSPECIMEN COLLECTION: Are you drawing any blood or collecting other biosamples (e.g. tissue, buccal swabs, urine, saliva, hair, etc.) for analysis under this protocol and/or storage for future research: (REQUIRED)

◉ Yes ○ No

* Could this study generate genetic data that may be broadly shared (e.g., submitted to NIH in compliance with **Genomic Data Sharing (GDS)/Genome-Wide Association Studies (GWAS)** requirements): **(REQUIRED)**

○ Yes ◉ No

Please check the Resource Sharing Plan section of your funding notice. You will not be able to share the data as required by your funding agency if the consent form doesn't include the required language.

8.13 STATISTICAL METHODS: Briefly summarize the methods and types of analyses that will be performed:

We will use generalized estimating equations (GEE) to estimate treatment effects on repeated study outcomes. Primary analyses will be by intention-to-treat (ITT). In prior trials, we had excellent visit retention and study completion. Nonetheless, in this high-risk population, missing data may be encountered.[215,216] We will conduct sensitivity analyses imputing all missing urine samples as positive, adjusting for baseline correlates of missingness, and using inverse probability of censoring weights.[217]

Specific Aim 1: *To determine the efficacy of ION vs. placebo in reducing meth use, as determined by the proportion of meth-positive urine tests.* As in our prior trial, a GEE Poisson model with robust standard errors will be used to compare weekly urine test results by treatment assignment; this provides easier-to-interpret risk-ratios[218] rather than odds-ratios. The treatment effect of ION vs. placebo will be modeled as linearly increasing and summarized by the between-group difference in means at 12 weeks, net of any baseline difference. *Minimum Detectable Effects (MDEs) with sample size:* Based on the prior trial (93% retention with an 8-week follow-up), we estimate that 80% of participants will be retained at 12 weeks, and within-subject correlation will be 0.45. Under these assumptions, the study sample will have 80% power in 2-sided tests with a type-I error rate of 5% to detect net between-group differences in the reduction in sweat patch positivity of ~14.5 percentage points. In the Project iN study, we have observed reductions on meth use between 18%-22% among the ION arm, compared to placebo, in ITT and sub-group analyses.[109] Therefore, we believe that the reductions in meth use we are powered to detect in this aim are reasonable to anticipate. *In sensitivity analyses*, we will also evaluate between-group differences on changes in: 1) any meth-positive samples or self-report of meth use in timeline follow back; and 2) meth positivity from self-report only. Concordance of the urine testing, and self-reported measures will be examined using weighted Kappa and correlations. We recognize that meth use is a stigmatize behavior that may be underreported. Hence, in the event of discrepancies between urine results and timeline follow back data on meth use, we will treat the urine test results as the gold standard. *Additionally, we will analyze participant's perception of whether the EMI prompts had effects on various HBM constructs and explore whether these moderate treatment effects on meth use.*[119,120]

Specific Aim 2: *To determine the efficacy of ION vs. placebo in reducing meth-associated sexual risk behaviors.* We will use GEE Poisson models with robust standard errors to assess evidence that the intervention reduces HIV risk behaviors, including number of sex partners, number of sex partners with whom meth is used and episodes of condomless sex with serodiscordant partners. *MDEs*: Using data from our prior trial on baseline means, within-subject correlation, and over-dispersion, we estimate that the study sample of 60 participants will have 80% power to detect ~46% net reductions in the numbers of sexual partners, ~67% reductions in partners with whom meth is used, and ~52% reductions in episodes of condomless sex with serodiscordant partners at 12 weeks. In our Project iN study, we have observed statistically significant reductions on sexual risk outcomes ranging between 85%-89% among the treatment arm, compared to placebo.[109] Therefore, given the results from the prior trial, we believe that the reductions we are powered to detect in this aim are reasonable to anticipate. *In sensitivity analyses*, we will examine how PrEP use and viral suppression status of participants and their partners (partner data assessed via self-reported egocentric data collection from participants)[219] modify treatment effects on sexual risk behaviors. We will also examine whether there is evidence of effect modification depending on whether both the study participant and partner, the

participant only, the partner only, or neither the participant nor the partner used a biomedical HIV prevention tool (PrEP or ART).[219]

Specific Aim 3: *To determine the efficacy of ION vs. placebo in increasing PrEP adherence among HIV-negative participants and ART adherence among participants living with HIV, as measured by serum drug-levels and viral suppression rates.* We will use GEE Poisson models with robust standard errors to assess evidence that the intervention increases PrEP and ART adherence. *MDEs:* Using the assumptions for loss to follow-up from Project iN for Aim 1, we estimate that the study sample of 60 participants will have 80% power to detect 10-19 percentage point increases in PrEP/ART adherence, depending on within-subject correlations and adherence levels in the reference group.[126,220]

Exploratory Aims Analyses: *To assess evidence for whether EMI plausibly contributes to reductions in meth use*, we will assess the temporal association of EMA responses, receipt of EMI, and taking ION or placebo, and assess whether the degree of the efficiency of this pathway moderates between-group differences in urine positivity, under the hypothesis that ION will be most effective among the most responsive participants. *To assess long-term treatment effects of ION versus placebo,* we will evaluate efficacy at 3 months post-treatment for the primary aim outcomes, using methods described above. **As-treated analyses with MEMs data:** We will conduct as-treated analyses, using cumulative adherence, calculated as the number of MEMs openings between baseline and the day of each urine test, divided by the length of that interval in days, as a time-dependent covariate in a log-link model for urine positivity, controlling for the placebo effects of adherence. Quadratic terms were used for adherence in this model to account for non-linearity.

Sex as a Biological Variable: Not applicable. All participants will be cisgender MSM, though we will conduct additional exploratory analyses to examine whether effects vary by other important variables including age and race/ethnicity. Additionally, given the differences in co-morbid psychosocial and clinical characteristics between racial/ethnic minority MSM versus non-minority MSM who use meth,[26-29] we will explore whether treatment effects for racial/ethnic minority MSM are modified by co-morbidities.

8.14 REFERENCES: List only the 5-10 most relevant references (a separate bibliography can be attached for reference purposes if this study involves novel approaches, agents, or an emerging technology that the IRB may not be familiar with):

1) Centers for Disease Control and Prevention. HIV Infection Risk, Prevention, and Testing Behaviors among Men Who Have Sex With Men—National HIV Behavioral Surveillance, 20 U.S. Cities, 2014. . HIV Surveillance Special Report 15 2016.

2) Shoptaw S, Peck J, Reback CJ, Rotheram-Fuller E. Psychiatric and substance dependence comorbidities, sexually transmitted diseases, and risk behaviors among methamphetamine-dependent gay and bisexual men seeking outpatient drug abuse treatment. J Psychoactive Drugs 2003;35 Suppl 1:161

3) Herbeck DM, Brecht ML, Pham AZ. Racial/ethnic differences in health status and morbidity among adults who use methamphetamine. Psychol Health Med 2013;18:262-74.

4) Reback CJ, Fletcher JB, Swendeman D. Associations between Sociodemographic Characteristics and Sexual Risk Behaviors among Methamphetamine-using Men who Have Sex with Men. Subst Use Misuse 2018;53:1826-33.

5) Mimiaga MJ, Reisner SL, Fontaine YM, et al. Walking the line: stimulant use during sex and HIV risk behavior among Black urban MSM. Drug Alcohol Depend 2010;110:30-7.

6) Li MJ, Okafor CN, Gorbach PM, Shoptaw S. Intersecting burdens: Homophobic victimization, unstable housing, and methamphetamine use in a cohort of men of color who have sex with men. Drug Alcohol Depend 2018;192:179-85.

7) Storholm ED, Volk JE, Marcus JL, Silverberg MJ, Satre DD. Risk Perception, Sexual Behaviors, and PrEP Adherence Among Substance-Using Men Who Have Sex with Men: a Qualitative Study. Prev Sci 2017;18:737-47.

8) Hojilla JC, Vlahov D, Glidden DV, et al. Skating on thin ice: stimulant use and sub-optimal adherence to HIV pre-exposure prophylaxis. Journal of the International AIDS Society 2018;21: e25103.

9) Jayaram-Lindstrom N, Hammarberg A, Beck O, Franck J. Naltrexone for the treatment of amphetamine dependence: a randomized, placebo-controlled trial. Am J Psychiatry 2008;165: 1442-8.

10.) King AC, de Wit H, McNamara PJ, Cao D. Rewarding, stimulant, and sedative alcohol responses and relationship to future binge drinking. Arch Gen Psychiatry 2011;68:389-99.

11.) O'Malley SS, Jaffe AJ, Chang G, Schottenfeld RS, Meyer RE, Rounsaville B. Naltrexone and coping skills therapy for alcohol dependence. A controlled study. Arch Gen Psychiatry 1992;49: 881-7.

12.) Volpicelli JR, Rhines KC, Rhines JS, Volpicelli LA, Alterman AI, O'Brien CP. Naltrexone and alcohol dependence. Role of subject compliance. Arch Gen Psychiatry 1997;54:737-42.

13) Galloway GP, Singleton EG, The Methamphetamine Treatment Project Corporate A. How long does craving predict use of methamphetamine? Assessment of use one to seven weeks after the assessment of craving: Craving and ongoing methamphetamine use. Subst Abuse 2009;1:63-79.

14.) Santa Maria D, Padhye N, Yang Y, et al. Drug use patterns and predictors among homeless youth: Results of an ecological momentary assessment. Am J Drug Alcohol Abuse 2018;44:551-60.

9.0 Biospecimen Collection and/or Bank Administration

9.1 * TYPE OF SPECIMENS (check all that apply): (REQUIRED)

- [x] Blood (provide amount below)
- [ ] Tissue (describe below)
- [x] Other type of biospecimen, such as sputum, cerebrospinal fluid, buccal swabs, etc. (describe below)
- [ ] Existing/archival materials (name source below)

Briefly describe the types of biospecimens that will be collected. Provide the amount of blood, if applicable. For leftover/existing/archival material, identify the source:

Urine samples will be collected for methamphetamine and other substance use metabolites. Sweat patches will be collected for methamphetamine, methamphetamine metabolites and other substance use metabolites. Among HIV-negative participants on PrEP and HIV-positive participants on ART, we will test for drug level concentration and RNA viral load from 5 ml. blood samples.

9.3 * SPECIMENS ARE: (check all that apply): (REQUIRED)

- [ ] Leftover specimens from a clinical diagnostic or therapeutic procedure
- [x] Specimens collected for research purposes only (including extra samples taken during a clinical procedure)
- [ ] Other

9.4 * FUTURE SPECIMEN USE: Will any specimens or portions of specimens be retained after the study is over for possible use in future research studies: (REQUIRED)

- ( ) Yes
- (•) No

9.6 * SPECIMEN DESTINATION: Indicate where specimens will ultimately be stored: (REQUIRED)

Outside Entities: Indicate where specimens will be sent if they will not remain at UCSF (choose at least one; check all that apply):

- [ ] Cooperative group bank
- [ ] NIH
- [ ] Other university or collaborator
- [ ] Industry sponsor
- [x] Other
- [ ] N/A - all specimens will remain at UCSF

Specify to what institution, cooperative group, or company specimens will be transferred:

San Francisco Department of Public Health

Internal Storage: If specimens will remain at UCSF, in what kind of facility will they reside (choose at least one; check all that apply):

- [ ] UCSF repository/bank being established under this protocol
- [ ] Existing UCSF specimen repository/bank with IRB approval
- [ ] National cooperative group bank housed at UCSF
- [ ] Other location at UCSF (please describe)
- [x] N/A - no specimens will be retained at UCSF facilities

9.7 SPECIMENS SENT OUTSIDE UCSF - IDENTIFIABILITY: Will direct identifiers be associated with specimens or shared with other researchers and/or outside entities:

- ( ) Yes
- (•) No
- ( ) N/A - Specimens will not be shared with others

10.0 Drugs and Devices

10.1 * DRUGS AND/OR BIOLOGICS: Are you STUDYING any drugs and/or biologics that are either approved or unapproved: (REQUIRED)

(•) Yes ( ) No

If you have questions about FDA requirements for drug or device research, you can send an email to request a consult.

10.2 LIST THE DRUGS OR BIOLOGICS: List the drugs or biologics that will be studied. In the drug details screen you will be asked questions such as:

- **Whether the drug or biologic is FDA approved**
- **If the drug or biologic will be provided at no cost**
- **If an IND is necessary, the IND number, and who holds the IND**
- **If the drug or biologic is FDA approved and an IND is not required, the rationale for the decision**
- **If the Investigational Drug Service (IDS) is dispensing the drug or biologic (required unless a waiver is obtained from the IDS)**

Please see the UCSF IRB website for more details about the use of drugs and biologics in research, including the IND Decision Worksheet. Verification of IND numbers: If the sponsor's protocol does not list the IND number, you must submit documentation from the sponsor or FDA identifying the IND number for this study. Attach this documentation in the Other Study Documents section of the Initial Review Submission Packet. If you have any correspondence from the FDA or sponsor regarding this drug or biologic, please attach it to the application.

View Details	Drug Name	FDA Approved	A new drug or a new use of an already approved drug:	IND Number
⊟	**Trade Drug Name:** NALTREXONE HYDROCHLORIDE **Generic Drug Name:** NALTREXONE HYDROCHLORIDE **Investigational Drug Name:**	Yes	Yes	

Trade Drug Name:	NALTREXONE HYDROCHLORIDE
Generic Drug Name:	NALTREXONE HYDROCHLORIDE
Investigational Drug Name:	
Identify the name of the manufacturer or source of investigational drug/biologic:	ReVia
Is the drug supplied at no cost?	No
Is the Drug FDA Approved:	Yes
Is this a new drug or a new use of an already approved drug	Yes
Is an IND necessary	No
IND Number	
Who holds the IND:	N/A
IND details:	
If FDA Approved and an IND is not required, Please provide a rationale for exemption:	This study meets exemption criteria under 21CFR312.2: the investigator is not intending to report the study in support of a new indication or change in advertising; there is no significant increase in risk in this study population and it uses the same dose and route as FDA-approved; the study will comply with IRB and informed consent requirements; and the investigator has no disqualifications. We have submitted the UCSF IND Decision worksheet in other study documents.
Are you currently using this IND in another research project?	No
If yes, list the IRB Number(s):	
Will the investigational pharmacy be dispensing?	No
If the source is not a FDA licensed facility, provide details regarding the purity, quality, stability and sterility of the investigational drug/biologic:	

10.3 * MEDICAL DEVICES: Are you STUDYING any medical devices, in vitro diagnostics, or assays that are either approved or unapproved:(REQUIRED)

○ Yes ◉ No

If you have questions about FDA requirements for drug or device research, you can send an email to request a consult.

10.6 * EXPANDED ACCESS: Is this an expanded access or compassionate use protocol, meaning the primary purpose is to diagnose, monitor or treat a patient's condition, rather than the collection of safety and efficacy data of the experimental agent: (REQUIRED)

○ Yes ◉ No

11.0 Sample Size and Eligibility Criteria

11.1 ENROLLMENT TARGET: How many people will you enroll:

60

If there are multiple participant groups, indicate how many people will be in each group:

The ION+EMI study will enroll 60 participants in the double-blinded placebo controlled clinical trial where 40 participants will receive Intermittent Oral Naltrexone and 20 participants will receive placebo.

11.3 SAMPLE SIZE JUSTIFICATION: Explain how and why the number of people was chosen. For multi-site studies, this is referring to the number that will be enrolled across all sites:

For the phase 2b clinical trail, a sample size of 60 was selected to provide 80% power in 2-sided tests with a type-I error rate of 5% to detect between a 18-22% reduction of meth use among the ION arm, compared to placebo, in ITT and sub-group analyses. We hypothesized on pharmacologic grounds that oral naltrexone will reach full efficacy against meth use almost immediately; accordingly we expect treatment-control differences to be approximately constant over the 12 weeks of the trial. Based on the prior trial (93% retention), we estimate that 90% of participants will be retained at 12 weeks. Under these assumptions, the minimum detectable effects for our outcomes are calculated as follows:

Specific Aim 1: *To determine the efficacy of ION vs. placebo in reducing meth use, as determined by the proportion of meth-positive sweat patch tests.* As in our prior trial, a GEE Poisson model with robust standard errors will be used to compare weekly urine test results by treatment assignment; this provides easier-to-interpret risk-ratios[218] rather than odds-ratios. The treatment effect of ION vs. placebo will be modeled as linearly increasing and summarized by the between-group difference in means at 12 weeks, net of any baseline difference. *Minimum Detectable Effects (MDEs) with sample size:* Based on the prior trial (93% retention with an 8-week follow-up), we estimate that 90% of participants will be retained at 12 weeks, and within-subject correlation will be 0.45. Under these assumptions, the study sample of 60 participants will have 80% power in 2-sided tests with a type-I error rate of 5% to detect net between-group differences in the reduction in urine positivity of ~24 percentage points, equivalent to a relative rate reduction of 32%. We have observed similar reductions on meth use in ITT and sub-group analyses in prior trials.[109] Therefore, we believe that the reductions in meth use we are powered to detect in this aim are reasonable to anticipate. *In sensitivity analyses*, we will also evaluate between-group differences on changes in: 1) any meth-positive samples or self-report of meth use in timeline follow back; and 2) meth positivity from self-report only. Concordance of the urine testing, and self-reported measures will be examined using weighted Kappa and correlations. We recognize that meth use is a stigmatize behavior that may be underreported. Hence, in the event of discrepancies between urine test results and timeline follow back data on meth use, we will treat the urine test results as the gold standard. *Additionally, we will analyze participant's perception of whether the EMI prompts had effects on various HBM constructs and explore whether these moderate treatment effects on meth use.*[119,120]

Specific Aim 2: *To determine the efficacy of ION vs. placebo in reducing meth-associated sexual risk behaviors.* We will use GEE Poisson models with robust standard errors to assess evidence that the intervention reduces HIV risk behaviors, including number of sex partners,

number of sex partners with whom meth is used and episodes of condomless sex with serodiscordant partners. *MDEs*: Using data from our prior trial on baseline means, within-subject correlation, and over-dispersion, we estimate that the study sample of 60 participants will have 80% power to detect ~46% net reductions in the numbers of sexual partners. In our Project iN study, we have observed statistically significant reductions on sexual risk outcomes ranging between 85%-89% among the treatment arm, compared to placebo.[109] Therefore, given the results from the prior trial, we believe that the reductions we are powered to detect in this aim are reasonable to anticipate. *In sensitivity analyses*, we will examine how PrEP use and viral suppression status of participants and their partners (partner data assessed via self-reported egocentric data collection from participants)[212] modify treatment effects on sexual risk behaviors. We will also examine whether there is evidence of effect modification depending on whether both the study participant and partner, the participant only, the partner only, or neither the participant nor the partner used a biomedical HIV prevention tool (PrEP or ART).[212]

Specific Aim 3: *To determine the efficacy of ION vs. placebo in increasing PrEP adherence among HIV-negative participants and ART adherence among participants living with HIV, as measured by serum drug-levels and viral suppression rates.* We will use GEE Poisson models with robust standard errors to assess evidence that the intervention increases PrEP and ART adherence. *MDEs:* Using the assumptions for loss to follow-up from Project iN for Aim 1, we estimate that the study sample with 60 participants will have 80% power to detect 10-19 percentage point increases in PrEP/ART adherence, depending on within-subject correlations and adherence levels in the reference group.[126,220]

The sample size of 60 participants is the minimum number required to have sufficient power to determine the MDEs of intermittent naltrexone in reducing meth use for the phase 2b study.

11.4 * PARTICIPANT AGE RANGE: Eligible age ranges: (REQUIRED)

- [ ] 0-6 years
- [ ] 7-12 years
- [ ] 13-17 years
- [x] 18-64 years
- [x] 65+

11.5 * STUDY POPULATIONS: Data will be collected from or about the following types of people (check all that apply): (REQUIRED)

- [x] Inpatients
- [x] Outpatients
- [ ] Family members or caregivers
- [ ] Providers
- [x] People who have a condition but who are not being seen as patients
- [ ] Healthy volunteers
- [ ] Students
- [ ] Staff of UCSF or affiliated institutions
- [ ] None of the above

11.6 * SPECIAL SUBJECT GROUPS: Check the populations that may be enrolled: (REQUIRED)

- [ ] Children / Minors
- [ ] Adult subjects unable to consent for themselves
- [ ] Adult subjects unable to consent for themselves (emergency setting)
- [ ] Subjects with diminished capacity to consent
- [ ] Subjects unable to read, speak or understand English
- [ ] Pregnant women
- [ ] Fetuses
- [ ] Neonates

☐ Prisoners
☐ Economically or educationally disadvantaged persons
☑ None of the above

11.7 INCLUSION CRITERIA: Briefly describe the population(s) that will be involved in this study. Include anyone that data will be collected from or about (e.g. patients, healthy controls, caregivers, providers, administrators, students, parents, family members, etc.):

Inclusion Criteria: 1) cisgender male (male gender and sex assigned at birth); 2) age 18-70 years* (naltrexone's tolerability and safety has been demonstrated among older adults up to age 70[166,167]); 3) self-reported condomless anal sex with men or missing PrEP or ART doses due to meth use in the prior three months while under the influence of meth; 4) self-reported meth use at least weekly; 5) positive meth sample via sweat patch or urine testing during screening; 6) mild, moderate, and severe meth use disorder as determined by DSM-V-SCID criteria; 7) interested in reducing meth use; 8) no current acute illness requiring prolonged medical care; 9) no chronic illness that is likely to progress clinically during trial; 10) able and willing to provide informed consent and adhere to visit schedule; 11) current CD4 count ≥ 200 cells/mm3; or CD4 count of 100-199 cells/mm3 and HIV viral load < 200 copies/mL (if living with HIV); 12) baseline CBC, total protein, albumin, glucose, alkaline phosphatase, creatinine, BUN, and electrolytes without clinically significant abnormalities as determined by study clinician in conjunction with symptoms, physical exam, and medical history.

11.8 EXCLUSION CRITERIA: List any exclusion criteria (e.g. reasons why someone would not be included in the study):

Exclusion Criteria: 1) any psychiatric (e.g., depression with suicidal ideation) or medical condition that would preclude safe participation; 2) known allergy or prior adverse reaction to naltrexone; 3) current use of any opioids or a known medical condition which currently requires or may likely require opioid analgesics; 4) opioid-positive urine test at screen/enrollment visits (naltrexone can induce opioid withdrawal); 5) moderate or severe liver disease (AST, ALT, or total bilirubin ≥ 3 times upper limit of normal); 6) impaired renal function (creatinine clearance < 60 ml /min); 7) currently participating in another intervention research study with potential overlap; 8) severe alcohol use disorder as determined by DSM-V SCID criteria; 9) any condition that, in the PI and/or study clinician's judgment interferes with safe participation or adherence to study procedures.

11.9 * RESEARCH CONDUCTED ON PATIENT CARE WARDS: Do any study activities take place on any patient care units including inpatient wards, peri- or post-operative care units, operating rooms, or in the Emergency Department at UCSF Health medical facilities: (REQUIRED)

○ Yes ◉ No

11.11 * EMERGENCY DEPARTMENT: Does your protocol or study involve any of the following patient related activities in the emergency department (e.g. subject identification, recruitment, consent, blood draws, specimen retrieval, involvement of ED staff (nursing, tech, and/or physician), or any other ED based procedures): (REQUIRED)

○ Yes ◉ No

12.0 Recruitment and Consent

12.1 * COMPETITIVE ENROLLMENT: Is this a competitive enrollment clinical trial? By competitive enrollment, we mean that sites who do not enroll participants early may not get to participate at all: (REQUIRED)

○ Yes ◉ No

12.2 * SUBJECT IDENTIFICATION METHODS: What kinds of methods will be used to identify potential participants for recruitment (check all that apply): (REQUIRED)

- ☐ Review of patients' conditions, history, test results, etc. (includes patients seen in clinic, scheduled for surgery, a procedure, imaging, or tests, or seen in the Emergency Department as well as searching through medical record data for possible cohort identification)
- ☐ Already approved recruitment registry
- ☑ Re-contact of participants from the investigators' previous studies
- ☑ Referrals from colleagues (attach the 'Dear Colleague' letter or other recruitment materials you will provide to colleagues)
- ☑ Referrals from the community / word of mouth
- ☑ Advertisements (flyers, brochures, radio or t.v. ads, posting on clinical research sites or social media, presentation of the study at community events/media, etc.)
- ☑ Online recruiting tool (describe below)
- ☑ CTSI Recruitment Services unit
- ☑ Posting on UCSF Clinical Trials, ClinicalTrials.gov or other publicly available clinical trial website
- ☐ Other method (describe below)

Attach your recruitment materials (e.g., flyers, ads, recruitment letter templates, email text, etc.) in the Other Study Documents section of the Initial Review Submission Packet Form.

* Provide details about the subject identification methods: **(REQUIRED)**

Snowballing sampling: Study participants enrolled in our pharmacologic trials are encouraged to refer
other potential participants. We will provide to participants IRB-approved educational materials about the
study that they can give to friends and acquaintances; the friend or aquanitance will then have the option
of contacting study staff if interested. We willl not accept names or phone numbers from the referring
participant. This is a method to reach some people we may miss via our other recruitment strategies. We
would like to add a stipend for situations in which a participant refers a person to the study and if that new
person completes a screening visit, the participant will receive $10 and if the new person enrolls in the
study, the participant will receive $40.

Mobile-based smart-phone apps recruitment: The team expects that many of our participants utilize
mobile technologies to connect with other participants. The team plans to recruit participants from the
popular mobile-based applications including Facebook, Instagram WhatApp, Grindr, Scruf, Jack'd, Barebarckrt,
Instagram and other social networking platforms. In previous studies we have placed ads on these sites
and if a person is interested they will send us a private message and we will respond to that message. We
do not create profiles and pro-actively reach out to potential participants on these apps.

Internet-based recruitment: ResearchMatch sends the study recruitment message to matched volunteers to inform them about a new opportunity to participate. Once individuals respond with permission to be contacted for that study, personal contact information is made available to the researcher
within the secure ResearchMatch system. Online advertising will be used to recruit potential participants.
Advertisements will be selected based on study eligibility criteria (e.g. age, sex, interest in study-related
topics). Advertisements will consist of a combination of ad text and images (see attached document

"Online Recruitment Ad text and images" and **https://buildclinicalmaterials.my.canva.site/bcfs00523-ucsf-santos-mud-materials**) that will be used in combination and may appear as banners,
posts, text, or URLs links for users to click on if they are interested in the study. By clicking on an advertisement, the user will be directed to our study screener. Until recruitment for the study is complete,
we will be assessing the advertisements on a regular basis.

* Did all the participants of previous studies provide permission to be contacted for future studies: **(REQUIRED)**

(•) Yes ( ) No

12.4 DETERMINATION OF ELIGIBILITY: How, when, and by whom will eligibility for recruitment be determined:

Potential participants will be recruited from via advertisements, active recruitment and snowball sampling.
Recruited individuals will be asked brief general eligibility questions through a web-based, IRB approved
field screeing survey in person or over the phone by research study staff after providing verbal consent. Potential participants who have phone-screened eligible wil be scheduled for an in-person visit where consenting and further eligibility will be assess via clinical examination, laboratory safety testing, meth use frequency, prior to randomization.

12.5 * INITIATION OF CONTACT: Who initiates contact (check all that apply): (REQUIRED)

- [x] Investigators/study team
- [x] UCSF recruitment unit (e.g. CTSI Consultation Services)
- [x] Potential participant
- [ ] Other (explain below)

Click here to review the process and rules for use of CTSI's Consultation Services for recruitment.

12.6 * HOW IS CONTACT INITIATED: (check all that apply): (REQUIRED)

- [ ] In person
- [x] Phone
- [x] Letter / email
- [x] Website or app
- [ ] Other (explain below)

Attach the telephone recruitment script in the Other Study Documents section of the Initial Review Submission Packet Form. If potential participants will initiate contact, attach the telephone screening script that will be used to provide more information about the study and determine if callers are eligible to participate.

Attach the recruitment letter or email template in the Other Study Documents section of the Initial Review Submission Packet Form.

Provide the URL for any website in Recruitment Plan section, or attach a mock-up of the website or the app screens in the Other Study Documents section of the Initial Review Submission Packet Form.

12.7 RECRUITMENT PLAN: Based on the checkboxes you chose above, please provide a narrative describing your recruitment plan. We want to know:

- **Who is conducting the search for potential participants, and how?**
- **How are potential subjects being approached for recruitment? By whom, and when?**

If there will be more than one participant group (e.g. patients, healthy controls, caregivers, family members, providers, etc.), provide details about the recruitment plans for each group. (Recommended length - 100-250 words)

Participants, prior to randomization, will be pre-screened by trained outreach staff using IRB-approved procedures. In a confidential manner, staff will inform participants of the study, emphasize that participation is voluntary, and provide the individuals with IRB-approved flyers that describe the study. Interested potential participants will be scheduled for an office visit to meet individually with study personnel who will begin the informed consent process. For the pilot randomized trial, recruitment will be conducted using techniques complementary to ongoing onsite research studies using several strategies that have proven successful in prior trials for people with meth use. The team will leverage our existing recruitment resources from our ongoing studies to recruit participants with the following approaches:
Advertisements: The team will run biweekly advertisements in the local papers.Mobile-based smart-phone apps recruitment: The team expects that many of our participants utilize mobile technologies to connect with other people with meth use disorder. The team plans to recruit participants from the popular mobile-based applications including Facebook, WhatApp, Grindr, Scruf, Jack'd, Barebarckrt, and Instagram.

Internet recruitment: As in our current studies, internet-based recruitment will occur through strategic placement of banner ads on Web sites frequented by people with meth use disorder, including Adam-4-Adam, craigslist.org, facebook, manhunt.net, barebackrt, Fridae.com, and tweaker.org. Additionally, we will use ResearchMatch to send potential matched volunteers the study recruitment message that will inform them about a new opportunity to participate. Once individuals respond with permission to be contacted for that study, personal contact information is made available to the researcher within the secure ResearchMatch system. Online advertising will be used to recruit potential participants. Advertisements will be selected based on study eligibility criteria (e.g. age, sex, interest in study-related topics). Advertisements will consist of a combination of ad text and images (see attached document "Online Recruitment Ad text and images") that will be used in combination and may appear as banners, posts, text, or URLs links for users to click on if they are interested in the study. By clicking on an advertisement, the user will be directed to our study screener. Until recruitment for the study is complete, we will be assessing the advertisements on a regular basis.

Active recruitment: The team will utilize the efforts of existing field recruiters from other ongoing studies to recruit for participants on the street in neighborhoods and at street fairs and other events frequented by meth using participants, collecting phone numbers of interested potential participants, and leaving cards and fliers in meeting places, local CBOs, bars, and clubs. Potential participants will be given

IRB
approved recruitment materiales with promotionals. Potential participants who complete the web-based
field screening survey and provide contact informaton will be entered into a drawing for a gift card. A list
of venues that will be canvassed by our field recruitment team is included in the Appendix.
Snowball sampling: Study participants are encouraged to refer their friends by taking cards and fliers so that potential participants can call us. This is a method to reach some people we may miss via our
other recruitment strategies.

Health providers and Community based organizations: Health providers and community-based organizations are encouraged to give IRB approved recruitment materiales to potential participants. We will recruit at some SFDPH
health clinics such as Ward 86 and Bayview clinic to expand our outreach activities. We can provide health provider's with a study presentation and refreshment.

12.8 * CONSENT METHODS: How will permission to participate (i.e., informed consent) be obtained from each potential participant. If there will be multiple groups and different plans for consenting each, check all that apply. See the orange Help bubble to the right for more detailed guidance. Participants will (check all that apply): (REQUIRED)

- [x] Sign a paper consent form at the end of the consent discussion (signed consent)
- [x] Sign an electronic consent form using DocuSign (signed consent)
- [x] Provide online consent through an app, a website, or a survey tool such as Qualtrics or REDCap (waiver of signed consent)
- [ ] Be told about the study and be given a handout/information sheet and be asked if they agree to participate (verbal consent - waiver of signed consent)
- [ ] Complete the study activities and turn in materials, as in the case of a completed survey that is placed in a drop box or mailed to the study team (implied consent - waiver of signed consent)
- [ ] Not be able to provide consent and will have a family member consent for them, as in the case of a critically ill or unconscious patient (surrogate consent)
- [ ] Not be able to provide consent (emergency waiver of consent - allowed for minimal risk research or greater than minimal risk research with an approved community consultation plan)
- [ ] Not know about the study, as in the case of chart reviews or observations of public behavior (waiver of consent)
- [ ] Other method (describe below)

Attach your consent form, information sheet, or electronic consent text in the Informed Consent Documents section of the Initial Review Submission Packet Form.

As of Winter 2020, the UCSF Version of DocuSign is not Part 11 compliant. Part 11 compliance is required for FDA-regulated studies (studies using of investigational drugs or devices or studies of approved drugs or devices for investigational use). UCSF is currently pursuing a Part 11-compliant version of DocuSign. Please check the UCSF 21 CFR Part 11 Compliance webpage for updated information about the availability of Part 11-compliant DocuSign at UCSF.

12.9 * CONSENT PROCESS: Describe the process for obtaining informed consent, including details such as who will have the consent discussion and when participants will be asked to sign the consent form in relation to finding out about the study: (REQUIRED) We encourage researchers to review our guidance on obtaining and documenting informed consent.

- **If there are multiple groups being consented differently, provide details about the consent process for each group.**
- **If you are relying on verbal or implied consent, provide details about how that will happen.**

- **For studies using online recruitment and consent or consent via mail, provide details here.**

Recruited individuals will be asked brief general eligibility questions through a web-based, IRB approved
field screeing survey in person or over the phone by research study staff after providing verbal consent.We are using the documentation for a waiver of signed consent (section 12.13) for verbal consent to ask the field screening questions (see other study documents). These questions are no more than minimal risk of harm to subjects and involves no procedures for which written consent is normally required outside of the research context. 46.117(c). Potential participants who have phone-screened eligible wil be scheduled for an in-person visit where consenting will take place.

The consent process will discuss the 2:1 random assignment of participants to receive oral naltrexone or placebo
and will detail the potential adverse effects of naltrexone. It will also discuss the weekly substance use
counseling sessions. The consent process also addresses participant rights, including the voluntary nature
of participation and ability to decline without penalty. Mechanisms for maintaining confidentiality will also
be discussed, as well as exceptions to confidentiality which is required by law. Participants will be given a
copy of the Human Subject's Bill of Rights, along with a copy of the consent form. Participants are given
the contact numbers of both the PI and the UCSF IRB to answer questions about the study or one's rights
as a human subject. All participants will meet with a study clinician for an additional opportunity to ask
questions. Similar to our prior pharmacologic studies, all participants must also correctly complete an
"Assessment of Understanding" quiz. The quiz will include 10 to 12 true/false study-related questions that
assess participants' understanding of basic study concepts, including the unknown efficacy of oral naltrexone to
reduce meth use, its side effect profile, the randomization process, and the nature of placebos. After the assessment of understanding has been completed and staff are satisfied that the participant is
able to give full informed consent (including, but not limited to, a participant completing the quiz with an
80% score or greater and a demonstrated ability to fully understand corrected answers), the consent form
will be signed by the participant. During COVID-19, we may administer the consent form over zoom on a remote visit and use an app (Docusign or Redcap) to sign the consent form online to reduce the amount of time the participant is at the study site. The staff member obtaining consent will also sign both the original and the copy as a witness, completing the informed consent process. A copy of the signed form will be given to the client; the original signed consent will be kept in a separate, locked file.

* It is important that the people obtaining consent are qualified to do so. Briefly describe the training and experience these individuals have in obtaining informed consent: **(REQUIRED)**

All staff have undergone the NIH-required training in human subject protections and good clinical practice
(GCP) procedures, and are extensively trained on proper procedures for obtaining informed consent.
Trained staff will obtain written informed consent prior to enrollment from all study participants using IRB approved
informed consent forms. The informed consent process involves a detailed verbal description of the study; an item-by-item reading of the consent form will be conducted by study staff while the participant reads along. Trained staff will explicitly cover the purpose, procedures, risks, and benefits of
the study.

12.10 * CONSENT COMPREHENSION: Indicate how the study team will assess and enhance the subjects' understanding of study procedures, risks, and benefits prior to signing the consent form (check all that apply): (REQUIRED) Tip: Review the Consent Comprehension - Learning Notes in the Help

bubble at the right for specific questions that can be asked to assess comprehension, consider using the UCSF Decision-Making Capacity Assesment Tool, and review our guidance on obtaining written or verbal informed consent for more detail on how to conduct the assessment.

- [x] The study team will engage the potential participant in a dialogue, using open-ended questions about the nature of the study or the experimental treatment, the risks and benefits of participating, and the voluntary nature of participation
- [x] Potential participants will be asked or shown a series of questions to assess their understanding of the study purpose, procedures, risks and benefits, as well as the voluntary nature of participation (especially appropriate when the consent process happens online or through a mobile health app)
- [ ] Other method (describe below):

Provide details of the other approaches that will be used, if using another method to assess comprehension:

At the moment, research staff are in the process of developing the "assessment of understanding" for this
study. We plan to submit a modification that will include all of these materials before start-up of this study.

12.13 * WAIVER OF DOCUMENTATION OF SIGNED CONSENT: Select the regulatory category under which the IRB may waive the requirement to obtain *signed* consent for this study:

- ○ The only record linking the subject and the research would be the consent document and the principal risk would be potential harm resulting from a breach of confidentiality. Each subject will be asked whether they want documentation linking them with the research. 46.117(c) (1)
- ◉ The research presents no more than minimal risk of harm to subjects and involves no procedures for which written consent is normally required outside of the research context. 46.117(c) (2)

12.14 TIME: What is the estimated time commitment for participants (per visit and in total):

Screening visits will run between 60-90 minutes. Weekly visits will last between 30-45 minutes. Enrollment
visits will last about 90-120 minutes. The monthly and post-treatment visits will take 90-120 minutes.
Total time visiting the study site will be about 930-1305 minutes (15-22 hrs) over a 7-month period, with
regular, weekly visits for a 12-week period.

IMPORTANT TIP: Ensure this information is consistent with the information provided in the consent form.

12.15 ALTERNATIVES: Is there a standard of care (SOC) or usual care that would be offered to prospective participants at UCSF (or the study site) if they did not participate in this research study:

◉ Yes ○ No

Describe the care that patients would ordinarily receive at the medical center if they did not participate in this study (provide details, assuming that some of the IRB members are not specialists in this field):

Psycotherapy for meth use disorders would be available. Additionally, participants can ask their providers
to prescribe, off-label, the FDA-approved medications for meth use disorder to help reduce with their cravings.

12.16 OFF-STUDY TREATMENT: Is the study drug or treatment available off-study:

- (•) Yes
- ( ) No
- ( ) Not applicable

13.0 Risks and Benefits

13.1 RESEARCH-RELATED RISKS: Check if your study involves any of these specific research-related risks to participants that may need to be disclosed in the consent form:

- [ ] For interventional studies, risk that the regimen may be more harmful or less effective than other available interventions
- [ ] Risks associated with radiation exposure for imaging studies specifically for research purposes
- [ ] Risks associated with the administration of contrast agent for imaging studies
- [ ] Risks associated with withholding of treatment or discontinuation of current treatment (e.g., washout period is required by the study protocol)
- [x] For randomized, placebo-controlled trials, possible temporary or permanent health consequences from the deprivation of effective therapies during the placebo administration period
- [ ] For studies involving a sham surgical procedure, the risk that participants may experience increased morbidity without the possibility of benefit
- [ ] Risks associated with modification or extension of a surgical procedure primarily for research purposes (e.g. risks associated with prolonging anesthesia, time in the operating room, etc.)
- [ ] Risk of pain or physical discomfort caused by the research intervention
- [ ] Possible personal discomfort due to sensitive topics (stress, embarassment, trauma)

* For any boxes checked above, describe how you will minimize these risks and discomforts, e.g., adding or increasing the frequency of monitoring, additional screening to identify and exclude people with diminished kidney or liver function, or modification of procedures such as changing imaging studies to avoid giving contrast agent to people who are more likely to suffer side effects from it, etc.: **(REQUIRED)**

This is a double-blind, placebo-controlled clinical trial where participants will be screened for diminished kidney or liver functions and if so excluded to participate in the study. The randomized participants will continue to be monitored through safety lab visits at weeks 4, 8 and 12 to minimize any risk to participant. AEs will be reported throughout the 12 week study.

13.2 * RISKS: Describe any anticipated risks and discomforts not listed above: (REQUIRED)

HIV and STI Testing risks. Participants may experience anxiety surrounding HIV testing results, regardless of the outcome. Positive results in particular may be stigmatizing, emotionally upsetting, and cause psychological distress. Testing will be done by a trained counselor and will include education on the meaning of results, risk-reduction counseling, and referral for treatment. Due to mandated reporting requirements, there could be a loss to confidentiality if there is a new case of HIV.

Naltrexone, Opiates and Fentanyl Risk: Naltrexone is a medication that blocks your body's ability to respond to opiate medicines or drugs, such as Oxycontin, methadone, or heroin. If you have taken opiates 7-10 days prior to taking naltrexone, there is a risk of mild to severe opiate withdrawal symptoms. If you take opiate medications for pain or are dependent on opiates for any reason. We have included a list of opioid medications in other study documents. If you are receiving naltrexone instead of placebo, you may not feel pain relief from opiate medications for 24 to 72 hours. This blocking effect can be overcome, but it must be done by an experienced physician, usually in the emergency room or hospital. If you take large amounts of opiates, including opiate-containing medications such as prescription pain pills (a guide will be given with

common names of opiate medications) or heroin, this can lead to overdose, including coma or death.

On the streets, dealers are mixing fentanyl with other drugs, such as heroin, cocaine, methamphetamine, and MDMA. Because fentanyl is cheap and very powerful, adding it to other drugs can be more profitable for dealers. This is especially risky when people taking drugs don't realize that fentanyl might be present in their drug supply. Fentanyl is known by such names as Actiq®, Duragesic®, and Sublimaze®. Street names for illegally used fentanyl include Apache, Dance Fever, Friend, Goodfellas, Jackpot, Murder 8, and Tango & Cash.

Other potential risks. All participants are informed of the risks involved in blood draws, including bruising around the needle site, the risk of infection at the needle site, and occasional equipment failure in the vacuum tubes. Other potential risks to participating in this study include: unauthorized disclosure of confidential information; discomfort or embarrassment related to specimen collection or questionnaires dealing with personal habits and lifestyle, including substance use; and possible unwanted encounters with friends or associates in the research setting.

13.3

MINIMIZING RISKS: Describe the steps you have taken to minimize the risks/discomforts to subjects. Examples include:

- **designing the study to make use of procedures involving less risk when appropriate**
- **minimizing study procedures by taking advantage of clinical procedures conducted on the study participants**
- **mitigating risks by planning special monitoring or conducting supportive interventions for the study**
- **having a plan for evaluation and possible referral of subjects who report suicidal ideation**

All potential participants will be evaluated by the study clinician for physical or psychiatric illnesses or other medical criteria that would preclude study participation. Once enrolled, all participants will be provided with a 24-hour pager number by which a study clinician may be contacted to answer questions or to provide direction in case of emergency. Study staff follow an aggressive set of safety procedures to ensure that participants receive a high and consistent level of monitoring that also meets reporting requirements to the IRB. Potential safety issues are reviewed weekly in meetings during which staff discuss potential adverse events for all participants. At any time, persons judged by project investigators to be a danger to self or others, or who are otherwise judged to be in grave danger due to medical or other conditions, will be escorted to the SFGH Psychiatric Emergency Unit. All staff, including research assistants and counselors, receive yearly training for identifying suicide/homicide risk and/or dangerous intoxication, and de-escalation of agitated or angry persons. All staff are trained to appropriately respond to these situations by immediately contacting a study clinician to evaluate the participant.

Minimizing the risks of medication side effects. At all times, participants will be encouraged to contact the study clinician if they have questions or concerns about their medication dosage. During each study visit, participants are given the opportunity to discuss any adverse medication effects with the study clinician. Participants will have monthly safety blood tests, including liver function tests, during the 12 weeks they are taking study drug. Participants who ultimately do not tolerate their medication may be

taken of study medication if needed and will continue to be followed throughout the duration of the trial.

We will be testing potential participants for opiates, other substances and fentanyl during screening since naltrexone can cause opioid withdrawl. Participants who test positive for opiates or fentanyl will not be enrolled in the study. We will also test participants for opiates, other substances and fentanyl during monthly in-office safety visits and any positive results will not be given naltrexone.

Minimizing the risks to privacy of individuals or confidentiality of data. The study consent form will inform participants of confidentiality guidelines. Strict confidentiality will be maintained. Records that have personal identifiers (e.g., clinical records) will be stored in a locked cabinet separate from the research record, which will contain only the participant's ID number. Only the research team and clinical staff assigned to the care of the participants will have access to non-anonymous records. All research data are maintained in binders in locked cabinets. Consent forms, which contain names, are stored separately.
Screening and randomization ID numbers are used to identify specific research forms. Files that link participants' names with screening and randomization ID numbers will be kept in a locked file. No presentation or publication of the study results will refer to participants individually. Exceptions to confidentiality for research participants are those required by law and include suspicion of child abuse, elder abuse, and threat of imminent action on suicidal or homicidal ideation. Participants will be informed of these exceptions in the informed consent process. In addition, representatives from NIH and the UCSF IRB will have limited access to the research records (i.e., in the event of an SAE, the IRB may request a review of the chart to assess adequacy of care during the trial). Prior to any sharing of the research dataset, all personal identifiers will be removed. Data will be shared only with researchers who have received IRB-approval for their studies, and who agree not to identify any specific study participant in any way, and who will destroy or return the dataset after completing their analyses.

We follow the Health Insurance Portability and Accountability Act of 1996 (HIPAA) regulations for the protection of private health information for individuals. All study participants screening or enrolling in our studies must sign the HIPAA Authorization Form (unless a waiver of authorization has been approved by the IRB). The Authorization Form is protocol-specific and must be signed along with the consent form when participants first screen or enroll into a study. Before participants sign the Authorization Form, study staff will explain the purpose of the Authorization Form and answer any of the participants' questions.
Participants will receive a signed copy of the Authorization Form. Potential participants who choose not to sign the HIPAA Authorization form will be excluded from study participation.

Ensuring medical or professional intervention for adverse events. The study clinician(s) will review data forms daily to monitor safety during the conduct of the trial. If serious or unexpected AEs occur during the trial, the PI will report these occurrences within the specified time frames to the Data and Safety Monitoring Board (DSMB), IRB, NIH, and the FDA as required. All study materials and protocols will be reviewed and approved by the UCSF IRB prior to their use. AE reporting plans are described in the Data and Safety Monitoring plan in this section.

13.4 RESOURCES: Describe the resources in place to conduct this study in a way that assures protection of the rights and welfare of participants: These resources typically include appropriately trained and qualified personnel (in terms availability, number, expertise and experience), funding, space, equipment, and time to devote to study activities. Depending on the nature of the research study, investigators should consider the proximity or availability of critical resources that may be essential to the safety and welfare of participants, such as

- **the proximity of an emergency facility for care of participant injury**
- **availability of psychological support after participation**
- **resources for participant communication, such as language translation services**

For the safety to participants and staff during COVID-19, the study has been designed with hybrid visits according to Interim UCSF research guidelines. The weekly visits (weeks 1, 2, 3, 5, 6, 7, 9, 10 and 11) will be conducted remotely through zoom. The participant will be given single M-AMP urine test kits and urine collection bottles at the in-office visits and trained how to conduct the urine test. The participant is asked to provide a urine sample in the urine collection bottle before the video visit. The participant will dip the M-AMP stick in the urine during the video visit and the dip stick will be shown to the counselor. Due to video resolution, a faint red line may not be able to be viewed by video. If this happens, the participant will be asked to take a picture of the dip stick and upload it to a secure portal or an encrypted e-mail. After IRB approval, we will test this option on RedCAP through the participant survey invitation and embedded image upload option.

13.5 * BENEFITS: (REQUIRED) Note: These are the benefits that the IRB will consider during their review. They are not necessarily appropriate to include in the consent form.

Possible immediate and/or direct benefits to participants and society at large (check all that apply):

- [ ] Positive health outcome (e.g. improvement of condition, relief of pain, increased mobility, etc.)
- [ ] Closer follow-up than standard care may lead to improved outcomes or patient engagement
- [x] Health and lifestyle changes may occur as a result of participation
- [ ] Knowledge may be gained about their health and health conditions
- [x] Feeling of contribution to knowledge in the health or social sciences field
- [ ] The research presents a reasonable opportunity to further the understanding, prevention, or alleviation of a serious problem affecting the health or welfare of children
- [x] Other benefit (describe below)
- [ ] None

Briefly discuss the other possible benefits:

Study participants may reduce their meth use by virtue of study participation. Study medication may
help them stop or decrease their meth use; the weekly substance use counseling sessions may also help
participants' recovery from meth use. HIV testing and counseling may help HIV-negative participants
decrease their risk of acquiring HIV. HIV-positive participants may also benefit from the prevention counseling messages. Possible benefits to society include potentially decreased meth use among individuals with a resultant decrease in meth use-related morbidity and mortality.

13.6 RISK TO BENEFIT RATIO: Explain why the risks to subjects are reasonable in relation to anticipated benefits, if any, to the participant or society:

There are few anticipated physical, psychological, social, or legal risks. As described above, intermittent oral naltrexone is well tolerated. Additional possible risks of participating in these studies include: unauthorized disclosure of
confidential information; discomfort or embarrassment related to urine collection or questionnaires dealing
with personal habits, lifestyle, drug or alcohol use; possible unwanted encounters with friends or associates in the treatment setting; and continued drug use. Study procedures are carefully crafted and

followed to minimize these risks. If participants were to find any aspects of their involvement in the study
physically, psychologically or otherwise uncomfortable, they will be able to discontinue the study immediately.

The potential social, psychological, and physical risks to participants described above are reasonable given
the need to develop new interventions to treat meth users. If naltrexone helps reduce meth use, results of this study would be of great benefit to meth-using individuals and the community at large.

Importance of the Knowledge to Be Gained
An efficacious treatment for persons with meth use would radically expand treatment options for meth use, and have significant public health impact. In addition, among our target population, reducing
meth use may have a profound effect in reducing HIV.

14.0 Data and Safety Monitoring Plan

14.1 * DATA AND SAFETY MONITORING PLAN (DSMP): (REQUIRED) Provide a summary of the DSMP:

All greater than minimal risk studies are required to provide a plan. Lack of an adequate plan is one of the most common reasons why IRB approval is delayed.

Instructions:

Describe the plan for monitoring data quality and participant safety. Key areas that should be included in the plan are:

- An explanation of the plan to monitor data collection, study progress, and safety
- A description of who will perform the monitoring and at what frequency (e.g., the PI only, a contract research organization, a Data and Safety Monitoring Board or Data Monitoring Committee, etc.)
- The type of data and events that will be reviewed (e.g., adverse events, breaches of confidentiality, unanticipated problems involving risk to participants or others, unblinded efficacy data, etc.)
- Procedures and timeline for communicating monitoring results to the UCSF IRB, the study sponsor, and other appropriate entities

As appropriate:

- A plan for conducting and reporting interim analysis
- Clearly defined stopping rules
- Clearly defined rules for withdrawing participants from study interventions

AE Reporting. Each AE will be classified by the study clinician as serious or non-serious, and appropriate
reporting procedures will be followed; these decisions will be reviewed on a real-time basis by the study
clinicians. An AE is defined as any reaction, side effect, or untoward event that occurs during the course of
the clinical trial, whether or not the event is considered medication-related. A new illness, symptom, or
worsening of a pre-existing condition or abnormality is considered an AE. Stable chronic conditions that
are present prior to clinical trial entry and do not worsen are not considered AEs. For this study,

AEs will
include symptoms reported by the patient and abnormal measures of clinical importance noted by study
staff.

Study staff will assess participants for any medical or psychiatric side effects by asking the participant
"How have you been feeling since I saw you last?" Study staff will also review the previous AE form and
inquire whether any of those events are continuing. Study clinicians will follow all AEs, regardless of
severity, until resolution or until four weeks following completion of the trial. Each new or unresolved AE
will be recorded on the AE case report form according to standard procedures. All AEs will be assigned a
severity (mild, moderate, severe or life-threatening), as defined by the DAIDS Table for Grading Severity
of Adult Adverse Experiences for HIV Prevention Trials.148 The study clinician will review the information
and offer an educated opinion about the relatedness of the event to the study drug. These data will be
reviewed by the PI or Co-Investigator on a weekly basis.

A summary report of all AEs (including SAEs) will be prepared at least every six months (frequency
determined by our IRB, DSMB, and NIH), to be submitted to the DSMB, IRB and NIH.
SAEs. SAEs are defined as any fatal event, any immediately life-threatening event, any permanent or
substantially disabling event, any event that requires or prolongs inpatient hospitalization, or any
congenital anomaly. This category also includes any other important medical event that a study
investigator judges to be serious because it may jeopardize the subject or require intervention to prevent
one of the above reportable outcomes, or which would suggest a significant hazard, contraindication, side
effect, or precaution. An unexpected event is one that is not described with respect to nature, severity, or
frequency in the current protocol, investigator's brochure, or product labeling. All AEs that are both
serious and unexpected will be reported to the DSMB and UCSF IRB, in writing, within 10 working days. If
the SAE is fatal or life threatening, the PI will notify the FDA by telephone within 24 hours, with a followup
written report within two working days.

As required, expedited reporting of SAEs to the NIH will adhere to the following guidelines:
1. Apply regardless of the investigator's assessment of the relatedness of the SAE to the intervention
under study;
2. Apply equally to trials requiring an IND and those not requiring an IND;
3. Apply to any SAEs that occur during the post-treatment observation period defined by the protocol; and
4. Apply to suicidal or homicidal behavior that causes an SAE in the participant or someone else (e.g.,
hospitalization or death).

SAE reporting will include a narrative that will provide details of relevant screening measures, medical
history and physical findings, treatment compliance, participant reports of SAEs, and any other required
information. The completed SAE report will contain: subject's ID, gender, 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, study screening for inclusion/exclusion, treatment received, outcome of
study treatment, 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. In cases of participant
death, the report will also include appropriate substantiation from clinic records, and, whenever

possible,
copies of the death certificate, autopsy report, or medical record. As Medical Monitor for the study, Dr.
Coffin, will state whether the event was expected and assess its relatedness to the study medication or
intervention.

Reporting of other study events. As the study is being conducted, Dr. Santos (PI) will inform the NIH,
IRB, and DSMB of any changes in recruitment or in the protocol that are relevant to safety, as well as any
actions taken by the IRB as a result of its continuing review of the study. In the event of any major
changes in the status of an ongoing protocol (which will occur only with IRB approval), the contact PI will
inform the NIH's program officer and the DSMB immediately. Such changes would include, but are not
limited to: amendments to the protocol; temporary suspension of patient accrual, or of the protocol; any
change in informed consent or IRB approval status; termination of patient accrual or of the protocol; or
other problems or issues that could affect the human subjects in the study.

Trial stopping rules: There are no formal trial stopping rules for this study. No formal interim efficacy
analysis will be conducted. 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 DSMB, IRB, and NIDA PO. The overall safety risk to study participants
will be determined through regular monitoring procedures. Safety issues will be evaluated as they arise;
participants are given the pager number of the clinician on call which they can page in the event of an
emergency or safety risk. Study clinicians will consult with Dr. Santos, the Principal Investigator and Dr.
Coffin, the medical director, 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 by the team's
research clinicians at the next weekly meeting with the PI Dr. Santos. During weekly meetings, study
clinicians will review all the safety issues and incident adverse events (including lab abnormalities) for the
study overall, by system category, and by possible relationship to the study drug. The PI will alert the
DMSB and the NIDA PO immediately if at any point the team observes an unexpected frequency of serious
AEs possibly related to kudzu. At that point, the PI will consult with the DSMB to determine if changes to
the protocol or consent form are needed, or if additional safety data are needed to evaluate participant
safety. The PI will consult the DSMB to determine if the trial should be stopped after the committee has
reviewed available safety data to date.

14.2 * DATA AND SAFETY MONITORING BOARD (DSMB): (REQUIRED) Will a Data and Safety Monitoring Board (DSMB) be established:

(●) Yes
( ) No

14.3 DSMB DETAILS: Provide details about the DSMB, including meeting frequency, and the affiliations and qualifications of members: Attach the DSMB charter to the Other Study Documents section. If the DSMB has not yet been established, submit details and the charter to us as soon as they become available.

The research team has used the UCLA Data Safety Monitoring Board (DSMB) for Addiction Medicine, of which Dr. Santos is currently a member, for past clinical trials; we will do so for this trial as well. The purpose of the DSMB is to monitor participants' progress in trials in order to identify emerging and unexpected events that change the known risks to subjects' participation. The UCLA DSMB reviews multiple studies in separate review committees. It has a project director who assigns committee reviewers to review studies. The reviewers remain anonymous to the PI and the coordinator communicates the concerns of the committee to the PI. When the PI responds to the concerns raised by the committee, they also send them through the coordinator who then passes it to the committee. The PIs are never part of, nor sit in the committee that reviews their own study.

The DSMB will be given blinded trial data, but may request unblinding if safety data warrant. The DSMB clinicians will review reported AEs that are identified by study clinicians or other staff members who evaluate the subjects. The statistician will review the data periodically to monitor problems that emerge from AE occurrences as well as subjects' self-report instruments that query about psychological and physical complaints. The safety monitoring process begins with the initial DSMB review and approval of the protocol. This review is conducted at multiple levels, including not only the DSMB, but also the NIH and the UCSF IRB. For this study,the DSMB will meet six months into the trial or earlier if warranted, and then annually and on an as-needed basis. The DSMB will review the data collected during this trial to provide ongoing information to Mr. Santos, to the IRB, to the NIH, and potentially (if clinically warranted) to subjects about changes in the risks and benefits from research participation. Communication between the DSMB and the study site will be forwarded to the UCSF IRB and the NIH, for consideration as to whether there are changes to risks and benefits, or if any unexpected events have occurred (see DSMBAM info sheet in other study documents).

Below are members who serve as committee chairs as well as clinical research experts:
• **Steven Shoptaw, PhD,** is Professor in both the Department of Family Medicine and the Department of Psychiatry and Biobehavioral Sciences at UCLA. Over the past 20 years, Dr. Shoptaw has conducted a series of clinical studies in community clinic settings, primarily on topics that involve developing medical and behavioral interventions to treat substance abusers.
• **Timothy M. Hall, MD, PhD,** is Health Sciences Assistant Clinical Professor at UCLA Department of Family Medicine and Center for Behavioral and Addiction Medicine. His research expertise is in sexual identity formation, social/sexual MSM networks, non-gay-identified MSM, ethnography and MSM substance use.
• **Gayle Baldwin, PhD,** is Associate Professor in the Department of Medicine at the University of California, Los Angeles. Her research focuses on how specific immune cells fight infectious diseases and cancer.
• **Dominick Frosch, PhD**, is an Associate Staff Scientist in the Department of Health Services Research at the Palo Alto Medical Foundation's Research Institute. He is also an Assistant Professor of Medicine at the University of California, Los Angeles. His research is focused on developing and implementing interventions to increase patient participation in clinical decision making and understanding the effects of health information in the media on behavior.

Below are members who serve as experts in biostatistics and epidemiology:
• Scott Comulada, PhD
• Sung-Jae Lee, PhD
• Jesse Fletcher, PhD
• Glenn-Milo Santos, MPH, PhD

Below are members who serve as clinical research experts:
• Adam Carrico, PhD
• David Farabee, PhD

- Timothy Fong, MD
- Liz Evans, PhD
- Phillip O. Coffin, MD, MIA
- Lara Ray, PhD

Administrative support staff:
- Uyen Kao, MPH, Director
- Oluwadamilola O. Jolayemi, MSc, Coordinator

15.0 Confidentiality, Privacy, and Data Security

15.1 PROTECTING PRIVACY: Indicate how subject privacy will be protected:

- [x] Conduct conversations about the research in a private room
- [x] Ask the subject how they wish to be communicated with – what phone numbers can be called, can messages be left, can they receive mail about the study at home, etc.
- [x] Take special measures to ensure that data collected about sensitive issues do not get added to their medical records or shared with others without the subject's permission
- [ ] Other methods (describe below)

15.2 SENSITIVE DATA: Do any of the instruments ask about illegal or stigmatized behavior:

(•) Yes ( ) No

IMPORTANT NOTE: Indicate in the consent form what kinds of sensitive information will be collected.

15.3 SIGNIFICANT CONSEQUENCES OF A LOSS OF PRIVACY OR CONFIDENTIALITY: Could a breach of privacy or confidentiality result in any significant consequences to participants, such as criminal or civil liability, loss of state or federal benefits, or be damaging to the participant's financial standing, employability, or reputation:

(•) Yes ( ) No

Check all that apply:

- [x] Embarrassment
- [ ] Criminal or civil liability
- [ ] Loss of state or federal benefits
- [x] Damaging to the participant's financial standing, employability, or reputation
- [ ] Potential risks to insurability (health, disability, or life insurance)

Describe the potential consequences:

Other potential risks to participating in this study 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; and possible unwanted encounters with friends
or associates in the research setting.

15.4 EXTRA CONFIDENTIALITY MEASURES: Explain any extra steps that will be taken to assure confidentiality and protect identifiable information from improper use and disclosure, if any:

The study consent form will inform participants of confidentiality guidelines. Strict confidentiality will be
maintained. Records that have personal identifiers (e.g., clinical records) will be stored in a locked

cabinet
separate from the research record, which will contain only the participant's ID number. Only the research
team and clinical staff assigned to the care of the participants will have access to non-anonymous records.
All research data are maintained in binders in locked cabinets. Consent forms, which contain names, are
stored separately. Enrollment and randomization ID numbers are used to identify specific research forms.
Files that link participants' name with enrollment and randomization ID numbers will be kept in a locked
file. No presentation or publication of the study results will refer to participants individually. Prior to any
sharing of the research dataset, all personal identifiers will be removed. Data will be shared only with
researchers who have received IRB-approval for their studies, and who agree not to identify any specific
study participant in any way, and who will destroy or return the dataset after completing their analyses.

The study will follow HIPAA regulations for the protection of private health information for individuals. All
study participants enrolled or enrolling in our studies must sign the HIPAA Authorization Form. The Authorization Form is protocol-specific and must be signed along with the consent form when participants
first screen or enroll into a study. Before participants sign the Authorization Form, study staff will explain
the purpose of the Authorization Form and answer any of the participants' questions. Participants will
receive a signed copy of the Authorization Form. Potential participants who choose not to sign the HIPAA
Authorization form will be excluded from study participation.

For the safety to participants and staff during COVID-19, the study has been designed with hybrid visits according to Interim UCSF research guidelines. The weekly visits (weeks 1, 2, 3, 5, 6, 7, 9, 10 and 11) will be conducted remotely through zoom. The participant will be given single M-AMP urine test kits and urine collection bottles at the in-office visits and trained how to conduct the urine test. The participant is asked to provide a urine sample in the urine collection bottle before the video visit. The participant will dip the M-AMP stick in the urine during the video visit and the dip stick will be shown to the counselor. Due to video resolution, a faint red line may not be able to be viewed by video. If this happens, the participant will be asked to take a picture of the dip stick and upload it to a secure portal or an encrypted e-mail. After IRB approval, we will test this option on RedCAP through the participant survey invitation and embedded image upload option.

15.5 * REPORTABILITY: Do you anticipate that this study may collect information that State or Federal law requires to be reported to other officials, such as elder abuse, child abuse, or threat to self or others: (REQUIRED)

(•) Yes ( ) No

The confidentiality and privacy section of the consent form should include this as a possible risk of participation.

* Describe the types of reportable information the research team may encounter and provide the details of the reporting plan: **(REQUIRED)**

Exceptions to confidentiality for participants are those required by law such as a diagnosis of sexually transmitted infections (STIs) including HIV, CD4 and Viral Load and threat of imminent action on suicidal or homicidal ideation. At any time, persons judged by project investigators to be a danger to self or others, will be escorted to San Francisco General Hospital. All staff, including research assistants and counselors, receive yearly training for identifying suicide /homicide risk and/or dangerous intoxication, and de-escalation of agitated or angry persons. All staff are trained to appropriately respond to these situations by immediately contacting a study clinician to evaluate the participant.

15.6 CERTIFICATE OF CONFIDENTIALITY: Will this study obtain a Certificate of Confidentiality:

(•) Yes ( ) No

Please include the recommended Certificate of Confidentiality language in the consent form.

15.7 SHARING OF RESEARCH RESULTS: Will there be any sharing of EXPERIMENTAL research test results with subjects or their care providers:

( ) Yes (•) No

15.9 * HIPAA APPLICABILITY: Study data will be: (REQUIRED)

- [x] Derived from a medical record (e.g. APeX, OnCore, etc. Identify source below)
- [ ] Added to the hospital or clinical medical record
- [ ] Created or collected as part of health care
- [ ] Used to make health care decisions
- [x] Obtained from the subject, including interviews, questionnaires
- [ ] Obtained ONLY from a foreign country or countries
- [ ] Obtained ONLY from records open to the public
- [ ] Obtained from existing research records
- [ ] None of the above
- [ ] Derived from the Integrated Data Repository (IDR) or The Health Record Data Service (THREDS) at SFGH

In addition to signing a consent form, each subject will have to sign the UCSF Research Subject Authorization Form (HIPAA Form). Upload the HIPAA Authorization Form in the Other Study Documents section of the Initial Review Submission Packet Form. Failure to have patients sign the HIPAA Authorization is one of the most common findings from QIU Routine Site Visits. Please call the IRB office at 415-476-1814 if you have questions about HIPAA research requirements.

If derived from a medical record, identify source:

Clarifying health data may be requested from PCP, inpatient and/or ED visits.

15.10 * IDENTIFIERS: Check all identifiers that will be collected and included in the research records, even temporarily: (REQUIRED)

- [x] Names
- [x] Dates
- [x] Postal addresses (if only requesting/receiving zip codes check Yes to the Zip Code question below instead of checking this box)
- [x] Phone numbers
- [ ] Fax numbers
- [x] Email addresses
- [x] Social Security Numbers*
- [ ] Medical record numbers
- [ ] Health plan numbers
- [ ] Account numbers

- [ ] License or certificate numbers
- [ ] Vehicle ID numbers
- [ ] Device identifiers or serial numbers
- [x] Web URLs
- [x] IP address numbers
- [ ] Biometric identifiers
- [ ] Facial photos or other identifiable images
- [ ] Any other unique identifier
- [ ] None

* Could study records include *ANY* photos or images (even 'unidentifiable' ones): **(REQUIRED)**

- ( ) Yes (•) No

* Please provide a justification for including the Social Security Number (SSN) in your data set. Best practices dictate that you store the SSN separately from the full data set in a password protected file. **(REQUIRED)**

California regulations require that positive HIV test results be reported to the county public health department, even if it is not a new diagnosis for the individual. HIV test result reporting includes CD4+ count (or T-cell count), viral load, and viral genotype for positive results. This information is used to track the disease statewide and nationwide.

The report includes details like participant name, social security number, and other identifying information. The San Francisco Department of Public health may share the results with the participant's home county health department if they do not live in San Francisco County. Other than this required reporting, test results will be treated confidentially by the study staff and personally identifying information will not be reported to other departments or agencies.

15.12 * PATIENT RECORDS: Will health information or other clinical data be accessed from UCSF Health, Benioff Children's Hospital Oakland, or Zuckerberg San Francisco General (ZSFG): (REQUIRED)

- (•) Yes ( ) No

15.15 * HIPAA - PERMISSION TO ACCESS SENSITIVE DATA: Does the research require access to any of the following types of health information from the medical record: (check all that apply) (REQUIRED)

- [x] Drug or alcohol abuse, diagnosis or treatment
- [x] HIV/AIDS testing information
- [ ] Genetic testing information
- [x] Mental health diagnosis or treatment
- [ ] None of the above

Important note: Ensure that participants initial the corresponding line(s) in Section C of the HIPAA authorization form during the consent process.

15.19 * DATA COLLECTION AND STORAGE: (check all that apply): (REQUIRED)

Collection methods:

- [ ] Electronic case report form systems (eCRFs), such as OnCore or sponsor-provided clinical trial

management portal
- [x] UCSF ITS approved Web-based online survey tools: Qualtrics or RedCap
- [x] Other web-based online surveys or computer-assisted interview tool
- [ ] Mobile applications (mobile or tablet-based)
- [x] Text Messaging
- [ ] Wearable devices
- [ ] Audio/video recordings
- [ ] Photographs
- [x] Paper-based (surveys, logs, diaries, etc.)
- [x] Other:

* Specify what other methods will you use to collect data: **(REQUIRED)**

If the counselor is unable to read the urine dip stick through the remote video visit, the participant will be asked to take a photo of the dip stick result and upload this to a secure portal or encrypted e-mail.

* What online survey or computer assisted interview tool will you use: **(REQUIRED)**

- [ ] Qualtrics (Recommended)
- [x] RedCAP (Recommended)
- [ ] Survey Monkey (NOT recommended and may require UCSF ITS Security review)
- [x] Other

* What's the name of the survey tool and who is it owned by: **(REQUIRED)**

We will use PiLR Health's Ecological Momentary Assessments (EMA)messages for the Ecological Momentary Interventions (EMI). To collect self-adherence measures we will use MEMs caps which we have used in previous studies.

If the survey tool is not provided by the study sponsor, and the survey tool stores data on a server, vendor, cloud, or 3rd party, contact datasecurity@ucsf.edu to determine if you need to complete a security assessment.

* Data will be collected/stored in systems owned by (check all that apply): **(REQUIRED)**

- [ ] Study sponsor
- [x] UCSF data center (including OnCore, RedCap, Qualtrics, and MyResearch)
- [ ] UCSF encrypted server, workstation, or laptop residing outside of UCSF data center
- [ ] Personal devices, such as laptops or tablets that are not owned or managed by UCSF
- [ ] SF VAMC
- [ ] Zuckerberg San Francisco General Hospital
- [ ] Benioff Children's Hospital Oakland
- [ ] Langley Porter Psychiatric Institution
- [ ] Other UCSF affiliate clinic or location (specify below)
- [ ] Cloud vendor such as Amazon Web Services (AWS), Salesforce, etc. (specify below)
- [ ] Other academic institution
- [ ] 3rd party vendor (business entity)
- [x] Other (explain below)

* Provide more details about where study data will be stored: **(REQUIRED)**

All data collected will be collected and stored at the San Francisco Dept of Public Health office on 25 Van
Ness Ave. Records that have personal identifiers (e.g., clinical records) will be stored in a locked cabinet
separate from the research record, which will contain only the participant's ID number. Only the

research
team and clinical staff assigned to the care of the participants will have access to non-anonymous records.
All research data are maintained in binders in locked cabinets. Consent forms, which contain names, are
stored separately.

Enrollment and randomization ID numbers are used to identify specific research forms. Files that link participants' name with enrollment and randomization ID numbers will be kept in a locked file in a
locked room.

Information collected through ecological momentary intervention messages will be stored only for the duration of the study. No sensitive information is collected. PiLR Health is also a HIPAA compliant system.

15.20 * ADDITION OF RECORDS TO A REGISTRY: Will patient records reviewed under this approval be added to a research database, repository, or registry (either already existing or established under this protocol): (REQUIRED)

○ Yes ◉ No

15.21 * DATA SHARING: During the lifecycle of data collection, transmission, and storage, will identifiable information be shared with or be accessible to anyone outside of UCSF: (REQUIRED)

○ Yes ◉ No

16.0 Financial Considerations

16.1 * PAYMENT: Will subjects be paid for participation, reimbursed for time or expenses, or receive any other kind of compensation: (REQUIRED)

◉ Yes ○ No

16.2 PAYMENT METHODS: Subjects payment or compensation method (check all that apply):

Payments will be (check all that apply):

- [x] Cash
- [ ] Check
- [x] Gift card
- [x] Debit card
- [ ] UCSF Research Subject Payment Card
- [ ] Reimbursement for parking and other expenses
- [x] Other:

Specify **other** payment/compensation method:

Paypal electronic cash transfers.

16.3 PAYMENT SCHEDULE: Describe the schedule and amounts of payments, including the total subjects can receive for completing the study:

- **If there are multiple visits over time, explain how payments will be prorated for partial completion**
- **If deviating from recommendations in Subject Payment Guidelines, include specific justification below**

Participants will be compensated for their time at each visit and in responding to daily ecological momentary messages (up
to a total of $556). Participants will receive $80 for the 2 screening visits ($35 at Screen 1 and $45 at Screen 2), $15 for run-in visits 1 and run-in visit 2, $55 for enrollment, $20 for weekly visits (1-3, 5-7, and 9- 11), $55 for week 4 (month 1) and week 8 (month 2) visits, and $65 for week 12 (month 3). In addition, they will receive $0.40 for each day that they
complete the daily EMA series throughout the 12-week treatment period (up to $36).

Participants could receive a gift card ($10) for partial screening visits. Participants could receive a gift card ($20) if they confirm and arrive at their scheduled screen 1 in-office visit. Participants who are given loaner phones could receive $50 if they return the loaner phone at the week 12 visit.

For any snowball referral that has completed a screening visit, the participant who referred the new participant will receive $10. If the new participant enrolls in the study, the participant who referred the new participant will receive $40.

16.4 COSTS TO SUBJECTS: Will subjects or their insurance be charged for any study activities:

○ Yes ◉ No

17.0 Other Approvals and Registrations

17.1 * ADMINISTRATION OF RECOMBINANT DNA: Does this study involve administration of vaccines produced using recombinant DNA technologies to human subjects (Help Link added Aug '15): (REQUIRED)

○ Yes ◉ No

17.2 * HUMAN GENE THERAPY: Does this study involve human gene therapy: (REQUIRED)

○ Yes ◉ No

17.4 OTHER APPROVALS: Indicate if this study involves other regulated materials and requires approval and/or authorization from the following regulatory committees:

☐ Institutional Biological Safety Committee (IBC)

Specify BUA #:

☐ Institutional Animal Care and Use Committee (IACUC)

Specify IACUC #:

☐ Controlled Substances

18.0 Qualifications of Key Study Personnel and Affiliated Personnel

NEW: January 2019 - Affiliated personnel who do not need access to iRIS no longer need to get a UCSF ID. Instead, add them below in the Affiliated Personnel table below.

18.1 Qualifications of Key Study Personnel:

Instructions:

For UCSF Key Study Personnel (KSP)* listed in **Section 3.0,** select the KSP from the drop down list and add a description of their study responsibilities, qualifications and training. In study responsibilities, identify every individual who will be involved in the consent process. Under qualifications, please include:

- Academic Title
- Institutional Affiliation (UCSF, SFGH, VAMC, etc.)
- Department
- Certifications

NOTE: This information is required and your application will be considered incomplete without it. If this study involves invasive or risky procedures, or procedures requiring special training or certification, please identify who will be conducting these procedures and provide details about their qualifications and training. Click the orange question mark for more information and examples.

Training Requirements:
The IRB requires that all Key Study Personnel complete Human Subjects Protection Training through **CITI** prior to approval of a new study, or a modification in which KSP are being added. More information on the CITI training requirement can be found on our **website.**

* **Definition of Key Study Personnel and CITI Training Requirements (Nov, 2015):** UCSF Key Study Personnel include the Principal Investigator, other investigators and research personnel who are directly involved in conducting research with study participants or who are directly involved in using study participants' identifiable private information during the course of the research. Key Personnel also include faculty mentors /advisors who provide direct oversight to Postdoctoral Fellows, Residents and Clinical Fellows serving as PI on the IRB application.

KSP Name	Description of Study Responsibilities - Briefly describe what will each person be doing on the study. If there are procedures requiring special expertise or certification, identify who will be carrying these out. Also identify who will be obtaining informed consent.	Qualifications, Licensure, and Training
	Dr. Santos is responsible for the overall scientific, clinical, and operational aspects of the study,	Dr. Santos is a Senior Research Scientist in the

Santos, Glenn-Milo PhD, PhD	including: protocol development, overseeing the study activities and the safety of participants, data collection and management, data analysis, and publication of study results. Dr. Santos holds ultimate responsibility for all study staff conduct.	Center on Substance Use and Health at the San Francisco Department of Public Health(SFDPH) and an Associate Professor at the Department of Community Health Systems at University of California, San Francisco.
Coffin, Phillip O, MD	Dr. Coffin will assist with clinical visits, including performing screening, enrollment, and follow-up visit. He will support study clinical staff in determination of participant eligibility when extensive medical expertise is required. He will be available on–call for study staff and for participant emergencies or questions and will meet regularly with staff to discuss adverse events and other clinical issues. Dr. Coffin will assist Mr. Santos in study design, formulation of the study protocol and structured interview guide, analysis of the data and integration and interpretation of quantitative data.	Dr. Coffin is Director in the Center on Substance Use and Health at the San Francisco Department of Public Health. He is a board certified infectious disease with expertise in HIV treatment adherence, epidemiology of substance use trends, and evaluation of pharmacologic interventions for substance use.
Dr. Vittinghoff, Eric PhD	Dr. Vittinghoff is responsible for the statistical integrity of the study, including developing randomization procedures, data collection instruments, ensuring integrity of the data collected,and developing data analysis plans. Dr. Vittinghoff will collaborate closely with Dr. Santos in study design, data analysis, and publication of study results.	Dr. Eric Vittinghoff, PhD is Adjunct Professor of Epidemiology and Biostatistics in the Division of Biostatistics at the University of California,San Francisco.
	Dr. Matheson has developed the substance use counseling sessions, trains and supervises the counseling staff, and ensures adherence to the protocol. He will meet with the counseling staff	Dr. Matheson, PhD is a psychologist in the

Matheson, Tim	on a weekly basis to resolve any counseling issues, as well as to ensure adherence to the counseling protocol. He will also oversee the operations related to HIV testing and counseling.	Center on Substance Use and Health of the San Francisco Department of Health.
Ikeda, Janet	Ms.Ikeda is responsible for coordinating the study,including overseeing the day to day activities and regulatory reporting, quality assurance checks, lab maintenance and assisting with data analysis.	Janet Ikeda is a Research Study Coordinator in the Center on Substance Use and Health at the San Francisco Department of Public Health.
Walker, John	John Walker is a study clinician who conducts screening visits and determines eligibility of potential participants, performs physical exams, medical histories, phlebotomy, administers study drug,revises adverse events and manages the laboratory and drug storage.	John Walker,MSN, FNP-C, is a nurse practitioner in the Center on Substance Use and Health at the San Francisco Department of Public Health.
Yuhas, Trent W	Mr. Yuhas is responsible for conducting study visits and assessments, including informed consent, performing phlebotomy and conducting STI and HIV risk reduction counseling and testing.	Trent Yuhas, M.A., is a Research Associate in the Center on Substance Use and Health of the San Francisco Department of Public Health.
Farley, John	Mr. Farley is responsible for recruiting potential participants for the research study, including field screen and the pre-screening form.	John Farley, BA, is a Recruitment coordinator in the Center on Substance Use and Health of the San Francisco Department of Public Health
Hoffmann, Thomas PhD, PhD	Dr. Hoffmann is the bio-statistician on the study and responsible for creating the ACASI questionnaire and overseeing the data collection and analyses of the study.	Thomas Hoffmann, PhD., is a Bio-statistician at the University of California at San Francisco.

Dunham, Alexandrea	Ms Dunham is responsible for conducting study visits and assessments, including informed consent, performing phlebotomy and conducting STI and HIV risk reduction counseling and testing.	Alexandrea Dunham, BA, is a Research Associate in the Center on Substance Use and Health of the San Francisco Department of Public Health.
Balcazar, Andrew L	Mr. Balcazar is responsible for recruiting potential participants for the research study, including field screen and the pre-screening form.	Andrew Balcazar is an Assistant Recruitment coordinator in the Center on Substance Use and Health of the San Francisco Department of Public Health
POPE, EMILY R	Ms. Pope is responsible for conducting study visits and assessments, including informed consent, performing phlebotomy and conducting STI and HIV risk reduction counseling and testing.	Emily Pope, BA, is a Research Associate in the Center on Substance Use and Health of the San Francisco Department of Public
Parker, Ella	Ms. Parker is is responsible for conducting study visits and assessments, including informed consent, performing phlebotomy and conducting STI and HIV risk reduction counseling and testing.	Ella Parker, BA is a Research Associate in the Center on Substance Use and Health at the San Francisco Department of Public Health.
Tavasieff, Sophia R	Ms. Tavasieff is responsible for recruiting potential participants for the research study, including field screen and the pre-screening form.	Sophia Tavasieff is an Recruitment assistant in the Center on Substance Use and Health of the San Francisco Department of Public Health
Jan, Fareshta	Ms. Jan is responsible for conducting study visits and assessments, including informed consent, performing phlebotomy and conducting STI and HIV risk reduction counseling and testing.	Ms Jan, BA, MPH is a Research Associate in the Center on Substance Use and Health of the San Francisco Department of Public Health.

18.2 Affiliated Personnel:

Instructions:

This section is for personnel who are not listed in **Section 3.0: Grant Key Personnel Access to the Study** because their names were not found in the User Directory when both the iRIS Database and MyAccess directories were searched. Add any study personnel who fit ALL of the following criteria in the table below:

- They meet the definition of Key Study Personnel (see above), **and**
- They are associated with a UCSF-affiliated institution (e.g., VAMC, Gladstone, Institute on Aging, Vitalant, NCIRE, SFDPH, or ZSFG), **and**
- They do not have a UCSF ID, **and**
- They do not need access to the study application and other study materials in iRIS.

Note: Attach a **CITI Certificate** for all persons listed below in the **Other Study Documents** section of the **Initial Review Submission Packet Form** after completing the **Study Application**.

Click the orange question mark icon to the right for more information on who to include and who not to include in this section.

Do not list personnel from outside sites/non-UCSF-affiliated institutions. Contacts for those sites (i.e. other institution, community-based site, foreign country, or Sovereign Native American nation) should be listed in the **Outside Sites** section of the application.

If there are no personnel on your study that meet the above criteria, leave this section blank.

Name	Institution	Telephone	E-mail	Role
No External Personnel has been added to this IRB Study				

Please describe the study responsibilities and qualifications of each affiliated person listed above:

19.0 End of Study Application

End of Study Application Form

To continue working on the Study Application:
Click on the section you need to edit in the left-hand menu. Remember to save through the entire Study Application after making changes.

If you are done working on the Study Application:
Important: Before proceeding, please go back to Section 4.0 Initial Screening Questions and **Save and Continue** through the form to make sure all the relevant sections and questions have been included. If you've changed any answers since you started, the branching may have changed. Your application will be incomplete and it will have to be returned for corrections.

Once you are sure the form is complete, click **Save and Continue**. If this is a new study, you will automatically enter the **Initial Review Submission Packet Form**,

where you can attach **consent forms** or other **study documents**. Review the **Initial Review Submission Checklist** for a list of required attachments.

Answer all questions and attach all required documents to speed up your approval.

The UCSF IRB welcomes feedback about the IRB Study Application Form. Please click the link to answer a **survey** about the application form.