Linking Infectious and Narcology Care – Part II (LINC-II)

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1. INTRODUCTION

1.1 SUMMARY

Russia and Eastern Europe continue to have one of the fastest growing HIV epidemics in the world, with highest transmission risks among people who inject drugs (PWID) and their sexual partners. While routine HIV testing within addiction treatment systems in Russia (i.e., narcology hospitals) is the norm, links between the narcology and HIV care systems are limited and ineffective. In St. Petersburg 50-60% of PWID are HIV-positive, yet among this population less than 10% are on antiretroviral therapy (ART). For Russia to make progress toward the UNAIDS 90-90-90 targets (i.e., 90% aware of HIV diagnosis, 90% of those diagnosed on ART and 90% of those on ART with suppressed HIV viral load [HVL]), a bold new strategy is required. The objective of this study, "Linking Infectious and Narcology Care – Part II (LINC-II)," is to implement and evaluate, via a two-armed randomized controlled trial among 240 HIV-positive PWID, a multi-faceted intervention combining pharmacological therapy (i.e., rapid access to ART and receipt of naltrexone for opioid use disorder) and 12 months of strengths-based case management. The central hypothesis is that LINC-II will lead to marked progress toward the achievement of the 90-90-90 HIV cascade of care targets among HIV-positive PWID, relative to current standard of care, and that LINC-II will facilitate health system coordination of narcology and HIV care. LINC-II aims to evaluate: 1) the effectiveness of LINC-II on undetectable HVL at 6 months and 12 months (primary outcome), initiation of ART within 28 days of randomization, change in CD4 count from baseline to 12 months, and retention in HIV care (i.e., ≥ 1 visit to medical care in 2 consecutive 6 month periods); 2) the impact of LINC-II on coordinated care across the narcology and HIV health care systems, using mixed methods data from health care providers, administrators, and patients; and 3) the cost-effectiveness of the intervention to inform policy makers on scaling up the LINC-II approach both within Russia and other countries with HIV epidemics driven by injection drug use. The study's goal is to improve upon current seek, test, treat, and retain efforts for HIV-positive Russian PWID in narcology care, a group routinely tested for HIV. If LINC-II is effective and can be embedded efficiently within the Russian and other medical systems challenged by HIV-positive PWID, then it has great potential to favorably impact the HIV epidemic in a key HIV population.

1.2 SIGNIFICANCE

The LINC-II study will assess the effectiveness and implications of an intervention designed to achieve 90-90-90 HIV care cascade targets by facilitating coordination of care between the addiction (i.e., narcology) and HIV treatment systems in Russia. Potential lessons learned in Russia should be applicable to all countries attempting to engage HIV-positive people who inject drugs in HIV care.

2. OVERVIEW OF STUDY DESIGN

2.1 STUDY AIMS

LINC-II's Specific Aims are the following:

Aim 1: ***Evaluate the effectiveness of LINC-II on HIV care and health*** compared to standard of care via a 2-armed RCT of 240 HIV-positive Russian PWID on the following outcomes:

a. Primary: Undetectable HIV viral load at 12 months

b. Secondary: Initiation of ART within 28 days of randomization;

Change in CD4 count from baseline to 12 months;

Retention in HIV care (i.e., ≥1 visit to medical care in 2 consecutive 6 month periods)

Undetectable HIV viral load at 6 months.

HVL suppression and past 30-day opioid abstinence assessed at 6 and 12 months

Aim 2: ***Evaluate the impact of LINC-II on coordinated care across the narcology and HIV health care systems*** using mixed methods data from health care providers and administrators from both systems, as well as with LINC-II study participants (i.e., patients within these systems) to determine trends over time. Survey data and interviews will assess perceptions of whether the narcology and HIV care systems increased coordination of care over the period of the study, and qualitatively, how and why coordination does or does not occur, as well as the system implications of such coordination.

Aim 3: ***Evaluate whether LINC-II is an affordable and cost-effective strategy*** for achieving undetectable HVL in HIV-positive PWID. If the intervention is successful, it will be important to understand the net cost to be incurred by the health system and patients and LINC-II's cost-effectiveness compared to standard of care. This economic perspective will inform policy makers on scaling up the LINC-II approach both within Russia and other countries with HIV epidemics driven by injection drug use.

2.2 STUDY HYPOTHESIS

We hypothesize that participants randomized to the LINC-II intervention will have improved HIV care outcomes as compared to the control group, which will receive narcology hospital's standard of care.

2.3 STUDY OUTCOMES

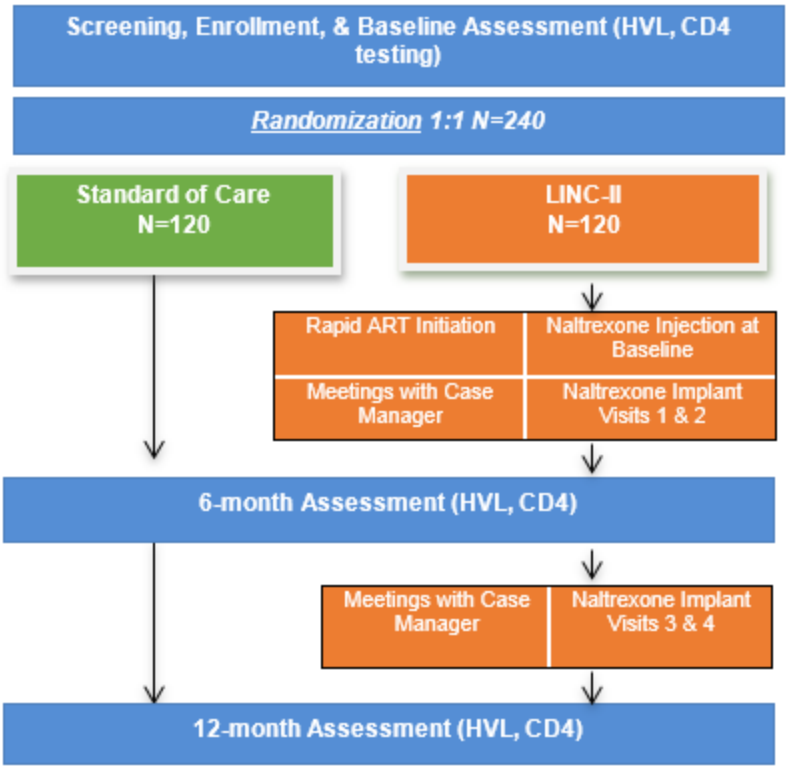
Aim 1. The primary outcome for aim 1 is defined as an undetectable HVL at 12 months post randomization, assessed by study test within a window of 9–15 months. Secondary outcomes are initiation of ART within 28 days of randomization, change in CD4 count between baseline and 12 months (assessed by study test), retention in HIV care (at least 1 visit to medical care in 2 consecutive 6 month periods within 12 months of enrollment, assessed by medical record review and by self-report), undetectable HVL at 6 months post randomization assessed by study test, and a composite outcome for achieving both HVL suppression and past 30-day opioid abstinence assessed at 6 and 12 months.

2.4 STUDY DESIGN

LINC-II is a Randomized Controlled Trial (RCT) among 240 HIV+ PWID, which aims to test the LINC-II intervention, evaluate its impact on coordinated care and evaluate its cost-effectiveness. Eligible participants will be randomly assigned into one of two groups: 1) Control group receiving narcology hospital's standard of care or; 2) LINC-II intervention. The intervention for those randomized to the intervention arm starts in the narcology hospital: an HIV case manager (CM) will meet with the participant, participant will have accelerated access to ART medication with potential to initiate ART right at the narcology hospital, and the participant will receive a dose of injectable naltrexone (i.e., Vivitrol) for treatment of their opioid use disorder. Following discharge from the narcology hospital, participants will meet with the case manager over 12 months, receive implantable naltrexone (Prodetoxon) every 10-12 weeks (4 doses), and ideally start on ART at their first HIV care visit, if ART was not initiated at the narcology hospital. Study outcomes will be assessed at 6 and 12 months (Figure 1).

Figure 1 illustrates the design of this 2-arm RCT with 120 participants per arm.

Figure: LINC-II Study Design



Throughout the course of the study, participants will be expected to participate in three in-person assessments and blood draw visits (baseline, 24 weeks and 52 weeks). Intervention participants will receive 4 naltrexone implants while in the study. Ideally, implants will be inserted every 10-12 weeks starting at week 4 post-study enrollment (weeks 4, 16, 28, 40). Participants will be invited to come in every 4 weeks following implantation for medication visits. Ideally, medication visits will occur at weeks 4, 8, 12, 16, 20, 24, 28, 32, 36, 40, 44, 48, and 52. Full study assessments occur at weeks 24 and 52 (in addition to medication visit procedures). Implant visits 2, 3, and 4 will involve the collection of blood for laboratory testing to monitor liver toxicity.

2.5 STUDY SITE

St. Petersburg City Addiction Hospital (CAH) will be the site of participant recruitment. CAH is a government-funded 510-bed hospital, providing free addiction care to residents of the city of St. Petersburg, who are registered as having a substance use disorder (drug or alcohol). The hospital provides detoxification, early stabilization, and inpatient rehabilitation. The typical length of stay for hospitalized patients is one to two weeks.

St. Petersburg City AIDS Center will provide HIV care for the intervention group. A typical initial outpatient visit to initiate HIV care includes examination by an infectionist (physician), lab testing (e.g., HVL, CD4), and referrals (e.g., psychologist or addiction specialist). Some clinics have a narcologist on

staff to refer HIV-positive PWID to drug addiction clinics. HIV case managers, including some HIV-positive PWID in recovery (i.e., peers) have been introduced at the clinics. ART is available at no cost to all patients in Russia; however, only a small percentage of PWID actually receive this treatment.

Follow up study visits, naltrexone implants, and adverse event monitoring will occur at the Laboratory of Clinical Pharmacology of Addictions at the First St. Petersburg Pavlov State Medical University (PSMU) in St. Petersburg, Russia. PSMU is the major educational, scientific, and clinical medical institution for northwestern Russia.

Blood specimens for AST/ALT will be processed and analyzed at ImmunoBioService (IBS) under the direction of Dr. Sergei Selkov. CD4 and HVL testing will take place at the City AIDS Center.

2.6 INCLUSION CRITERIA

To be eligible to participate in the trial, participants will need to meet the following inclusion criteria:

1. 18 years or older
2. HIV-positive
3. Hospitalized at a narcology hospital
4. History of injection drug use
5. Current diagnosis of opioid use disorder
6. Provision of contact information for 2 contacts to assist with follow-up
7. Address within 100 kilometers of St. Petersburg
8. Possession of a telephone (home or cell)
9. Able and willing to comply with all study protocols and procedures

2.7 EXCLUSION CRITERIA AT STUDY ENTRY

1. Not fluent in Russian
2. Cognitive impairment resulting in inability to provide informed consent based on research assessor (RA) assessment
3. Pregnancy, planning to become pregnant, or breastfeeding
4. ART use in past 30 days prior to hospitalization

5. Acute severe psychiatric illness (i.e. ,answered yes to any of the following: past three month active hallucinations; mental health symptoms prompting a visit to the ED or hospital; mental health medication changes due to worsening symptoms; presence of suicidal ideations)
6. Known history of liver failure
7. Known hypersensitivity to naltrexone
8. ALT or AST >5 times the upper limit of normal ((ALT > 225 for men and 170 for women; AST > 185 for men and women)
9. Known severe thrombocytopenia (<50K)
10. Known coagulation disorder/taking anticoagulation medications
11. Body habitus that precludes intramuscular injection (e.g., BMI < 17 or >45)
12. Known hypersensitivity to naloxone
13. Known history of Raynaud's disease
14. Known history of Itsenko-Cushing syndrome
15. Known history of generalized mycoses
16. Known history of glaucoma
17. Known history of osteoporosis.
18. Planned surgeries in the next 12 months

2.8 RECRUITMENT GOALS

We aim to randomize 240 participants over 30 months into the trial. Three to five days after City Addiction Hospital (CAH) admission and treatment for withdrawal symptoms, patients who have typical stays of 1 to 2 weeks will be recruited. This strategy will allow time to obtain HIV results (if not known), determine eligibility, obtain informed consent, perform baseline assessment, randomize, and, if applicable, schedule and conduct the 1st HIV case manager intervention session, conduct the naloxone challenge, and receive injectable naltrexone. This research study will focus on people who inject drugs (PWID), who comprise >90% of the CAH HIV-positive population.

In addition to the 240 RCT participants, we will also recruit up to 50 providers and administrators from HIV and narcology care systems to participate in a survey at study launch and up to 26 providers to participate in in-depth interviews at study launch and 12, and 24-months post-launch (plus short surveys) to explore their perspectives and experiences with care coordination between the narcology and HIV care systems.

A subset of LINC-II participants (at each time point n=10; 5 from intervention group, 5 from control group for a total n of up to 30 with 15 participants from each study arm) will also be invited to participate in in-depth interviews to discuss their experiences with care coordination at baseline, 6- and 12-months post enrollment.

2.8.A. SAMPLE SIZE CALCULATION AND POWER

We provide power calculations for the key hypotheses to be tested in this RCT. Sample size calculations assume an alpha level of 0.05 and 240 patients enrolled into the trial.

Aim 1: primary study outcome, undetectable viral load at 12-months post randomization: Based on data from the LINC study, we expect 10% of controls will have undetectable viral load at 12 months. Given this and assuming 20% loss to follow-up (i.e., 192 evaluable subjects) the study will have 80% power to detect an absolute difference of 17% (i.e., 27% vs. 10% in the intervention and control arms, respectively) using a chi-square test with continuity correction. We anticipate larger effects may be observed in our study, which would result in even higher power.

Aim 1: secondary study outcome, retention in HIV care (within 12 months): Because this secondary outcome will be assessed using medical records, we expect loss to follow-up to be minimal and estimate 10% loss to follow-up due to death and subject withdrawals. Based on data collected from LINC, we expect 20% of controls will attend 2 appointments in 12 months. Based on these assumptions and with 216 evaluable subjects, the proposed study has 80% power to detect an absolute difference of 19% (i.e., 39% vs. 20% in the intervention and control groups, respectively) in the proportions retained in HIV care, based on a chi-square test with continuity correction.

3. INTERVENTION

3.1 INTERVENTION OVERVIEW

The study will randomize 240 HIV+ persons with injection drug use. Participants will be recruited from St. Petersburg City Addiction Hospital (CAH), an inpatient narcology hospital in St. Petersburg, Russia. Three to five days after City Addiction Hospital (CAH) admission and treatment for withdrawal symptoms, patients who have typical stays of 1 to 2 weeks will be recruited.

After consent and enrollment, participants will be randomly assigned to either the LINC-II intervention or standard of care. Following randomization, participants in the intervention arm will receive one intramuscular gluteal injection of 380 mg of naltrexone for extended-release injectable suspension at CAH. Since naltrexone can precipitate withdrawal in participants with a physiological dependence on opioids, participants will be given a naloxone challenge prior to receiving naltrexone, as per the protocol used by Dr. Krupitsky's research team on previous research studies. The challenge is done by administering 0.8-mg naloxone slowly by IV or IM, and if no withdrawal symptoms occur within 5-20

minutes (depending on whether it was administered IV or IM) the absence of physiologic dependence is confirmed. At this point the patient is started on study medication. If participant fails the naloxone challenge, it will be repeated the next day.

Following CAH discharge, participants will come to PSMU to receive a 1000mg dissolvable naltrexone implant (IN) at four time points (ideally weeks 4, 16, 28, and 40), unless the participant relapsed. Relapse will be examined by self-report, evidence of fresh puncture marks, signs and symptoms of withdrawal or intoxication, and a urine drug screen that must be negative for opioids before receiving an implant. Seven to eleven days after the implant, participants will again come to PSMU for removal of stitches, and an inspection of the implant site.

Participants randomized to the intervention arm will also be assigned a case manager for 12 months. The first LINC-II CM session will be held at the City Addiction Hospital following randomization; the second session will be scheduled to take place at the City AIDS Center and subsequent sessions can occur at any location of preference, or via phone if necessary. LINC-II will offer SMS messaging between sessions to reinforce the CM-patient relationship and contact.

Participants randomized to the intervention arm will have rapid access to ART at their first HIV visit, given that as of 2016, CD4 cell count no longer determines timing of ART initiation in Russia. Participants in this study will receive streamlined access to ART through a City AIDS Center infectionist who also sees patients at the City Addiction Hospital. The infectionist will facilitate initiation of ART medications either while the patient is still hospitalized at the City Addiction Hospital, or at their first visit to City AIDS Center following CAH discharge. CMs will work with study participants to arrange for the visit to the City AIDS Center (to initiate ART, if not initiated at CAH, or to get the second refill) and will be available to accompany participants to this visit. Once the initial HIV visit is made, participants will be able to receive follow up care and medication refills at their local HIV outpatient clinic.

Throughout the course of the study, participants will be expected to participate in three in-person assessments and blood draw visits (baseline, 6- [24 weeks], and 12 [52 weeks]-months). Intervention participants will receive 4 naltrexone implants while in the study. Ideally, implants will be inserted every 10-12 weeks starting at week 4 post-study enrollment (weeks 4, 16, 28, 40). Participants will be invited to come in every 4 weeks following implantation for medication visits. Ideally, medication visits will occur at weeks 4, 8, 12, 16, 20, 24, 28, 32, 36, 40, 44, 48, and 52. Full study assessments occur at weeks 24 and 52 (in addition to medication visit procedures). Implant visits 2, 3, and 4 will involve the collection of blood for laboratory testing to monitor liver toxicity.

In addition to the 240 RCT participants, we will also recruit providers and administrators from HIV and narcology care systems to participate in surveys and in-depth interviews at study launch and 12, and 24-months post-launch to explore their perspectives and experiences with care coordination between the narcology and HIV care systems. A subset of LINC-II participants will also be invited to participate in in-depth interviews to discuss their experiences with care coordination at baseline, 6- and 12-months post enrollment.

3.2 RANDOMIZATION

Randomization will be stratified based on one factor that could relate to study outcome: ever ART use. Blocked randomization using random block sizes will be used within each stratum. A computer-generated randomization table will be created to allow randomization to occur via a custom web-application.

3.3 INTERVENTION

The LINC-II intervention is comprised of 3 main components: strengths-based HIV case management, rapid ART initiation, and pharmacotherapy for opioid use disorder.

3.3.A STRENGTHS-BASED CASE MANAGEMENT

LINC-II is a behavioral and structural intervention that uses a strengths-based case management approach in which a trained case manager (CM) meets individually with patients to motivate them to engage in HIV medical care by supporting the recognition of their own strengths to make positive changes in their lives and ultimately improve their HIV outcomes.[1] This approach is grounded in Social Cognitive Theory,[2] offering psychoeducational support and counseling to increase knowledge of benefits of HIV care services and to build comfort and self-efficacy to acquire those services. It also uses Psychological Empowerment Theory,[3] supporting patients to recognize their strengths and capacities to improve their health and circumstance.

The CM serves as a coordinator between the narcology and HIV systems of care, utilizing HIV strengths-based case management delivered via 10 one-on-one sessions by a peer case manager (i.e., HIV-positive man or woman in recovery from addiction) over a 12-month period to help motivate and reduce barriers to HIV care. The first LINC-II CM session will ideally be held at the City Addiction Hospital following randomization; the second session will be scheduled to take place at the City AIDS Center. Sessions will be planned to occur with approximately 3-6 weeks between sessions, with a goal of 5 sessions for every 6 months of intervention, for a total of 10 sessions. Following session 2, subsequent sessions can occur at any location of preference, or via phone if necessary.

The first two sessions will consist of ascertaining the patient's psychological and resource-related strengths and developing goals related to obtaining HIV care, as well as discussing with the patient the most recent CD4 count and HVL and the benefits of regular HIV care.

Follow-up sessions will reinforce prior sessions, reviewing previously set goals and patients' strengths and creating new goals as needed.

All sessions will be audiorecorded for quality assurance purposes. Case Manager will use discretion to turn the recorder off if participant feels uncomfortable disclosing certain sensitive information, and will

turn it back on as soon as possible. Audiorecordings of case management sessions will be deleted seven years after the completion of study analyses and publication of all study manuscripts.

LINC-II will also offer SMS messaging between sessions to reinforce the CM-patient relationship and contact. SMS will be sent to participants, encouraging them to contact their CM if they so wish. Participants can either exchange SMS or have their CM call for additional support when needed, for example in a craving crisis. SMS will be sent in-between in-person sessions (i.e., every two weeks to start) and case managers will be able to adjust the schedule as needed. The standard script below will be used.

"Hi this is NAME OF CM. Just checking in on how you are doing and whether I can help you with any appointments or care. Would you like to speak about this? If yes, please SMS or call me at this number. Stay well!"

"Добрый день! Это (имя КМ). Как дела и нужна ли помощь в назначении визита к врачу или по другим вопросам? Если это надо обсудить, то позвоните мне или напишите смс. До свидания."

Process Evaluation Components

Form	Who Completes Form	When is Form Completed	Type of Form	Purpose of Form	How Is Data Processed
1. Case Manager Checklist (Intervention Sessions 1 – 10) and brief tracking form	Case Manager	During Each Intervention Session and immediately after EVERY contact with every participant	Electronic	Quality control to ensure all activities are covered in each session Record # of contacts with Case Manager	Reviewed by Russian coordinator and Case Manager Supervisor; Feedback provided to CMs in meetings; Update provided to US Team in Monthly Meetings Used to measure dose of intervention; Case Manager Supervisor to review report to ensure that forms are being filled out and that intervention sessions are occurring
2. Case Manager Clinical Records – case notes	Case Manager	Immediately after EVERY contact with every participant	Electronic		Data is used by Case Manager Supervisor for clinical supervision; will not be evaluated for research

3. Participant Satisfaction Survey – Intervention and Control	Participant	Self-administered on computer as part of the 6 and 12 month interview	Electronic (part of the assessment)	Participant satisfaction with (response to) case managers and case management linkage to HIV care	Prevalence data used for reports
4. LINC Case Manager Observer Form	Case Manager Supervisor	Each CM will have their audiotapes reviewed/observed for the first 3 sessions and then 10% of cases after that.	Electronic	Quality assurance to ensure adherence to curriculum and CM skill	Data run every 3 months to review fidelity; Data team to generate a list of study IDs for review. Case Manager Supervisor to listen to sessions weekly and to provide feedback to interventionists in individual or group meetings every two months.
5. CM Evaluation of Intervention Form	Case Managers	Every 3 months subsequent to implementation start	Electronic	Feasibility of replication, how useful and beneficial is the program, how easy is it to implement	Reviewed by Case Manager Supervisor; Feedback provided to Interventionists in individual/group meetings; Update provided to US Team in Monthly Meetings

3.3.B. RAPID ACCESS TO ART

With all HIV-positive individuals now eligible for ART in Russia, regardless of CD4 count, participants randomized to the intervention, will have rapid access to antiretroviral medications. Rapid access to ART will be facilitated by the infectionist (HIV physician) employed by the City AIDS Center, who sees patients at the St. Petersburg CAH. All participants will meet with the infectionist and have their blood drawn for CD4 and HVL testing. The infectionist will order a blood draw for HVL and CD4 for all participants. The

blood will be sent to CAC for testing. All ART initiation requests in St. Petersburg must be approved by a special committee at the City AIDS Center. For participants randomized to the intervention group, the infectionist will streamline this approval with the ultimate goal of starting participants on ART while they are still hospitalized at CAH. If participant remains hospitalized at CAH at the time of ART approval, the infectionist will deliver the first set of medications (1-month supply) to the patient at CAH. Case Manager will help schedule the subsequent visit to the AIDS Center in 1 month to pick up the next refill of medication. If a participant is no longer admitted at CAH, CM will help patient schedule his or her visit to CAC as soon as possible, where the first set of medications will be provided. Once the initial visit to City AIDS Center is made, participants can continue HIV care at one of two possible sites: St. Petersburg AIDS Center or their local HIV outpatient clinic, and all subsequent ART refills can be picked up at a local clinic.

3.3.C. Pharmacotherapy for Opioid Use Disorder

Procedures at CAH – Injectable Naltrexone and Naloxone Challenge

Participants in the intervention arm will receive one intramuscular gluteal injection of 380 mg of naltrexone for extended-release injectable suspension at CAH. Since naltrexone can precipitate withdrawal in participants with a physiological dependence on opioids, participants will be given a naloxone challenge prior to receiving naltrexone, as per the protocol used by Dr. Krupitsky's research team on previous research studies (e.g. Adherence to HIV Therapy in Heroin Addicts: Oral vs. Extended Release Naltrexone study). The challenge is done by administering 0.8-mg naloxone slowly by IV or IM, and if no withdrawal symptoms occur within 5-20 minutes (depending on whether it was administered IV or IM) the absence of physiologic dependence is confirmed. If the participant fails the naloxone challenge, it will be repeated the next day. The naloxone challenge will only be administered if the participant's urine is negative for opioids. The procedures for the naloxone challenge and Vivitrol injection will be facilitated and administered by the participant's treating narcologist and nurse at CAH.

Naloxone Challenge Risks

Discomfort during the naloxone challenge will occur if the participant is physically dependent on opioids. Naloxone can induce opioid withdrawal, such as feeling sick, stomach cramps, muscle spasms, feelings of coldness, heart pounding, muscular tension, aches and pains, yawning, runny eyes, and insomnia. If participants have withdrawal after the naloxone test, their symptoms may be treated with clonidine or phenazepam and are not anticipated to last more than 45-60 minutes.

In the unlikely situation that emergency treatment is needed, participants may be treated with clonidine [75-150 ug] or diazepam [5 mg].

> The most frequent side effects (which appear to be dose-related) of clonidine are dry mouth, occurring in about 40 of 100 patients; drowsiness, about 33 in 100; dizziness, about 16 in 100; constipation and sedation, each about 10 in 100.

The following less frequent adverse experiences have also been reported in patients receiving clonidine tablets, but in many cases patients were receiving concomitant medication and a causal relationship has not been established: fatigue, fever, headache, pallor, weakness, and withdrawal syndrome. Also reported were a weakly positive Coombs test and increased sensitivity to alcohol, bradycardia, congestive heart failure, electrocardiographic abnormalities (i.e., sinus node arrest, junctional bradycardia, high degree AV block and arrhythmias), orthostatic symptoms, palpitations, Raynaud's phenomenon, syncope, and tachycardia. Cases of sinus bradycardia and atrioventricular block have been reported, both with and without the use of concomitant digitalis, agitation, anxiety, delirium, delusional perception, hallucinations (including visual and auditory), insomnia, mental depression, nervousness, other behavioral changes, paresthesia, restlessness, sleep disorder, and vivid dreams or nightmares, alopecia, angioneurotic edema, hives, pruritus, rash, and urticaria, abdominal pain, anorexia, constipation, hepatitis, malaise, mild transient abnormalities in liver function tests, nausea, parotitis, pseudo-obstruction (including colonic pseudo-obstruction), salivary gland pain, vomiting, decreased sexual activity, difficulty in micturition, erectile dysfunction, loss of libido, nocturia, and urinary retention, thrombocytopenia, gynecomastia, transient elevation of blood glucose or serum creatinine phosphokinase, weight gain, leg cramps and muscle or joint pain, dryness of the nasal mucosa, accommodation disorder, blurred vision, burning of the eyes, decreased lacrimation, and dryness of eyes.

The most frequent side effects of phenazepam use are drowsiness, sedation, muscle weakness, and ataxia. These side effects generally decrease on continued administration and are a consequence of CNS depression.

Less frequent effects include vertigo, headache, confusion, depression, slurred speech or dysarthria, changes in libido, tremor, visual disturbances, urinary retention or incontinence, gastrointestinal disturbances, changes in salivation, and amnesia. Some patients may experience a paradoxical excitation, which may lead to hostility, aggression, and disinhibition.

Jaundice, blood disorders and hypersensitivity reactions have been reported rarely. Raised liver enzyme values have occurred.

<u>Procedures at Pavlov – Implantable Naltrexone and Naloxone Challenge</u>

At this point the participant is started on study medication. Following CAH discharge, participants will come to PSMU to receive a 1000mg dissolvable naltrexone implant (IN). Participants will receive 4 naltrexone implants while in the study. Ideally, implants will be inserted every 10-12 weeks starting at week 4 post-study enrollment (weeks 4, 16, 28, 40), unless the participant relapsed. Relapse will be examined by self-report, evidence of fresh puncture marks, signs and symptoms of withdrawal or intoxication, and a urine drug screen that must be negative for opioids before receiving an implant. Participants will undergo a naloxone challenge at study visits during which the naltrexone implant is inserted and only if the participant's urine is opioid-free. If participant does not pass the naloxone challenge due to relapse, they will be referred to detox and will be invited to return upon completion of that treatment for a repeat naloxone challenge. Naltrexone implantation is an outpatient procedure to be conducted on site by a surgeon with the assistance of a study nurse. The implant will be inserted under the skin in the abdomen through a 1cm incision. The site will be treated with a local anesthetic prior to

insertion. The implant site will be inspected 7-11 days later when the participant returns for removal of sutures. Participants will receive discharge instructions to help care for the insertion site at home. Details on the procedure are presented at the end of this section.

Medication Risks

The most serious risk of naltrexone (both implant and injection) is the potential for hepatocellular injury when taken in excessive doses (the margin of separation between the apparently safe dose of naltrexone and the dose causing hepatic injury may be only five-fold or less). Harm is less likely at the dosage provided in this study. In alcohol dependence trials, liver enzymes that are initially elevated (likely due to excessive alcohol use) decreased in participants taking naltrexone.[4] As a precaution, participants will have ALT and AST repeated at implant visits 2,3, and 4, and if either liver enzyme is >5 times the upper limit of normal, results will be shared with participant during their suture removal visit and a repeat test will be done during their next medication visit. If any repeat test result is again >5 times the upper limit of normal, or if a patient is symptomatic (e.g. fatigue, anorexia, jaundice, nausea, vomiting, dark urine, light stool, abnormal pain), the patient will be referred to a hepatologist for further evaluation and a recommendation about continuing study medication. We expect this situation to be rare or non-existent based on prior experience with naltrexone. These precautions, combined with frequent contact with study staff, will provide thorough monitoring and appropriate response if evidence of liver damage emerges in the course of the study.

Normal ranges:

AST: Male: to 38 units/L; Female: to 32 units/L

ALT: Male: to 41 units/ L; Female: to 31 units/L

Exposure to naltrexone can precipitate severe withdrawal if the participant is physiologically dependent on opioids. To avoid unintended withdrawal, participants will be given a naloxone challenge prior to starting naltrexone, as described earlier.

Though data from the Lucey et al study (2008) using injectable naltrexone showed no effect of nonsteroidal anti-inflammatory drugs (NSAIDs) in patients taking naltrexone,[5] other studies have shown that non-steroidals taken with naltrexone can increase the chances of liver damage. As a precaution, participants will be warned of this possibility and advised to take NSAIDs only if necessary, and to take low doses if use of these medications is necessary. Non-steroidal use will be recorded so that the potential for such interactions can be evaluated.

There is also the possibility that participants will experience side effects from the antiretroviral treatment that they receive as a result of participating in HIV care. The fact that naltrexone is metabolized by extra hepatic sites suggests that interactions with antiretroviral medications are unlikely, though the possibility for interactions at the level of excretion by the kidneys or other sites exists since no studies have been done to examine them. The effect of naltrexone on HIV replication is unknown, though a study done by Xu Wang et al did not find an increase in viral replication associated with naltrexone.[6] If adverse interactions occur, they are likely to be detected quickly since patients will be seen monthly and tested for viral load, CD4 count, and liver enzymes at specified intervals.

If a participant chooses to try to override the opioid blockade with high doses of illicit opioids, s/he risks potentially fatal overdose. Also, after a course of naltrexone treatment, the participant may be more sensitive to opioids, which, again, if used, could lead to overdose. These possibilities will be explained to participants in the consent form.

The most common side effects of injectable naltrexone are a reaction at the injection site (could be pain, tenderness, swelling, redness, and/or itching) and nausea. Other common side effects are: headache, fatigue, dizziness, vomiting, decreased appetite, painful joints and muscle cramps.

Other common adverse effects of injectable naltrexone (>5%) versus placebo, respectively, include nausea (33% vs 11%), vomiting (14% vs 6%), decreased appetite (14% vs 3%), headache (25% vs 18%), dizziness (13% vs 4%), asthenia (e.g. malaise and fatigue 23% vs 12%), anxiety (12% vs 8%) and depressive symptoms (8% vs 4%). Additional risks are injection site reaction (including pain, tenderness, induration, swelling, erythema, bruising or pruritis), joint pain/stiffness (12% vs 5%), and muscle aches or cramps (8% vs 1%). These effects are generally mild and are responsive to dose reductions and/or symptomatic therapies. Any injection site reaction (vs placebo) occurred in 69% vs 50%, but pruritis occurred in 10% vs 0%, nodules/swelling 15% vs 4%, pain 17% vs 7%, induration 35% vs 8%.

The most common side effect of the implant is mild/moderate local irritation, including pain, redness, swelling, bruising, or infection, lasting 2-3 days. A low dose of triamcinolone is part of the implant formulation to minimize this risk and local irritation has not been a significant problem. Precautions taken to minimize the risk of infection include having a physician insert the implant using sterile disposable equipment in a room used only for phlebotomy and minor surgery with thorough cleaning of the site before and after the procedure.

The small dose of triamcinolone added to the naltrexone implant to prevent inflammation has not been associated with complications.

Other potential side effects of implantable naltrexone are: loss of appetite, nausea, vomiting, diarrhea, constipation, abdominal pain, liver dysfunction, tachycardia, hypertension, phlebitis, headaches, weakness, sleep disorder, anxiety, giddiness, depression, dysphoria, runny nose, coughing, difficulty with breathing, edema, acne, itching, retardation of ejaculation, decreased potency, increased or decreased libido, shivering, tremor, joint pain, local aseptic inflammation, increase of lymphatic nodes, relapse of hemorrhoids.

For implantable naltrexone, non-surgical side effects were documented among patients who remained in treatment and were reported in 15.7% of the patients in the implant group, 3.9% of the patients in oral naltrexone group ($p<0.01$), and 6.9% of the patients in placebo group (no significant difference to other groups). The most common adverse events were abdominal discomfort, nausea, and drowsiness; none required any medication for treatment.

The proportion of surgical adverse events (i.e., wound infections or local site reactions) with the number of patients as denominator were significantly higher in naltrexone implant group: 10.8% compared to 1.0% in the placebo group ($p=0.02$) and 1.0% in the oral naltrexone group ($p=0.002$).

The following serious adverse events of lidocaine have been most commonly reported:

Central nervous system: lightheadedness, nervousness, apprehension, euphoria, confusion, dizziness, drowsiness, ringing in the ears, blurred or double vision, vomiting, sensations of heat, cold or numbness, twitching, tremors, convulsions, unconsciousness, respiratory depression and arrest.

Cardiovascular system: slow heart rate, low blood pressure, cardiovascular collapse, which may lead to cardiac arrest.

Allergic reactions: skin lesions, rash, edema. Allergic reactions as result of sensitivity to lidocaine hydrochloride are extremely rare.

Naltrexone Implant Procedure

1. Naloxone Challenge - observe for signs of withdrawal
2. Local Anesthesia
    a. Wash hands with antimicrobial soap
    b. Apply antimicrobial handcream
    c. Apply non-sterile gloves
    d. Cleanse skin with antimicrobial wipe
    e. Cleanse skin with isopropyl alcohol
    f. Inject area with 2% lidocaine 5cc syringe with a 25g x S" needle under ~ 1" of skin
3. Pellet insertion
    a. Apply antimicrobial handcream
    b. Apply non-sterile gloves
    c. Open packet of sterile supplies
    d. Prepare Area with 3 sterile betadine swabs
    e. Apply sterile gloves
    f. Apply sterile drapes
    g. Make ~1cm incision with sterile #15 scalpel
    h. Inject 5cc of 2% lidocaine in 5cc syringe with a 18g x 1 S" needle through the wound in a medial direction anesthetizing a tract through which to insert the pellet insertion device.
    i. Insert sterile pellet within sterile insertion device
    j. Close wound with stitches

4. Clean and dress wound
5. Provide wound care instruction sheet to patient

Implantation Discharge Instructions

1. Wash hands before touching site.

2. Keep clear dressing over pellet site for 24 hours.

3. Pull dressing off after 24 hours.

4. Clean with soap and water as usual in shower every day.

5. Make sure stitches stay dry - pat dry after shower.

6. Pour peroxide over stitches after shower.

7. Stitches will be removed when you return to Pavlov 7-11 days after implantation.

For redness or swelling in first 24 hours use ice. May use over the counter pain relievers such as Tylenol, Ibuprofen, Naproxen Sodium.

Bruising may occur on abdomen secondary to numbing medication administration.

If pellet site bleeds, hold pressure over site. Ice will also help stop bleeding at site.

If pellet site irritated during working hours - cover with band-aid during day - keep site open to air at night (No band-aid).

Notify office if fever develops, redness or swelling occur, or any discharge occurs.

Counseling

Assessors will administer brief counseling (~5 minutes) to participants during the medication visits. The brief counseling will be conducted by study RAs (addiction psychiatrists) based on standard clinical protocols.

3.4 Control Group

Participants in the control group will receive standard care as normally provided to patients in the narcology hospital. This could include detoxification with medications, substance use counseling and treatment for comorbid psychiatric conditions, as well as possible inpatient rehabilitation for up to 30 days. They will also be given printed information, including phone numbers, on places that provide HIV medical care and will be referred to outpatient narcology care. Detoxification takes 5-7 days, most commonly using clonidine, antidepressants, non-opioid analgesics, hypnotics, and Imodium. Stabilization occurs within the same ward, takes 1-2 additional weeks, and includes drug counseling and treatment of comorbid psychiatric problems. Upon hospital admission, HIV testing is routinely performed in all patients who are not documented to be HIV-positive. Prior to discharge, those identified as HIV-positive

are given contact details for an HIV clinic, not an appointment. Upon discharge, patients are encouraged to receive outpatient narcology treatment, monthly, for 1 year. If control participants are newly diagnosed with HIV infection at the CAH, they will receive HIV post-test counseling consistent with CDC recommendations. Participants who visit the AIDS center will be able to receive ART medication provided they undergo required pre-ART testing and examinations. Enrollment in the study will not preclude participants from receiving any HIV or narcology care that would normally be accessible to them.

3.5 MEDICATION CONSIDERATIONS

3.5.A SYMPTOM MONITORING

The study staff (research clinicians [addiction physicians with extensive experience performing pharmacotherapy trials]) have extensive experience administering implantable and injectable naltrexone, and specimen collection via prior OUD pharmacotherapy studies. They will be trained to assess for adverse medication effects and will follow established protocols for identifying and monitoring any ongoing adverse events, including referral to treatment as appropriate. Study participants will be actively monitored for adverse events. Symptoms will be monitored every four weeks (and more frequently, if necessary) by trained clinical staff, while the participants are administered study medications.

3.5.B. DISCONTINUATION OF STUDY MEDICATION

Despite known side effects of naltrexone (both implant and injectable), most people taking the medications do not discontinue them due to side effects. Those who discontinue medication will be followed and analyzed by intention to treat.

Participants found to be pregnant during the study will have their study medication (i.e., naltrexone) discontinued (including removal of the implant if necessary), but will still be followed-up for the duration of the study. Participants who report pregnancy outside of study visits will be requested to come to Pavlov for a confirmatory pregnancy test where the need for implant removal will be assessed and the implant may be removed if deemed necessary.

3.6 SCHEDULE OF DATA COLLECTION

Intervention Group							
		Pre-screen	Screener and Baseline	Implant visits	Medication Checks (every 4 weeks post implant)	6-month visit (24 weeks)	12 month visit (52 weeks)

			Screener	Baseline				
Screening	Verification of HIV, pregnancy, AST/ALT	X						
	Screening Questions		X					
Enrollment	Sign Informed Consent		X					
	Complete contact information/verify numbers			X				
	Randomization			X				
Laboratory	Clinical Values			X	X	X	X	X
	Pregnancy Test		X		X	X	X	X
	Urine Drug Test			X	X	X	X	X
	CD4			X			X	X
	HVL			X			X	X
	ALT/AST				X			
Assessment	Full Study Assessment			X			X	X
	Qualitative Assessment			X			X	X
	Medical Record Review	X					X	X
Intervention	Symptom Management/Adverse Events			X	X	X	X	X
	Naloxone challenge			X	X			
	Naltrexone Injection			X				
	Naltrexone Implant				X			
	Brief Counseling				X	X	X	X
Other	Compensate for Participation			X	X	X	X	X
	Provide Resource Card			X				
	Report Adverse Events			X	X	X	X	X
	Complete Tracking Forms			X	X	X	X	X

Control Group						
		Pre-screen	Screener and Baseline Visit		6 mo (24 weeks)	12 mo (52 weeks)
			Screener	Baseline		
Screening	Verification of HIV, pregnancy, AST/ALT	X				
	Screening Questions		X			
Enrollment	Sign Informed Consent		X			
	Complete contact information/verify numbers			X		
	Randomization			X		
Laboratory	Clinical Values			X	X	X
	Pregnancy Test		X			
	Urine drug Test				X	X
	CD4			X	X	X
	HVL			X	X	X
Assessment	Full Study Assessment			X	X	X
	Qualitative Assessment			X	X	X
	Medical Record Review	X			X	X
Other	Provide Resource Card			X		
	Compensate for Participation			X	X	X
	Complete Tracking Forms			X	X	X

3.6.A. VISIT WINDOWS

Research Assessment Windows for Intervention and Control Group

6 Month (24-week) Visit

- Window open: 120 days post baseline
- Target date: 180 days post baseline
- Window close: 270 days post baseline
- Window length: 150 days

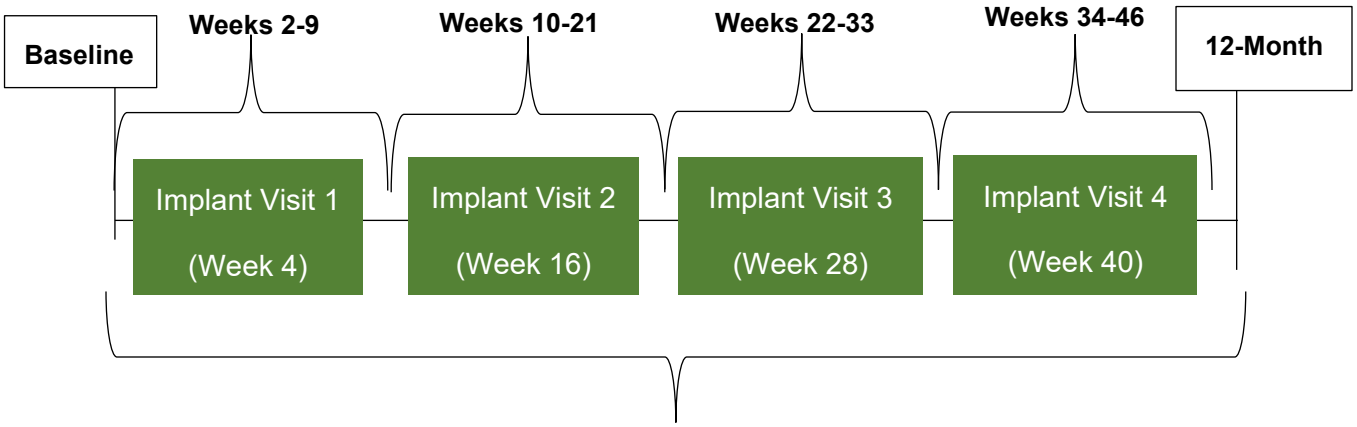
12 Month (52-week) Visit

- Window open: 271 days post baseline
- Target date: 365 days post baseline
- Window close: 455 days post baseline
- Window length: 184 days

Intervention Group Medication Visit Windows

Implant visits will take place 10-12 weeks apart starting with week 4. Ideally, implant visits will occur 4, 16, 28, and 40 weeks post enrollment, but we will accommodate the following windows.

Naltrexone Implant Windows



Study Timeline

(52 Weeks)

Medication visits will take place every 4 weeks following the implant visit, with ideally 2 medication visits after each implant

Windows listed above are used as guides for scheduling visits, but early/late visits are expected due to participant/laboratory scheduling.

3.7 DATA SOURCES

3.7.A QUESTIONNAIRES

Questionnaires will be administered at baseline, 6-, and 12-month study visits to collect information about participant demographics (e.g., age, gender), general and mental health and health-related behaviors such as substance use.

Questionnaires for providers are described in section 5.3 SYSTEM-LEVEL ASSESSMENT OF LINC-II IMPACT.

3.7.B. BLOOD

Blood will be collected at baseline, implant visit 2, 3, and 4, and 24 and 52 weeks to assess the following:

1. CD4, HIV-1 RNA
    a. Measured at baseline, 24- and 52-week study visits among control and intervention participants. Samples collected at City Addiction Hospital (baseline) and Pavlov University (follow-up) are sent to the City AIDS Center for testing. Results from the testing are placed in participant medical records at City AIDS Center and provided to the Pavlov University research team.

i. If CD4 and HVL results are already available at the City AIDS Center within the 24- and 52-week visit windows, a new study test will not be conducted and existing results will be used.
ii. If recent (within one month) CD4 and HVL results are available at the City AIDS Center, a new baseline study test will not be conducted and existing results will be used.
iii. If a participant is unable to provide blood during their 6 or 12 month study visit and does not have a blood draw scheduled at the City AIDS Center within the study visit window, we will take the following approach:
    1. Control group: Participant will be invited to come in for a second blood draw attempt in 4 weeks. Participants will receive compensation in the amount of 500 rubles to cover costs associated with traveling to the laboratory.
    2. Intervention group: A second attempt at a blood draw will be made in 4 weeks (at their scheduled 28 week medication visit or after the completion of the 12 month visit). At the 28-week visit, participants will receive planned compensation for attending the medication visit but will not receive additional compensation for the blood draw. For the second attempt after the 12 month visit, participants will receive compensation in the amount of 500 rubles to cover costs associated with traveling to the laboratory.
iv. If a participant is unable to provide blood during their 6- or 12-month study visit due to COVID-19 restrictions and does not have a blood draw scheduled at the City AIDS Center within the study visit window, we will take the following approach:
    1. Control group: Participants will be invited back to Pavlov for a blood draw once restrictions are lifted. Participants will receive compensation in the amount of 500 rubles to cover costs associated with traveling to the laboratory.
    2. Intervention group: A blood draw attempt may be made during a medication check-in visit, if one is scheduled. In which case, participants will receive planned compensation for attending the medication visit but will not receive additional compensation for the blood draw. If a blood draw does not take place during a scheduled medication visit, or if no visit is scheduled, participants will be invited to come to Pavlov once restrictions are lifted. For the blood draw attempt outside of their scheduled visit, participants will receive compensation in the amount of 500 rubles to cover costs associated with traveling to the laboratory.
v. If CD4 and HVL results are available in participant's medical chart at the CAC, we will enter them as part of the Chart Review process.

2. AST, ALT
    a. AST/ALT will be measured only among intervention participants during implant visits 2, 3, and 4 to assess liver toxicity.
3. HIV Antibody Test
    a. If a participant has an undetectable HIV viral load at baseline, an HIV antibody test will be conducted during their next study visit to verify their HIV status.

3.7.C. URINE

A pregnancy test will be administered by trained clinical research staff to all participants at screening and at each study visit for intervention participants. Pregnant women will be excluded from the study due to some reports suggesting possible adverse events with study medications. Participants found to be pregnant may have their implant removed but will still be followed-up for the duration of the study. For these participants the naltrexone implant will be removed (if removal is indicated) by clinical staff at Pavlov.

Urine will also be used to conduct urine drug testing on all intervention participants at all study visits and for control participants at the 6 and 12-month study visits. Urine drug tests must be negative for opioids before participants can receive the implant. Urine toxicology will test for a range of opioids, specifically opiates (products of the poppy plant – morphine, heroin, codeine) and synthetic opioids (specifically methadone). If new opioids appear on the scene in Russia, such as fentanyl, then we will begin testing for this, but currently that is not thought to be an issue.

3.7.D. MEDICAL RECORD REVIEW

Medical chart review will be utilized to obtain HIV and addiction care and treatment history. Medical records will be reviewed at screening, 6- and 12-months. All LINC-II participants' medical records will be reviewed including those who have withdrawn from the study unless participant refuses future chart review at the time of withdrawal. The timeframe of the chart reviews for the withdrawn participants will be done one time at the conclusion of the 12-month study window. At the time of withdrawal, research assessor will ask permission to continue to perform chart review at the City AIDS Center and document this permission on the Study Conclusion Form.

4. STUDY PROCEDURES

4.1 RECRUITMENT

Participants enrolled in Linking Infectious and Narcology Care – Part II (LINC-II) study will be recruited from St. Petersburg City Addiction Hospital (CAH), an inpatient narcology hospital in St. Petersburg, Russia.

Qualitative assessment:

In addition to the 240 RCT participants, we will also recruit providers and administrators from HIV and narcology care systems to participate in surveys and in-depth interviews at study launch and 12-and 24-months post-launch to explore their perspectives and experiences with care coordination between the narcology and HIV care systems. The assessment will consist of a short survey and a qualitative interview. At study launch, all available providers and administrators from the CAH and CAC will be

invited to participate in the short survey (approximately 50 participants). A subset of providers/administrators will be invited to participate in a qualitative interview, more specifically, we will aim to interview the following from each care system: 1 administrator, 3 doctors, 1 social worker or other frontline staff. Twelve and 24 months post study launch a subset of providers and administrators, who have been exposed to the LINC-II study, will be invited to participate in the survey and a qualitative interview. We aim to survey and interview the following from each care system: 1 administrator, 2 doctors, 1 social worker or other frontline staff. An effort will be made to ensure that the qualitative assessment is representative of the whole sample in terms of provider experience, such that we would like 50% of the providers to be "junior" (less than 10 years of experiences) and 50% to be senior (>10 years of experience). We will keep a record of the total number of participants who declines and the reasons for declination. Providers and administrators will be approached by a research assessor at their place of employment (HIV or narcology care location) and invited to participate in the survey and interviews.

A subsample of LINC-II patient participants (n=30) will be purposively selected by research assessors, based on their comfort and capacities to discuss HIV and/or narcology systems of care, to participate in in-depth interviews and to ensure representation of a variety of potentially relevant characteristics such as gender and duration of HIV infection. We will select 15 from each arm (5 at each time point: baseline, 6-months, 12-months) to ensure equal representation of control and intervention participants. LINC-II participants will be invited to participate in the qualitative component of the study following their baseline and follow up study interviews. Study staff will be trained to identify participants who are 1) willing and able to communicate appropriately in an interview; and 2) insightful about structural issues around narcology and HIV care. At follow up, only participants who reported having an HIV care visit in the past 6 months during the study interview are eligible to participate in the qualitative interview. We will also monitor recruitment of participants into the qualitative component to ensure that we have representation of the whole sample in terms of gender (roughly 2 women and 3 men at each time point). We will also keep a record of the total number of participants who decline and the reasons for declination. The interview will occur a day or two after their baseline visit (while the participant is hospitalized). Efforts will be made to interview participants from the intervention group after the first case management session has taken place .Once participants are recruited and consent to study participation, they will be assessed in a private location by research staff trained in qualitative methods. Interviews at 6 and 12 months will take place at Pavlov State Medical University.

Qualitative In-Depth Interviews in LINC-II					
	Baseline, study launch	**6 months**	**12 months**	**24 months post launch**	**Total**
Participants	5 intervention 5 controls	5 intervention 5 controls	5 intervention 5 controls		30
Providers	2 admins (1 narcology, 1 HIV) 3 narcologists 3 infectionists 2 frontline cadre (e.g., nurse, social worker)		2 admins (1 narcology, 1 HIV) 2 narcologists 2 infectionists 2 frontline cadre	2 admins (1 narcology, 1 HIV) 2 narcologists 2 infectionists 2 frontline cadre	26

4.2 SCREENING

Recruitment will take place at two or more departments of the City Addiction Hospital where the admissions department directs patients who have HIV and an Opioid Use Disorder. To assist the team in understanding patient flow, admissions department staff will provide the team with information on the number of patients admitted to CAH who have HIV and an Opioid Use Disorder (OUD) out of the total number of admissions. All HIV-positive patients with an OUD admitted to the detoxification/rehabilitation departments where study staff are based at the City Addiction Hospital are eligible for screening. Patients will be screened three to five days after admission to the narcology hospital and after treatment for most severe initial withdrawal symptoms.

Screening for the LINC-II study will take place in two steps: 1) a pre-screen conducted through chart review and 2) in-person screening of participants who are eligible following the pre-screen.

Pre-screening will be conducted by narcologists (Addiction Physicians) within the department. They have access to medical charts and will be trained on the research protocol by the Russian and US study investigators. The narcologist will search in the electronic study system for the name of the patient prior to screening him/her for the study to see if the patient has been previously enrolled in LINC-II. This is to prevent double randomization. If the name does not appear in the system, the narcologist will proceed with pre-screening procedures. If HIV status is unknown in the medical record, the narcologist will wait until test results conducted at the narcology hospital are completed.

Research Assessors (RAs) who are Addiction Hospital staff (psychologists not involved in the patient's care) will be conducting the in-person screening process. If a patient is identified by the narcologist as meeting criteria based on chart review, the narcologist will notify the RA that the patient in their department is available to be screened for the study. RA will be introduced to the patient by the narcologist and will then meet with the patient in a private location (e.g. hospital room or exam room) to briefly describe the study and conduct in-person screening to confirm the presence of inclusion criteria and the absence of exclusion criteria. We will not write down names and room number of potential participants.

If a patient is sick and/or still in withdrawal when approached for screening, the RA will re-approach that person every day (if the person is interested) while the patient is still at the CAH (as in, once the person is eligible for screening and/or eligible for the study, they should be enrolled once they are feeling better).

We will not keep a list of names screened to prevent re-screening. We will include a note in the participant's medical chart that s/he was screened for the study to make sure that s/he is not approached again during the same visit.

Protocol for ensuring double randomization and double enrollment do not occur

1. Prior to screening, narcologist must confirm that the patient's chart does not contain a note that the patient was already screened for the LINC-II study during this hospital stay. If such a note has been filed, narcologist does not proceed with screening.

2. Narcologist searches the name of the patient in the LINC-II Tracking Website to confirm that the patient has not been previously enrolled in the LINC-II Study. If a match appears, narcologist checks DOB and address (this will be done very confidentially, so that the patient does not know that there is someone with the same last name already in the study, to protect the confidentiality of the enrolled participant). If no match is found, narcologist proceeds with screening.

4.3 INFORMED CONSENT

Research assessors (RA) will conduct the consent process as well as obtain written consent. After eligibility and interest in enrollment is determined, an RA will administer and document the informed consent of the participant in a private location. If participants are unsure whether they would like to participate, they will be allowed any amount of time they need to consider participation in the study. If the participant is not able to make a decision on the day of the initial visit, s/he will be invited to contact the study team once s/he have made their decision. The study will be explained to eligible participants who will be offered participation in the study. Research assessors will answer any questions the patients may have including risks, benefits and alternatives (including non-participation) to participation, and will provide written materials describing the study. The written informed consent (in Russian), including the risks, benefits and alternatives, will be signed and dated by the participant and the research assessors. A signed copy of the informed consent will be provided to the participant, and a copy will be maintained by the research team. Potential participants will be informed that refusal to participate will not affect their medical care in any way and they will be informed of their right to drop out of the study at any time.

For administrators, providers, and participants invited to participate in in-depth interviews, informed consent will be administered by RAs from PSMU in a private location. If participants are unsure whether they would like to participate, they will be allowed any amount of time they need to consider participation in the study. If the participant is not able to make a decision on the day of the initial visit, they will be invited to contact the study team once they have made their decision. The study will be explained to eligible participants who will be offered participation in the study. Research assessors will answer any questions the participants may have including risks, benefits and alternatives (including non-participation) to participation, and will provide written materials describing the study. The written informed consent (in Russian), including the risks, benefits and alternatives, will be signed and dated by the participant and the research assessor. A copy of the informed consent will be provided to participant, and a copy will be maintained by the research team. Potential participants will be informed that refusal to participate will not affect their medical care or employment in any way and they will be informed of their right to drop out of the study at any time.

4.4 VISIT FLOW

After eligible participants are consented and enrolled, the following will take place at the **Baseline visit and while participants are still hospitalized at the City Addiction Hospital**:

- Collection of locator/contact information and verify contact phone numbers
- Collection of clinical data (height, weight, blood pressure)
- Administration of assessment questionnaire
- Randomization
- Provision of resource card
- **Subset of all participants:** In-depth interview
- Compensation and scheduling next visit
- Blood draw (CD4, HVL)
- Intervention procedures (medication procedure, meeting with case manager, ART initiation procedures)

Intervention Group:

- At the **medication visits,** the Pavlov RA will perform the following:
    - Review and update locator/contact information, verifying new numbers, as necessary
    - Collect a urine sample to check for pregnancy and conduct drug testing
    - Collect clinical data (weight, blood pressure)
    - Assess opioid use
    - Perform symptom monitoring (including inspection of implant site) and brief counseling
    - Compensate participant and schedule next visit

- In addition to the above, at the **implant visits,** the Pavlov RA will perform the following:
    - Administer naloxone challenge
    - Provide naltrexone implant
    - Implant visits 2, 3, and 4: send participant for phlebotomy to check ALT/AST levels

- During the **24-, and 52-week assessments,** in addition to the medication visit procedures described above, the Pavlov RA will:
    - Send participant for phlebotomy (CD4, HVL)
    - Administer assessment questionnaire
    - **Subset of all participants:** In-depth interview

Control Group:

- During the **24-, and 52-week assessments,** the Pavlov RA will:
    - Review and update locator/contact information, verifying new numbers, as necessary
    - Send participant for phlebotomy (CD4, HVL), collect clinical data (weight, blood pressure)
    - Administer assessment questionnaire
    - Conduct urine drug test
    - Compensate participant and schedule next visit
    - **Subset of all participants:** In-depth interview

4.5 QUALITY ASSURANCE

Informed consent quality assurance

The RA will review Informed Consent Forms (ICFs) for completeness with the participant present. Items to check will include, but are not limited to: responses/initials collected for all questions, correct version of ICF used, signed and dated by both subject and RA. Local Study Coordinator will review all completed consent forms weekly and will complete the Consent Form Deviation log if any errors are identified.

Assessment quality assurance

During the assessment, if the participant provides conflicting answers or answers that did not make logical sense (either within the same section or between sections), the RA will gently try to help the participant arrive at more logical answers. However, the RA will not force the participant to change his or her answers. Certain quality assurance checks are built into the assessment. The system will flag any inappropriate responses and prevent the RA from continuing until the issue is resolved. The RA will review the self-administered section with the participant present. If many "refused" options are selected, the RA will offer the participant the opportunity to complete those sections (the RA will accept the participant's refusal if he or she does not wish to complete the section). The RA will never guess to correct a mistake. The only instance when a change can be made to the completed assessment is in the event that the RA is 100% certain that an error was made in data entry. Local data manager will QC all paper forms used for the assessment (i.e., rulers for VAS, TLFB calendar, pain rulers). Upon completion of QC of paper forms, the reviewer will write their initials and date of review at the bottom of the forms.

CM intervention quality assurance

We will evaluate fidelity of the intervention through 1) observations of encounters with participants by CMs via audiotaped recordings of all sessions, reviewing the first 3 sessions for each CM; and 10% thereafter; 2) review of CM session checklists; 3) feedback based on observations and staff meetings, provided by the interventionist supervisor, Dr. Toussova, using a strengths-based supervision approach; and 4) survey on program satisfaction, completed by the interventionists (every 3 months) and all study participants at 6 and 12 months. If concerns between participant and staff arise, reassignment to an alternate CM is possible, but efforts will be made to maintain the same CM who initiates contact with each intervention participant. Collecting these data will enable quality control by the research team and pragmatic feedback for the program staff to maintain high quality and standardization of treatment conditions.

4.6 COMPENSATION

Participants will be compensated for their time and travel with 1000 rubles in goods or currency at baseline, 500 rubles in cash or goods at medication visits, 1500 rubles at medication visits in which implantable naltrexone is inserted, and 2000 rubles for their participation at 24 and 52 week follow-up

visits. Participants who complete phone assessments for the follow-up visits will be compensated 500 rubles for their participation (this will be offered as a last resort option for 24- and 52-week assessments).

In the event that baseline compensation is not received at the City Addiction Hospital due to early discharge, it will be provided in full at the next study visit.

If a participant is unable to provide blood during their 6 or 12 month study visit and does not have a blood draw scheduled at the City AIDS Center within the study visit window, we will take the following approach:

- Control group: Participant will be invited to come in for a second blood draw attempt in 4 weeks. Participants will receive compensation in the amount of 500 rubles to cover costs associated with traveling to the laboratory.
- Intervention group: A second attempt at a blood draw will be made in 4 weeks (at their scheduled 28 week medication visit or after the completion of the 12 month visit). At the 28-week visit, participants will receive planned compensation for attending the medication visit but will not receive additional compensation for the blood draw. For the second attempt after the 12 month visit, participants will receive compensation in the amount of 500 rubles to cover costs associated with traveling to the laboratory.

Providers and administrators will be compensated 500 rubles in goods or currency for completing the system-level survey. Participants and providers/administrators will be compensated 1500 rubles for their participation in each qualitative interview.

Similar compensation has been used in a previous collaborative Russian-Boston research study and was deemed by the PSMU IRB to be an appropriate, non-coercive amount of funds for involvement in a clinical research project.

Phone assessments will be completed by participants who are unable to come in to Pavlov due to restrictions related to COVID-19. Participants will receive full compensation for these phone assessments. Upon the restrictions being lifted, participants will be invited back to Pavlov to complete 6- and 12-month blood collection if they did not have a blood draw scheduled at the City AIDS Center within the study visit window. Participants will receive full compensation for completing these phone assessments. Participants in the control group will receive an additional 500 rubles to cover costs associated with traveling to the laboratory. Participants in the intervention group will not receive additional compensation for the blood draw if the blood draw takes place during their scheduled visit (for which they will already be receiving compensation). For the blood draw attempt outside of their scheduled visit, participants will receive compensation in the amount of 500 rubles.

4.7 RETENTION

Baseline visit: Retention begins at baseline by ensuring that the participant enjoys the experience of participating in the study, by explaining the informed consent and what would happen in the study, and by collecting excellent contact information, including both the address where the participant is registered and the address where the participant is currently staying. Participants will be asked to provide contact information for 4-5 alternative contacts (although only 2 will be required as per eligibility criteria), who

may know their whereabouts. Alternative contacts can include friends, family members, and social workers. Participants will be asked if any of their friends are participating in the study and to include them as alternative contacts, if possible. Contact numbers must be verified by calling the numbers with the participant present, using the following script: "I work with a team at Pavlov University. Your friend/relative [NAME] is here with me and just enrolled in a study. He/she has listed you as an alternative contact. We will only call you if we are having trouble reaching [NAME] to see if you can help us connect with them. Today I am just calling to confirm that this number is active."

Participants will also be asked for their email address and membership to any social networking platforms.

All visits: Participants will be offered tea, coffee, water, and snacks at each study visit to make their experience in the research study more enjoyable.

RA will offer to help participants add the next scheduled study visit to the calendar in their phone and set a reminder in their phone.

Follow up visits: Contact information for participant and alternatives will be reviewed and updated at every visit.

Other strategies: Participants will be contacted by telephone with appointment reminders and email if one is provided. The study team will also utilize social networking to connect with participants. If participants are unable to be reached via phone, in addition to attempting to reach them via text messaging and email, participants will be sent private messages on Vkontakte (Russian social network) utilizing an existing standard script to remind them of their upcoming study visit. No sensitive information will be revealed or ascertained using this method.

Standard reminder text: This is a reminder that your visit to Pavlov Medical University is scheduled for____at_____. Please reply to confirm or call 973-53-96 to reschedule.

Study participants will be asked to contact the study team if their phone number changes between study visits; participants will be compensated 200 rubles in goods or currency for this information. All no-shows will be followed up to reschedule appointments.

Transportation will be arranged (i.e., a social taxi or Uber) for participants who are unable to come to First St. Petersburg Pavlov State Medical University due to a lack of available transportation.

5. ASSESSMENTS

5.1 BASELINE ASSESSMENT

The baseline assessment will be conducted immediately following the screening and informed consent. The assessment will be interviewer-administered with the exception of sections deemed to ask sensitive questions, which will be self-administered by the participant.

Participants will be assessed as part of this study using validated interview instruments covering the following topics:

- Demographics, modified from the ASI Lite-CF Clinical/Training Version and Addiction Severity Index[7]
- Opportunistic Infections, using questions adapted from the HIV Cost and Services Utilization Study (HCSUS)[8]
- HIV Testing and HCV Diagnosis, using the HIV/HCV/STI Testing Status and Organizational Testing Practices Questionnaire[9]
- Healthcare Utilization, using questions created by the Russian and US teams
- Barriers to Medical Care [10]
- Perceived Discrimination in Health Care[11]
- ART Use and Adherence[12, 13]
- Medications
- Pain Assessments[14-16]
- Reproductive Health
- HIV Sex Risk Behaviors, questions are adapted from the Women's Health Coop Baseline Questionnaire
- Sexual Partners, created by the US and Russian teams
- HIV Risk Categories, using questions adapted from the American Red Cross and Navaline et al.[17]
- HIV Disclosure, using questions from Stein et al. (1998)[18] and Raj et al. (2006)[19]
- HIV Stigma, using the Berger et al. HIV stigma scale[20]
- Substance Use Stigma[21, 22]
- Depressive symptoms through the Center for Epidemiologic Studies Depression Scale (CES-D)[23, 24]
- Anxiety by the State Trait Anxiety Inventory (STAI- Short Form)[25]
- Partner Violence and Sexual Assault, adapted from the TAJ assessment
- Tobacco Use, using a shortened modified Fagerstrom Test for Nicotine Dependence[26, 27]
- Alcohol Use, via the AUDIT[28]
- Opioid use disorder diagnosis via the DSM 5 criteria[29]
- Drug use by an adapted version of the Risk Behavior Survey[30, 31]
- 30-Day Timeline Followback for Opioid Use[32, 33]
- Overdose and Suicide, using adapted questions from Britton et al. (2012)[34]
- Social Support, using the harmonized STTR document[35, 36]
- VR-12 Health Survey & MOS-HIV[37, 38]
- Primary Activity
- Costs of Illness and Treatment in Last Month
- Attitudes Toward Care Coordination, using questions from Schang et al. (2013)[39]
- Care Continuity, modified from Nijmegen Continuity Questionnaire[40]

5.2 FOLLOW UP ASSESSMENTS

Content of assessments administered at the 6-, and 12- month visits will be subsets of the baseline assessment (see table below). Phone assessments will be permitted for 6 and 12 month (24 and 52

weeks) assessments, as a last resort, for participants who are unable to come in-person. Questions about COVID-19 will only be asked at one time-point, either the 6- or 12-month assessment.

	Study Time Point			
Administered Assessment	**Baseline**	**Medication Check-Ins**	**6-Month**	**12-Month**
Demographics	X			X
HIV Testing and HCV Diagnosis	X			X
ART Use and Adherence	X		X	X
Health Care Utilization	X		X	X
Costs of Illness and Treatment in Last Month	X		X	X
Attitudes Toward Care Coordination & Care Continuity	X		X	X
Barriers to Medical Care	X		X	X
Perceived Discrimination in Health Care	X		X	X
DSM-5 Opioid Use Disorder	X			
Drug Use	X		X	X
TLFB: Opioids	X	X	X	X
Tobacco Use	X			
Alcohol Use: AUDIT	X			X
Opportunistic Infections			X	X
Medications	X		X	X
Pain assessment			X	X
HIV Sex Risk Behaviors and Reproductive Health				X
*Sexual Partners	X			X
*HIV Risk Categories	X			
*HIV Disclosure	X		X	
*HIV Stigma	X			X
*Substance Use Stigma	X			X
*Barriers to Medical Care Part 2	X		X	X
*Depressive Symptoms (CES-D)	X			X
*Anxiety (GAD-7)	X			X
*Case Manager Questions			X	X
*Partner Violence and Sexual Assault			X	
Overdose and Suicide			X	X
Social Support Scale	X			
VR-12 Health Survey – MOS-HIV	X			X
Primary Activity	X		X	X
Visit Costs			X	X
COVID-19 Questions			X	X

5.2.A. MEDICATION VISITS ASSESSMENTS

Medication symptoms and opioid use will be assessed during the medication check-in visits.

5.3 SYSTEM-LEVEL ASSESSMENT OF LINC-II IMPACT

The system-level assessment will focus on provider, administrator, and patient perspectives and experiences with care coordination between the narcology and HIV care systems. System-level variables will be assessed from providers, administrators, and study participants (i.e., patients in the narcology or HIV care systems). Questions will assess demographics, role in the care system, attitudes toward care coordination, level of engagement in coordinated care, stigma toward patients with HIV and substance use disorders, and connection, if any, to LINC-II.

For the purpose of this study, care coordination will be defined as "the deliberate organization of patient care activities between two or more treatment settings involved in a patient's care to facilitate the appropriate delivery of health care services," referring in this case to the narcology and HIV care systems.

Providers and administrators will also be asked to what extent they are aware of LINC-II, if they have worked with a LINC-II CM, and what their experiences have been with LINC-II, including whether the presence of LINC-II had any other effects on the system, such as patient flow and patient engagement.

Surveys will be followed by an open-ended qualitative exploration to obtain details regarding perceptions of and experiences with care coordination, including concrete examples of connections between narcology and HIV care service delivery. It will explore organizational and systemic challenges that impede care coordination and opportunities to improve care coordination. Among LINC-II intervention participants, the role of LINC-II in addressing these issues and connecting people to both narcology and HIV care will be explored. We will conduct in-depth interviews with all providers and administrators and recruit a purposively chosen sub-sample of 30 participants from the LINC-II study. Interviews will be audio recorded, translated, and transcribed for analysis.

For administrators and providers in each system (n=26), all surveys and in-depth interviews will be conducted within 20-60 minutes and will occur at study launch, 12, and 24 months post-launch. This will not necessarily include the same providers and administrators at each assessment, in event of staff turnover. Written informed consent will be obtained prior to each interview. LINC-II study participants (N=240) will provide survey data on system perceptions at baseline, 6 and 12 month follow-up as part of their RCT study assessment. A subsample of participants selected for in-depth interview (n=30) will be interviewed subsequent to survey completion. Interviews will be audio recorded, translated, and transcribed for analysis. We will maintain a roster of interview refusals so as to consider potential biases in our sample of interviewees.

5.4 Estimates of Cost and Cost-Effectiveness

Costs will be measured from the provider perspective and will include the cost of all resources utilized for each study participant from the date of randomization for a period of 12 months. Average provider cost per patient will then be stratified by study arm and outcome to generate cost-effectiveness estimates with 95% confidence intervals.

Resource or outcome	Method for estimating unit cost or cost/outcome
Resources	*Method for estimating unit costs*
Medications, laboratory tests, and other supplies	Types of antiretroviral and narcology medications and other drugs dispensed to study participants and types of laboratory investigations performed between study enrollment and the primary 12-month endpoint will be extracted from individual study records and clinic records for the intervention arm and from self-report and clinic records for the control arm. For each medication dispensed, a unit cost will be assigned that represents local investigators' best estimate of the procurement prices that study sites would have to pay if they adopted the intervention as standard care, using data from invoices and local medication price lists. For each type of laboratory test, the fee charged to conduct the test will be used as its unit cost. If a fee schedule is not available, a cost/test will be estimated using an ingredients costing method. Laboratory tests that are done solely for research purposes and are not likely to be included if the intervention were adopted as standard care will be excluded. Supplies that are used for individual patient care will be assigned a unit cost from procurement invoices.
Outpatient visits	An average unit cost per outpatient visit to each type of facility will be estimated by dividing total clinical staff cost per month by the number of visits made to the facility that month. If data are available to stratify this estimate by purpose of visit or staff cadre required, this will be done, but the overall average has proven to be sufficient for outpatient settings. Clinical staff salaries (total cost to the employer) for each staff cadre will be obtained from the study sites or the administrative entity responsible for the sites' payrolls.
Case manager costs	As case managers are an intervention-specific resource, costs will be calculated from study invoices and expenditure reports and estimated as an average cost per session conducted. Case manager transport, SMS fees, and other costs associated with this component of the intervention will be included in the cost/session estimate. (Although every patient in the intervention arm will be assigned a case manager, some patients will complete all ten planned sessions, while others will not. As participation in sessions may be associated with outcomes, a cost/session attended will be a more useful estimate than a cost per patient.)
Fixed costs--buildings and equipment and furnishings	The total floor space that is required for study-related service delivery, excluding research-specific activities such as administration of informed consent, will be measured in each facility, including a proportion of shared spaces such as waiting areas. If the study sites or local administrative entity use a standard cost/square meter for clinic space, this will be accepted as the cost of buildings. Otherwise, a market-related average rental cost per square meter will be applied to estimate the cost of the building. Utilities will be added as a percentage mark-up based on site-specific planning documents or other local sources. The replacement cost of equipment and furnishings will be obtained and an appropriate working life applied to each instrument to obtain an average cost/month. If laboratory instrument procurement costs are not included in lab fees, these will be estimated in the same way as other equipment costs. Total building and equipment and furnishing costs per month will be divided by the number of relevant clinic visits made each month to estimate a fixed cost/clinic visit.

Resource or outcome	Method for estimating unit cost or cost/outcome
Resources	*Method for estimating unit costs*
Fixed costs--management and administration and general supplies	Costs of all staff members who do not provide direct patient care but provide some support to the delivery of study-related services (e.g. clinic manager, data clerks) will be calculated, with salaries obtained from the study sites or the administrative entity responsible for the sites' payrolls. The cost of general supplies (e.g. cleaning materials, stationery) will be obtained from facility financial reports. Total management, administration and supply costs per month will be divided by the total number of clinic visits made each month to estimate a fixed cost/clinic visit.
Outcomes	*Methods for estimate cost/outcome*
Cost/patient served	Total costs in study period/total number of patients enrolled, stratified by arm. This estimate is useful for budgeting purposes, as the difference between the arms indicates the additional budgetary resources needed to implement the intervention per patient served.
Cost/patient initiating ART	Total cost from enrollment to 28 days/total number of patients initiating ART within 28 days, stratified by arm. This estimate looks at the difference in cost between the intervention and standard care up to the point of ART initiation.
Cost/outcome	Total costs for patients stratified by arm and outcome. The difference in cost between outcomes indicates the anticipated difference in budgetary needs if outcomes improve.
Total cost/patient suppressed	Total cost from enrollment to 12 months/total number of patients achieving primary outcome of 12-month viral suppression, stratified by arm. This estimate focuses on cost differences between the arms for patients who do achieve the primary outcome. It takes into account all costs incurred for all patients but divides by only the number with a successful outcome, and thereby links the cost of service delivery to the primary outcome.
Cost-effectiveness	Incremental cost-effectiveness ratio (ICER) = Difference in costs (intervention arm-control arm)/ difference in outcomes (intervention arm-control arm). The ICER indicates the incremental additional cost to achieve one additional successful outcome.

6. PARTICIPANT SAFETY

Participant safety will be monitored by study staff every 4 weeks through in person visits.

6.1. SPECIFICATION OF SAFETY PARAMETERS

An **Adverse Event (AE)** is defined as any untoward or unfavorable medical occurrence in a human subject, including any abnormal sign (for example, abnormal physical exam or laboratory finding), symptom, or disease, temporally associated with the subject's participation in the research, whether or not considered related to the subject's participation in the research.

An AE can therefore be any new sign, reaction, symptom, event, disease or a worsening in frequency or severity of a preexisting condition that occurs during the course of the study.

Stable chronic conditions that were present prior to study entry and do not worsen are not considered AEs.

SERIOUS Adverse Event (SAE) – is any adverse event that

(1) results in death;

(2) is life-threatening;

(3) results in inpatient hospitalization or prolongation of existing hospitalization;

(4) results in a persistent or significant disability/incapacity;

(5) results in a congenital anomaly/birth defect; or

(6) based upon appropriate medical judgment, may jeopardize the subject's health and may require medical or surgical intervention to prevent one of the other outcomes listed in this definition (examples of such events include allergic bronchospasm requiring intensive treatment in the emergency room or at home, blood dyscrasias or convulsions that do not result in inpatient hospitalization, or the development of drug dependency or drug abuse).

Life-threatening means that the event places the subject at immediate risk of death from the event as it occurred.

Unanticipated Problem (UP) – is defined as an event, experience or outcome that meets all three of the following criteria:

- is unexpected; AND
- is related or possibly related to participation in the research; AND
- suggests that the research places subjects or others at a greater risk of harm (including physical, psychological, economic, or social harm) than was previously known or recognized.

  Possibly related means there is a reasonable possibility that the incident, experience, or outcome may have been caused by the procedures involved in the research

Unexpected means the nature, severity, or frequency of the event is not consistent with either:

- the known or foreseeable risk of adverse events associated with the procedures involved in the research that are described in (a) the protocol–related documents, such as the IRB-approved research protocol, any applicable investigator brochure, and the current IRB-approved informed consent document, and (b) other relevant sources of information, such as product labeling and package inserts; or
- the expected natural progression of any underlying disease, disorder, or condition of the subject(s) experiencing the adverse event and the subject's predisposing risk factor profile for the adverse event.

Suspected Adverse Drug Reaction – Any adverse event for which there is a reasonable possibility that the drug caused the adverse event. Reasonable possibility means there is evidence to suspect a causal relationship. It is considered unexpected if it is not consistent with the risk information described in the general investigational plan. A suspected adverse drug reaction will be defined as a recorded adverse event that is unexpected and deemed to be possibly, probably, or definitely related to the study drug.

6.2 THE METHODS AND TIME FOR ASSESSING, RECORDING, AND ANALYZING SAFETY PARAMETERS

- For participants randomized to the LINC-II intervention, symptoms will be assessed at baseline to document any chronic conditions or symptoms that existed prior to introduction of study medication. These will be documented on the Baseline AE log. This list will be reviewed and compared to reported events throughout the study. *If the participant reports the same ongoing symptom (same severity) during subsequent visits, the symptom should not be recorded as an Adverse Event (AE). If the event is new (not previously reported) or worsened, as determined by RA, then it will be considered an AE and recorded and reported as described below.*

- During each scheduled visit, the RA will ask the participant how he or she feels and review the previously reported symptoms. Any event that meets the above criteria for an AE/SAE/UP must be recorded. In the case of unresolved AEs, clinical staff will update the AE log with any follow-up information that is gathered during their investigation.

- The site will receive the results of all blood work that is performed on study participants from the designated lab. If the lab results meet the criteria described in the protocol as an AE and are considered clinically significant by the site clinician then an AE will be recorded.

    - Participants will be alerted of abnormal lab results and will receive a recommendation to see their local provider (please see section 3.3C for protocol specific to AST/ALT results). All abnormal lab results obtained at the baseline visit will be listed on the Baseline AE log. During follow-up visits, abnormal lab results will be listed as an AE only if the abnormal lab results meet one of the points below:
        - Develop at follow-up (i.e., were not previously recorded at baseline).
        - Worsen in severity compared to what was previously recorded at baseline.
        - Or are considered clinically significant.

- All AEs will be assessed to determine if they meet criteria for a Serious Adverse Event (SAE). If the AE is serious, then the SAE form must be completed and appropriate reporting measures followed (see below). Investigators are encouraged to consult with the US team, if they are uncertain how to classify an event.

- The list of participant's current medications will be reviewed and updated at every study visit, starting at baseline.

- If an event is discovered outside of the scheduled study visits, it must still be recorded accordingly.

- Action Taken will be determined by the RAs for all AEs that are Mild and Moderate and by Drs. Krupitsky or Blokhina for SAEs and AEs that are severe, life-threatening or fatal.

6.3. PROCEDURES FOR ELICITING REPORTS OF AND FOR RECORDING AND REPORTING ADVERSE EVENT AND INTERCURRENT ILLNESSES

For any reported side effect: While with the participant, study personnel will listen, identify, and document the symptoms. All events will be documented on AE forms.

6.3.A. OTHER EVENTS

- Any participant who voices current suicidality or is experiencing a psychiatric emergency during the interview will be reported to Dr. Krupitsky or his designee immediately. Dr. Krupitsky and the assessor (Addiction Psychiatrist at City Addiction Hospital or at Pavlov University) will determine the appropriate course of action, which will depend on location of the event and the clinical situation. Emergency psychiatric consultation is available on site at the CAH and will be requested as indicated; patients will be escorted to receive care by appropriate staff if deemed necessary.

6.3. B. ADVERSE EVENT REPORTING

The following information should be present to complete AE and SAE forms during the initial report (on the day of finding out about the event):

- Description of the event
- Date of onset and resolution (if known)

- Severity – based on established criteria: https://evs.nci.nih.gov/ftp1/CTCAE/CTCAE_4.03_2010-06-14_QuickReference_5x7.pdf * See Box 1

Box 1. Guidelines for Severity Grades

*Research assessor will refer to the guide for unique clinical descriptions of severity for each AE, which will follow the general guideline below:

- Grade 1 Mild; asymptomatic or mild symptoms; clinical or diagnostic observations only intervention not indicated.
- Grade 2 Moderate; minimal, local or noninvasive intervention indicated; limiting age-appropriate instrumental activities ADL*.
- Grade 3 Severe or medically significant but not immediately life-threatening; hospitalization or prolongation of hospitalization indicated; disabling; limiting self care ADL**.
- Grade 4 Life-threatening consequences; urgent intervention indicated.
- Grade 5 Death related to AE.

Not all Grades are appropriate for all AEs. Therefore, some AEs are listed with fewer than five options for Grade selection. Grade 5 (Death) is not appropriate for some AEs and therefore is not an option.

Activities of Daily Living (ADL)

*Instrumental ADL refer to preparing meals, shopping for groceries or clothes, using the telephone, managing money, etc.
**Self care ADL refer to bathing, dressing and undressing, feeding self, using the toilet, taking medications, and not bedridden.

- Assessment of expectedness (is the event anticipated in terms of nature, severity, or frequency) given (a) the research procedures that are described in the IRB protocol and informed consent document; and (b) the characteristics of the subject population being studied
- Assessment of relatedness to Naltrexone
- Any actions taken

Following the initial report, additional information may need to be gathered to complete the AE and SAE forms and to evaluate the event for relatedness. This process may include seeking hospital discharge reports, physician records, autopsy records or any other type of records or information necessary to provide a complete and clear picture of the SAE and events preceding and following the event.

6.3.C. SAE REPORTING

If the SAE is not resolved or stabilized at this time or new information becomes available after the SAE form is completed, the SAE form should be updated as soon as possible. Any changes or updates to the SAE form will need to be re-reviewed and re-authorized by the study clinician.

In some cases, the study clinician may be unsure upon first learning of an SAE whether it is study related and/or expected, because study staff are awaiting more complete medical records. In such cases, the study clinician should make his/her best estimate of relatedness and expectedness, understanding that these determinations can be updated later. When updating determinations at a later date, the rationale for the change should be included in the SAE narrative.

The site must actively seek information about the SAE until the SAE is resolved, stabilized or until the participant is lost to follow-up and terminated from the study.

To summarize: upon determining an Adverse Event is Serious, the following procedures should be followed:

- The study staff, while meeting/talking with the participant or person providing details on the event, will gather as much information about the event from these individuals as possible and complete the appropriate forms.

- The completed AE and SAE forms will be reviewed by key personnel on the Pavlov team (e.g. Drs. Krupitsky or Blokhina). Any relevant clinical documents (labs, physician notes) available at that time will be provided to key personnel on the Pavlov team (e.g. Drs. Krupitsky or Blokhina) within 24 hours of finding out about the event.

- After initial notification, the SAE must be updated with any additional information.

Any Adverse Events will be entered on the study website and Dr. Samet will be alerted immediately of any SAEs or UPs.

BUMC Reporting Guidelines:

The Principal Investigator at BMC/BU Medical Campus will report Unanticipated Problems and Adverse Events to the BMC/BU Medical Center IRB in accordance with IRB policies:

- Unanticipated Problems involving a fatal or life-threatening event will be reported to the IRB within 2 days of the investigator learning of the event.
- Unanticipated Problems not involving a fatal or life-threatening event will be reported to the IRB within 7 days of the investigator learning of the event.
- Adverse Events (including Serious Adverse Events) will be reported in summary at the time of continuing review, along with a statement that the pattern of adverse events, in total, does not suggest that the research places subjects or others at a greater risk of harm than was previously known.

Pavlov Reporting Guidelines:

What Event is Reported	When is Event Reported
Fatal or life-threatening unexpected, suspected serious adverse reactions	Within 7 calendar days of initial receipt of information
Non-fatal, non-life-threatening unexpected, suspected serious adverse reactions	Within 15 calendar days of initial receipt of information

AEs and UPs	On a quarterly basis

6.4 THE TYPE AND DURATION OF THE FOLLOW-UP OF SUBJECTS AFTER ADVERSE EVENTS

All events will be followed until the event is resolved, stabilized, or until the end of individual's participation in the study.

Drs. Krupitsky or Blokhina will determine a follow-up plan on a case-by-case basis based on their clinical judgment and this plan will be documented.

7. DATA MANAGEMENT

7.1 DATA COLLECTION

All study data will be captured electronically on netbooks via a secure, web-based data capture system.

7.2 QUALITY CONTROL PROCESS

Quality control measures will include: detailed and unambiguous specifications for completion of data forms, including rules for coding skipped questions and missing data, training of study staff responsible for data collection and built-in validation rules, error checks, question skips for electronic data capture, and computer algorithms to check for out-of-range codes and internal inconsistencies. All data, regardless of capture method, will be converted to SAS datasets and reviewed for logic, skip patterns, response ranges, out-of-range codes, and internal inconsistencies. The RAs will be queried regarding any noted inconsistencies.

7.3 DATA SECURITY AND CONFIDENTIALITY

Screening forms and most other research paperwork will not include the participant's name; instead, a unique ID will be assigned to each person screened, and another number assigned to those who enrolled. Any documents with identifiable participant data will only be accessible to the Russian Co-Investigators (Drs. Krupitsky and Blokhina), the project management staff, and the RAs who recruit and follow participants.

Tracking information will be kept similarly. Computer data will be password protected, and accessible only to research associates needing the information for follow-up purposes.

The Boston University Biostatistics & Epidemiology Data Analytics Center (BEDAC) will design, develop and maintain the electronic data collection forms, participant and data tracking, and underlying SQL database systems, and implement procedures for data quality control, including multiple checks for entered data. Electronic data collection forms will be designed to read easily, have clear instructions, preprogrammed skip patterns, real-time range checks and internal logic to minimize missing data and result in "cleaner" data at capture. The website and accompanying database will be located on secure, password-protected servers, behind the BU firewalls. The BEDAC has access to two Unix servers, including a Linux Beowulf cluster currently configured with 118 CPUs, as well as an SMP Linux server with 4 x Six-Core AMD Opteron processors (a total of 24 cores x 2.4 GHz each), 64 GB of RAM, and 6 TB (4TB usable) storage capacity. Additionally, the BEDAC has three dedicated servers, all of which are dual processors with 150 gigabytes for data storage: an SQL database server; a server used for Web site development and management, running Internet Information Server for web page hosting; and a server used for web development pre-production testing environment. The web and database servers will use Secure Socket Layering (SSL) to ensure data security and confidentiality. Two fax servers, an additional server, and a flatbed scanner comprise the Teleform® system. Servers incorporate RAID hard drives for data redundancy. A separate web server dedicated for Cold Fusion applications is also available.

The in-depth qualitative interviews will be recorded, and the clinician's or patient's name could be mentioned or their identity could otherwise be revealed during the interview; however sensitive information will not be the content of the interviews. Names will not be transcribed and audiorecordings will be destroyed after transcription. The audiorecordings will be kept in a locked cabinet when not in use.

7.4 WEB SYSTEMS

The study will use two web systems: a computerized tracking system and REDCap. The computerized tracking system will contain all participant tracking details. This system will be web-based, allowing multiple users to access the system. REDCap is a secure web application for building and managing online surveys and databases and will be used for screening and assessment purposes. Study forms will be completed according to the schedule below.

FORM	Screen & Baseline Visit		Implant Visits	Medication Checks	6-month visit (24 weeks)	12-month visit (52 weeks)	As Needed
	Screen	Baseline					
Screener	X						
Consent and enrollment form	X						
Contact info		X	X	X	X	X	X
Phlebotomy form (Paper)			X		X	X	X
Full assessment		X			X	X	
Short assessment		X	X	X			
Contact log							X
Baseline Event Form		X					X
Medication use collection (Paper)		X	X	X	X	X	X
Baseline tracking form		X					
Follow-up tracking form		X	X	X	X	X	
Participant tracking overview Participant tracking entry							X
Study conclusion form							X
AE/SAE form (paper and Web)							X
Incarceration form							X
Naloxone challenge tracking form		X	X				
Medication form			X	X	X	X	X
Detox form							X
Qualitative interview tracking							X
Provider interview tracking							X
Case Manager forms							X

8. STATISTICAL ANALYSIS

This study will use an intent-to-treat analysis that includes all participants according to their randomized assignment. Descriptive statistics will be calculated for variables at baseline and each follow-up time to assess whether there appear to be any differences across treatment arms.

Our Specific Aims are to compare the effects of LINC-II and standard of care following outcomes:

a. Primary: Undetectable HIV viral load at 12 months

b. Secondary: Initiation of ART within 28 days of randomization;

Change in CD4 count from baseline to 12 months;

Retention in HIV care (i.e., ≥1 visit to medical care in 2 consecutive 6 month periods)

Undetectable HIV viral load at 6 months;

HVL suppression and past 30-day opioid abstinence assessed at 6 and 12 months.

8.1 PRIMARY ANALYSES

The primary outcome for this aim is HIV viral load suppression at 12 months. Initial analyses will be performed comparing this binary outcome between groups using a chi-square test. The primary analysis will use multivariable logistic regression analyses to control for the stratification factor to improve efficiency, (i.e., ever ART use). If there are any baseline factors that appear to differ by randomized group, additional sensitivity analyses will be conducted controlling for these factors to assess for potential confounding. The secondary outcomes of undetectable viral load at 6 months, ART initiation within 28 days and retention in HIV care will be analyzed using the same approach described above. Change in CD4 count between baseline and 12 months will be analyzed using multiple linear regression adjusting for the stratification factor. If the distribution of change in CD4 is skewed, transformations of the data will be considered. If an appropriate transformation is not identified, a median regression model will be used.[41, 42]

8.2 ADDITIONAL EXPLORATORY ANALYSES

Effect Modification

We will perform additional analyses to explore potential effect modifiers of the LINC-II intervention. The 3 potential effect modifiers of interest are: gender, ever ART, and 30-day IDU. We will fit separate models including 2-way interactions between randomization group and each potential effect modifier. If an interaction is significant, subsequent stratified analyses will be conducted to explore and describe the effect of the LINC-II intervention by categories of the moderator.

Mediation

Exploratory analyses will be conducted to assess potential mechanisms that may drive LINC-II's ability to improve HIV care outcomes using the Baron and Kenny approach.[43] The 3 potential mediators we will explore are decreases in substance use, HIV stigma, and substance use stigma. However, because the interpretation of the degree of mediation in logistic models is complicated by their inherent nonlinearity, we will conduct additional analyses using the recently developed causal inference approach to mediation (also referred to as the counterfactual framework), an approach that allows potential interactions between the interventions and mediators and derives direct and indirect effects for binary outcomes.[44-47] We will use the Stata mediation package to conduct these analyses.[48, 49]

Aim 2

The analyses for this aim will be descriptive in nature; formal hypothesis testing will not be conducted. Descriptive statistics (e.g., means, medians, interquartile ranges, and confidence intervals) will be obtained to assess quantitative data from provider, administrator, and patient surveys over time on perceptions and experiences of coordinated care. We will also conduct repeated measures analyses of

patients' attitudes and experiences using mixed effects regression models controlling for randomized group to assess overall changes over time and to explore and describe potential differences between study arms. Qualitative interview data will be analyzed following a thematic approach.[50] Content analysis of qualitative data will reveal themes regarding care coordination and will identify best practices for LINC-II implementation in similar settings, (e.g., where addiction and HIV care systems are largely separate). Qualitative and quantitative results will be triangulated.[51]

Aim 3

Aim 3 is to estimate cost and cost-effectiveness. For this analysis, we will adapt methods developed by co-investigator Professor Rosen and colleagues in South Africa.[52, 53] When all follow-up to the primary outcome (12-month viral suppression) has been completed, patient resource utilization will be extracted from patients' medical records for HIV care and study forms for narcology care in the intervention arm. Narcology care (number of outpatient visits and services provided) for patients in the control arm will be estimated from patient self-report at the time of 6 and 12-month outcome assessments. Unit costs will be obtained from published information, external suppliers, and the study sites' finance and procurement records and applied to the resource usage data to provide an average cost per study patient. Costs will be measured from the provider perspective and will include the cost of all resources utilized for each study participant from the date of randomization for a period of 12 months, including all drugs, laboratory tests, outpatient visits, case manager costs, and fixed costs such as building space, equipment, and administrative staff. For patients referred to local clinics, rather than the study hospital, for ongoing HIV care after ART initiation and/or for narcology care, fixed costs will be estimated at the facility level for a typical local clinic for each type of care.

We will estimate average cost with 95% confidence intervals to the provider per patient enrolled, per patient initiating ART, and per patient achieving viral suppression by 12 months. We will also estimate total cost per patient achieving the primary outcome, which takes into account all the costs for all the patients but divides by only the number with a successful outcome (i.e., 12-month viral suppression) and thereby links the cost of service delivery to the primary outcome. The cost-effectiveness of the intervention, compared to standard care, will also be estimated as an incremental cost per incremental outcome. The cost and cost-effectiveness results will then be evaluated in the context of existing healthcare budgets, resource availability (e.g., trained case managers) other relevant interventions that have been studied in Eastern Europe, and cost estimates for similar countries to help inform policy makers about the affordability and priority of scaling up the program.

In addition to the provider cost estimates described above, the baseline questionnaire will elicit information about patient costs of seeking care, such as transport fares, lost wages, and substitute labor costs (e.g., for childcare). The average cost to patients by arm and by outcome will be estimated and used both to help explain study results (e.g. there may be an association between patient costs and retention in care) and as a component of the overall economic evaluation.

9. STAFF TRAINING

9.1 Training of Study Staff

All study staff will be trained on the study protocol. Training will take place in-person in St. Petersburg and via webinars.

For baseline study activities, staff at CAH will be trained addiction psychiatrists, who have experience administering injectable naltrexone to patients. In-person screening, enrollment, and baseline assessment will be performed by CAH staff who are psychologists who have experience working with this population.

Study staff at PSMU are research addiction physicians and nurses with extensive experience performing pharmacotherapy trials, including trials of implantable naltrexone, and are experienced in the surgical procedure of naltrexone implantation. The staff are trained to assess for adverse medication effects and will follow established protocols for identifying and monitoring any ongoing adverse events.

9.2 Training of Interventionists (Case Manager)

The LINC-II intervention training was led by Dr. Raj, who has substantial experience conducting behavioral intervention trainings internationally and in engaging HIV-positive PWID in medical care. Over the course of 2 days, Dr. Raj trained the interventionists in St. Petersburg, providing them with an overview of the theoretical framework, assessment techniques and the LINC-II intervention; they modeled the intervention delivery to assure the use of a strengths-based approach. As per previous trainings in earlier studies, simultaneous translation was used to allow multiple role-playing sessions to be critiqued. Booster trainings will be conducted annually and as necessary based on findings from quality assurance efforts. These intensive trainings as well as the monitoring and observation for quality assurance are designed to limit potential variability due to individual interventionists.

10. STUDY CONTACTS

Dr. Samet will be responsible for the financial management of the study and communication between NIH and the rest of the leadership team. He will manage the implementation of the study in Russia and oversee all components of the study. He will lead the weekly study team research meetings. He will help create the study protocol, oversee its administration, and assist in training interventionists. He will participate in analysis and presentation of study results and preparation of papers for publication.

In Russia, the study will be led by site PI, Dr. Evgeny Krupitsky. The study will be managed by Dr. Elena Blokhina in St. Petersburg and Natalia Gnatienko in Boston.

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