# Research Consent Form

## Linking Infectious and Narcology Related Care Part II-(LINC-II)

**NCT03290391**

**Jeffrey Samet, MD MA MPH**
**jsamet@bu.edu**

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# RESEARCH CONSENT FORM

## Basic Information

**Title of Project:** Linking Infectious and Narcology Care – Part II (LINC-II)

**IRB Number:** H-36706

**Sponsor:** National Institute on Drug Abuse (NIDA)

**Principal Investigator:** Jeffrey Samet, MD, MA, MPH
jsamet@bu.edu
801 Massachusetts Avenue, Crosstown, 2nd Floor, Boston, MA 02118

**Study Phone Number:** Regular business hours: 7-812-338-6051
24 hours: 7-952-097-8173

## Background

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. An intervention that targets both HIV infection and injection drug use has potential to improve the health of HIV-positive people.

You are being asked to participate in this study because you are HIV-positive, are a patient at a narcology hospital, and have a history of injection drug use. If you agree to participate, you will be involved in this research study for about 12 months.

## Purpose

The purpose of this study is to test whether combining medications to treat HIV and opioid use disorder with case management can improve HIV care outcomes among HIV-infected persons who inject drugs. We call this project Linking Infectious and Narcology Care – Part II (LINC-II).

## What Will Happen in This Research Study

You will be one of approximately 240 participants to be asked to participate in this study.

The study is being carried out at the following locations in St. Petersburg, Russia: St. Petersburg City Addiction Hospital, St. Petersburg City AIDS Center, and First St. Petersburg Pavlov State Medical University.

Although your participation will be at the above mentioned locations in Russia, your data will be transferred to Boston, Massachusetts (US): Boston Medical Center and Boston University Campus for evaluation with the collaborative Russian-US research team.

*Screening Visit:*

As part of the screening process, all women will be asked to complete a urine pregnancy test to make sure that they are not pregnant. This is because the medications that you may get as part of the study could be dangerous for the baby.

*Baseline Visit:*

After you are enrolled in the study, you will be asked about your demographics (e.g., age, gender), general health, substance use and HIV medical care. The interview will take place in person. Some questions will be asked by a research assessor and some questions you will complete by yourself. It will take approximately 75 minutes to complete. We will also review your medical record to find information about your HIV care and treatment history.

We will ask to take a blood sample from you (10-20ml [or 2-4 teaspoons]). It will be used to measure your HIV viral load and CD4 count. The testing will be performed at the City AIDS Center. The results of these tests will be put in your medical record at the City AIDS Center. We will not need a blood sample if you already have a recent (within one month) CD4 and HVL result in your City AIDS Center medical chart. If you are assigned to the intervention group the results will be shared with your assigned HIV case manager.

If you are unable to provide a blood sample or have an undetectable HIV viral load at baseline, we will conduct an HIV antibody test during a subsequent study visit to verify your HIV status.

After completion of the interview, you will be randomly (like flipping a coin) placed in one of two study groups. You will have an equal chance of being in either group.

**Group 1 – Comparison group:**

If you are in the comparison group you 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. You will also be given printed information, including phone number, on clinic that provides HIV medical care and you will be referred to outpatient narcology care.

**Group 2 – Intervention group:**

If you are in the intervention group, you will also receive printed information, including phone numbers, on places that provide HIV medical care, as well as these three components:

- **Medication for opioid use disorder:** You will receive one intramuscular gluteal injection of 380 mg of naltrexone for extended-release injectable suspension (vivitrol) while still at the hospital. You will then come to Pavlov University to receive a 1000mg dissolvable naltrexone implant (prodetoxon). You 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). You will be asked to return 7-11 days after the implant for removal of sutures. You will also be asked to come in every 4 weeks for brief medication check visits, during which you will receive brief counseling.

- **HIV case manager:** You will participate in 10 individual sessions with an HIV case manager (ideally 1 during your stay at the narcology hospital and 9 after you are discharged) over a period of 12 months. The remaining sessions can be held at your convenience at an HIV clinic, a non-governmental organization, or in the community. The case manager will help you understand the importance of HIV care, identify barriers to receiving care and to recognize your own strengths and abilities to reduce self-identified barriers to care. As part of the LINC-II intervention, the case

manager will help you attend HIV medical appointments and adhere to HIV treatment. The case manager will contact you to remind you about your appointments and you could also communicate with your case manager by text messaging or phone. Your individual sessions with the case manager will be audiorecorded to make sure the sessions are performed well.

- **Rapid access to antiretroviral therapy (ART):** As part of this study, your HIV care will be streamlined, which may allow you to get rapid access to ART medication.

Before getting your naltrexone injection or implant, you will receive a naloxone challenge to make sure there are no opioids in your system, as taking naltrexone with opioids in your system will make you feel sick. Naloxone blocks the effects of opioids. It works only if it is injected and lasts about 30 minutes. It is used in hospitals and by emergency services to reverse the effects of a heroin or other opioid overdose. It will cause withdrawal if injected into someone who is currently physically dependent on opioids and will be administered to you as a way of making sure that you are not physically dependent on heroin or other opioids before you receive injectable or implantable naltrexone. The naloxone challenge will only be administered if your urine is negative for heroin or other opioids. The challenge will be done by administering 0.8-mg naloxone slowly, either intravenously or intramuscularly. You will be observed for signs of withdrawal for 5-20 minutes. If you experience withdrawal after the naloxone test, your symptoms may be treated with clonidine or phenazepam and will go away in 45-60 minutes. You will not be started on the study medication until you pass a naloxone challenge, which means that you have no signs or symptoms of opioid withdrawal after naloxone is administered.

You may be one of a small number of participants, who will be asked to take part in an interview that will last about 60 minutes after your baseline, 6-, and 12-month LINC-II study visits. A trained member of the research team will contact you to complete the interview. During the in-depth individual interviews, among 30 study participants, we will ask about your perceptions and experiences with care coordination, including examples of connections between narcology and HIV care service delivery. The interview will be audio-recorded if you agree to it, or else we will take notes

*Follow-Up Visits:*

*Medication check-ins (for Intervention group only)*
If you are in the intervention group you will be invited to come in every 4 weeks following implantation for medication visits, where you will be monitored for side effects. Ideally, medication visits will occur at weeks 4, 8, 12, 16, 20, 24, 28, 32, 36, 40, 44, 48, and 52. Implant visits 2, 3, and 4 will involve the collection of blood for laboratory testing, in order to monitor liver toxicity. If your liver enzymes are high (>5 times the upper limit of normal), we will collect another blood draw to check your liver status at your next medication visit. The results of the tests will not be put in your medical record. If a lab value for a test performed at the time blood is drawn is abnormal, the research assessor will share the result with you and will recommend to see your local provider to discuss the results.

You will receive 4 1000mg dissolvable 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).The naltrexone implant will be inserted by a trained surgeon at Pavlov University. The implant will be inserted under the skin in your 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. You will receive discharge instructions to help you care for the insertion site at home.

At all visits you will be asked to provide a urine sample to check for pregnancy, if female, and to check for opioids in your system.

If you are randomized to the intervention group and you suspect that you have become pregnant during the study, you must notify the study doctor immediately and arrange to have the naltrexone implant removed. If you become pregnant while you are participating in this study, it could be dangerous for the baby. You must use birth control if you are a woman having sex with men while you are taking study medication and for 8 weeks afterward. Some of the most effective birth control methods are: oral contraceptives (the pill), intrauterine devices (IUDs), contraceptive implants under the skin, contraceptive rings or patches or injections, diaphragms with spermicide, and condoms with foam. You should not participate in this study if you are a woman who has sex with men and cannot use one of these birth control methods.

*In-person study visits (both comparison group and intervention group)*
All participants will be asked to come in for in-person assessments and blood draw visits at 24 and 52 weeks after enrollment. The follow-up interviews will occur in-person at the First St. Petersburg Pavlov State Medical University with a research assessor. These interviews will take approximately 75 minutes to complete and will ask questions about your demographics (e.g., age, gender), general health, substance use and HIV medical care. We will also review your medical records to find information on medical appointments, HIV medications, and laboratory test results (for example, HIV viral load and CD4 count). You will also be asked to provide a urine sample to check for opioids in your system.

We will ask to take a blood sample from you (10-20ml [or 2-4 teaspoons]). It will be used to measure your HIV viral load and CD4 count. Your blood will be sent to the City AIDS Center for testing and the results of these tests will be put in your medical record at the City AIDS Center.

If blood cannot be obtained during your 24- or 52-week study visit, you will be invited to come in for a second blood draw attempt 4 weeks later. If you are in the intervention group, the second attempt will take place during your scheduled 28-week visit and you will not receive additional compensation. If the second draw attempt is outside of a planned study visit, you will receive compensation in the amount of 500 rubles to cover costs associated with traveling to the laboratory.

We will contact you via phone calls, text message, email, and/or letters to remind you about your follow-up appointments.

*1) Data repository*

We would like permission to store your research data for future studies. Please indicate below if you will allow that.

My research data may be kept for future clinical, virological, and immunological research studies related to HIV disease, substance use disorder, and other associated illnesses. Yes [ ] _____(initial or sign ) No [ ] _____(initial or sign)

If you would like to use my research data for future studies not listed above, I am willing to be contacted about those studies for my permission. Yes [ ] _____(initial or sign) No [ ] _____(initial or sign)

*2) Future studies*
We would like to be able to contact you in the future about additional studies for which you may be eligible.

[ ] Yes, I agree to be contacted after my active participation in this study has ended_____(initial or sign )

[ ] No, I do not give permission to be contacted after my active participation in this study has ended.
_____(initial or sign )

**Risks and Discomforts**

You may experience stress from the research assessments, as you will be asked sensitive questions regarding substance use and HIV status. The risk of stress from interviews will be minimized by using trained interviewers, self-administration for particularly sensitive questions, and a standard interview process. You may be stressed by the length of the interviews (estimated 75 minutes). You will be allowed to stop at any time during the interviews to take a break and come back to complete them.

Another risk of taking part in this study is loss of confidentiality. However, the chance of someone seeing the responses to your interview assessments is unlikely because specific procedures will be put in place to prevent this from occurring. There is a small risk that you may experience a loss of confidentiality when research assessors contact you for follow-up. All study staff received training on the protection of human subjects in research. Study records are confidential, but there is a very small chance that someone outside the study could see them. Paper records are kept locked up and electronic records are in password protected computers.

You may experience bruising and minor pain as a result of the blood draw. Other risks such as infection are rare. These risks will be minimized by using trained phlebotomists to draw your blood.

You may experience withdrawal symptoms after the naloxone challenge. The symptoms usually resolve untreated within 45-60min, but in rare occasions may require the use of clonidine and phenazepam. The most frequent side effects (which appear to be dose-related) of clonidine are dry mouth, drowsiness, dizziness, constipation and sedation. The most frequent side effects of phenazepam are drowsiness, sedation, muscle weakness, and ataxia. These side effects generally decrease on continued administration and are a consequence of CNS depression.

Some people have had side effects while taking these study medications. The most serious risk of naltrexone (both implant and injection) is the potential for liver injury when taken in excessive doses. Harm is less likely at the dosage provided in this study. As a precaution, you will have liver blood tests (ALT and AST) repeated during implant visits 2, 3, and 4, and if any level is >5 times the upper limit of normal, a repeat test will be done. If any repeat test result is again >5 times the upper limit of normal, or if you have symptoms such as fatigue, anorexia, jaundice, nausea, vomiting, dark urine, light stool, abnormal pain, you 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.

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.

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. The small dose of triamcinolone added to the naltrexone implant to prevent inflammation has not been associated with complications. For implantable naltrexone, the most common non-surgical side effects are abdominal discomfort, nausea, and drowsiness. Other potential side effects include loss of appetite, nausea, vomiting, diarrhea, constipation,

abdominal pain, liver dysfunction, rapid heart rate, hypertension, vein swelling, headaches, weakness, sleep disorder, anxiety, giddiness, depression, dysphoria, running nose, coughing, difficulty with breathing, edema, acne, itching, ejaculation problems, decreased potency, increased or decreased interest in sex, shivering, tremor, joint pain, local inflammation, increased size of lymph nodes, and relapse of hemorrhoids.

The local anesthetic (numbing medicine) that is used in order to make the small cut in your skin and place the medication implant is safe when given in the small amounts that are used to numb the skin. There are some risks that can happen. The most serious is if the needle goes into a blood vessel so the medicine gets into the blood stream. Steps are taken routinely to prevent this from happening before injecting the medication. Serious risks that rarely occur can happen from excessive dosage or injecting into a blood vessel and can include light-headedness, dizziness, blurred vision, restlessness, tremors and, occasionally, seizures, passing out and stopping breathing and your heart stopping beating. These would not be likely with the amount of lidocaine you would get and the steps to prevent serious complications. Allergic reactions may also occur.

If you try to use excessive opioids to override the effect of naltrexone, you risk experiencing a potentially fatal overdose. After completion of naltrexone treatment, your body may become more sensitive to opioids, and if you use opioids at doses used before treatment, you also risk a potentially fatal overdose.

To minimize medication risks the study team will frequently and regularly monitor you for adverse effects, particularly liver enzyme elevation, injection and implant site reactions or infections, and common side effects. Please contact the study personnel or another health care provider, if you experience any adverse effects.

In the event of an emergency, in which you may require acute pain management, opioids may not be a therapeutic option to address the pain while on the study drug, which is a long-acting opioid antagonist medication, an injectable or implantable form of naltrexone. In addition, we will provide you with a wallet card to be presented to your provider to indicate that you are receiving naltrexone, which has potential impact on pain management.

There may be unknown risks/discomforts involved. Study staff will update you in a timely way on any new information that may affect your health, welfare, or decision to stay in this study. If you are harmed as a result of your participation in this study First St. Petersburg Pavlov State Medical University has medical and professional staff available to help. Also, Dr. Krupitsky, Co-Investigator, or his designee, will be available to assist you and make referrals as needed.

## Potential Benefits

You may not receive any benefits from participating in the study. However, you may benefit from discussing your health with an assessor. If you are enrolled in the intervention group, you may benefit by improving your health through work with a case manager, medications for your opioid use disorder, and rapid access to ART medication.

## Alternatives

Your alternative is to not participate in the study. If you choose not to participate you will be able to access any HIV or narcology services that are currently available to you. You will be able to continue receiving standard narcology treatment, such as detoxification with medications, substance use counseling and treatment for comorbid psychiatric conditions, as well as possibly inpatient rehabilitation for up to 30 days. You can discuss with your doctor the possibility of receiving medications, such as naltrexone, for treatment of your opioid use disorder. You can seek HIV care, including ART medications and help from a case manager at the City AIDS Center or another HIV treatment provider closer to you.

## Costs

There are no costs to you for being in this research study. You may incur costs traveling to and from study visits. All research procedures will be paid for by the study; these include blood draws, medication, assessments, and tests. Outside of the study, you may choose to receive additional health services such as medical care, tests and/or medications. Payment for services outside of the study will not be paid for by the study.

## Payment

You will receive 1000 rubles in cash or goods at baseline, 2000 rubles at 24 and 52-week study visits. If you are randomized to the intervention group, you will also receive 1500 rubles for visits in which implantable naltrexone is inserted, and 500 rubles for monthly medication check-ins.

If you leave the City Addiction Hospital early before receiving your baseline compensation, you will receive this baseline compensation in full during the next study visit you attend.

## Confidentiality

We will do our best to keep your information safe. However, we cannot guarantee confidentiality.

Federal and state agencies, if they are required by law or are involved in research oversight, may access information about you from this study. Such agencies may include the U.S. Department of Health and Human Services, the Food and Drug Administration, the National Institutes of Health, and the Massachusetts Department of Public Health.

Research assessment questionnaires will be completed with the majority of data entered directly into laptop computers, which will require a username and password to logon. Data will not have your name, only your unique study ID number. Locator contact information and the master enrollment list will have participant names. Paper forms will be kept in locked filing cabinets and electronic data will be stored on password protected computers. Study information will be accessible to study staff for purposes of conducting or monitoring the study. Intervention sessions with the case managers will be recorded, and your name could be mentioned or your identity could otherwise be revealed during the interview; however, audio files will be stored on password protected, secure computers accessible only to Russian study staff. The files will be labeled with your study ID number and not with your name or any other identifying information.

If during the interview the assessor determines that there is evidence that you are in clear and imminent danger of harming yourself, they will contact Dr. Krupitsky or his designee to decide on the appropriate course of action, which will depend on where you are during the interview and on the clinical situation. You may be referred to emergency psychiatric consultation, which is available on site at the City Addiction Hospital and may be escorted to receive emergency psychiatric care. In such a situation, the assessor may need to reveal certain identifiable information about you to the emergency psychiatric clinician.

A description of this clinical trial will be available on http://www.ClinicalTrials.gov, as required by U.S. Law. This Web site will not include information that can identify you. At most, the Web site will include a summary of the results. You can search this Web site at any time.

We might use your research data in future studies. These future studies might be done by us or other investigators. Before we use your data, we will remove any information that shows your identity.

This study is covered by a Certificate of Confidentiality (CoC) from the National Institutes of Health. All studies funded by the National Institutes of Health that involve identifiable information or biological samples are covered by a CoC. The CoC provides how we can share research information or biological samples. Because we have a CoC, we cannot give out research information or biological samples that may identify you to anyone that is not involved in the research except as we describe below. Even if someone tries to get your information or biological samples in connection with a legal proceeding, we cannot give it to them. The CoC does not prevent you from sharing your own research information. The Certificate of Confidentiality applies to information and samples collected for this study which are sent to or kept in the United States of America.

Information from this study may be reviewed and photocopied by the National Institute on Drug Abuse and/or state and federal regulatory agencies such as the Office of Human Research Protection and the Institutional Review Board of Boston University Medical Center. Information from this study and from your medical record may be used for research purposes and may be published; however, your name will not be used in any publications.

**Compensation for Injury**

If you think that you have been injured by being in this study, please let the investigator know right away. You should seek treatment for the injury at your local medical center. We do not offer a program to provide compensation for the cost of care for research related injury or other expenses. Other expenses might be lost wages, disability, pain, or discomfort. If you do not go to a state-operated facility you will be responsible for paying for the medical treatment you receive. You are not giving up any of your legal rights by signing this form.

**Protection of Subject Health Information**

You have certain rights related to your health information. These include the right to know who will get your health information and why they will get it. If you choose to be in this research study, we will get information about you as explained below.

You authorize Jeffrey Samet and study staff at Boston Medical Center who are working on this research project and their employees to use and disclose information concerning you and your identity, medical history, and information collected during this study for the following purpose: to study how combining medication (such as rapid access to ART and naltrexone for opioid use disorder) and case management can improve HIV care outcomes among HIV-infected persons who inject drugs.

Such information may also be disclosed to or used by others involved in or overseeing the study including Boston University and Boston Medical Center Institutional Review Board and the study's sponsor, the United States National Institutes of Health (NIH). We share your health information only when we must. We ask anyone who gets it from us to protect your privacy. If you do not want to let us use your health information, you cannot be involved with this research study. This is because your health information is necessary to the conduct of this research. You may withdraw authorization to collect additional information about you at any time by writing to the local Principal Investigator, but information already collected may continue to be used and disclosed. This authorization has no expiration date.

**Subject's Rights**

By consenting to be in this study you do not waive any of your legal rights. Consenting means that you have been given information about this study and that you agree to participate in the study. You will be given a copy of this form to keep.

If you do not agree to be in this study or if at any time you withdraw from this study you will not suffer any penalty or lose any benefits to which you are entitled. Your participation is completely up to you. Your decision will not affect your ability to get health care or payment for your health care. It will not affect your enrollment in any health plan or benefits you can get.

You may obtain further information about your rights as a research subject by calling the Ethical Committee of First St. Petersburg State Pavlov Medical University at 7-812-338-6617..

**Questions**

The investigator or a member of the research team will try to answer all of your questions. If you have questions or concerns at any time, contact EDWIN ZVARTAU at 7-812-338-7023 during the day and EVGENY KRUPITSKY at 7-952-097-8173 after hours. Also call if you need to report an injury while being in this research.

You may also call +7(812)3386617. You will be talking to someone at the St. Petersburg State Pavlov Medical University IRB. The IRB is a group that helps monitor research. You should call or email (spbgmutrials@yandex.ru) the IRB if you want to find out about your rights as a research subject. You should also call or email if you want to talk to someone who is not part of the study about your questions, concerns, or problems.

**Subject:** _____
Printed name of subject

By signing this consent form, you are indicating that you have read this form (or it has been read to you), that your questions have been answered to your satisfaction, and that you voluntarily agree to participate in this research study.

_____ _____
Signature of subject Date

**Researcher:** _____
Printed name of person conducting consent discussion

I have personally explained the research to the above-named subject and answered all questions. I believe that s/he understands what is involved in the study and freely agrees to participate.

_____ _____
Signature of person conducting consent discussion Date

*To be completed by witness if researcher reads this form to the subject*
This consent form was read to and apparently understood by the subject in my presence.

_____

Printed name of witness (a person not otherwise associated with the study)

_____ _____

Signature of witness Date