NYU School of Medicine
NYU LANGONE MEDICAL CENTER

Tool Revision History:

Version Number	Version Date	Summary of Revisions Made
FINAL	16 April 2021	FINAL version

NYU School of Medicine
NYU LANGONE MEDICAL CENTER

ACCESSIBLE CARE INTERVENTION FOR ENGAGING PEOPLE WHO INJECT DRUGS (PWID) IN HEPATITIS C CARE

Principal Investigator:	Benjamin Eckhardt Department of Medicine – Division of Infectious Diseases 462 1st Ave., NBV16S-5, New York, NY 10016 Benjamin.eckhardt@nyumc.org 347-237-6490
Additional Investigators:	Kristen Marks (Co-PI) Weill Medical College of Cornell University – Department of Medicine 1300 York Avenue, 4th Floor, New York, NY 10021 markskr@med.cornell.edu 212-746-7602 Pedro Mateu-Gelabert (Co-PI) CUNY School of Public Health Pedro.Mateu-Gelabert@sph.cuny.edu
NYULMC Study Number:	i17-00811
Funding Sponsor:	CUNY School of Public Health
IND/IDE Number:	*N/A*
Regulatory Sponsor:	*N/A*
Study Product:	*N/A*
Study Product Provider:	N/A
ClinicalTrials.gov Number	NCT03214679

Initial version: 4.26.17
Amended:
Amended:

Statement of Compliance

This study will be conducted in accordance with the Code of Federal Regulations on the Protection of Human Subjects (45 CFR Part 46), 21 CFR Parts 50, 56, 312, and 812 as applicable, any other applicable US government research regulations, and institutional research policies and procedures. The International Conference on Harmonisation ("ICH") Guideline for Good Clinical Practice ("GCP") (sometimes referred to as "ICH-GCP" or "E6") will be applied only to the extent that it is compatible with FDA and DHHS regulations. The Principal Investigator will assure that no deviation from, or changes to the protocol will take place without prior agreement from the sponsor and documented approval from the Institutional Review Board (IRB), except where necessary to eliminate an immediate hazard(s) to the trial participants. All personnel involved in the conduct of this study have completed Human Subjects Protection Training.

Table of Contents

List of Abbreviations

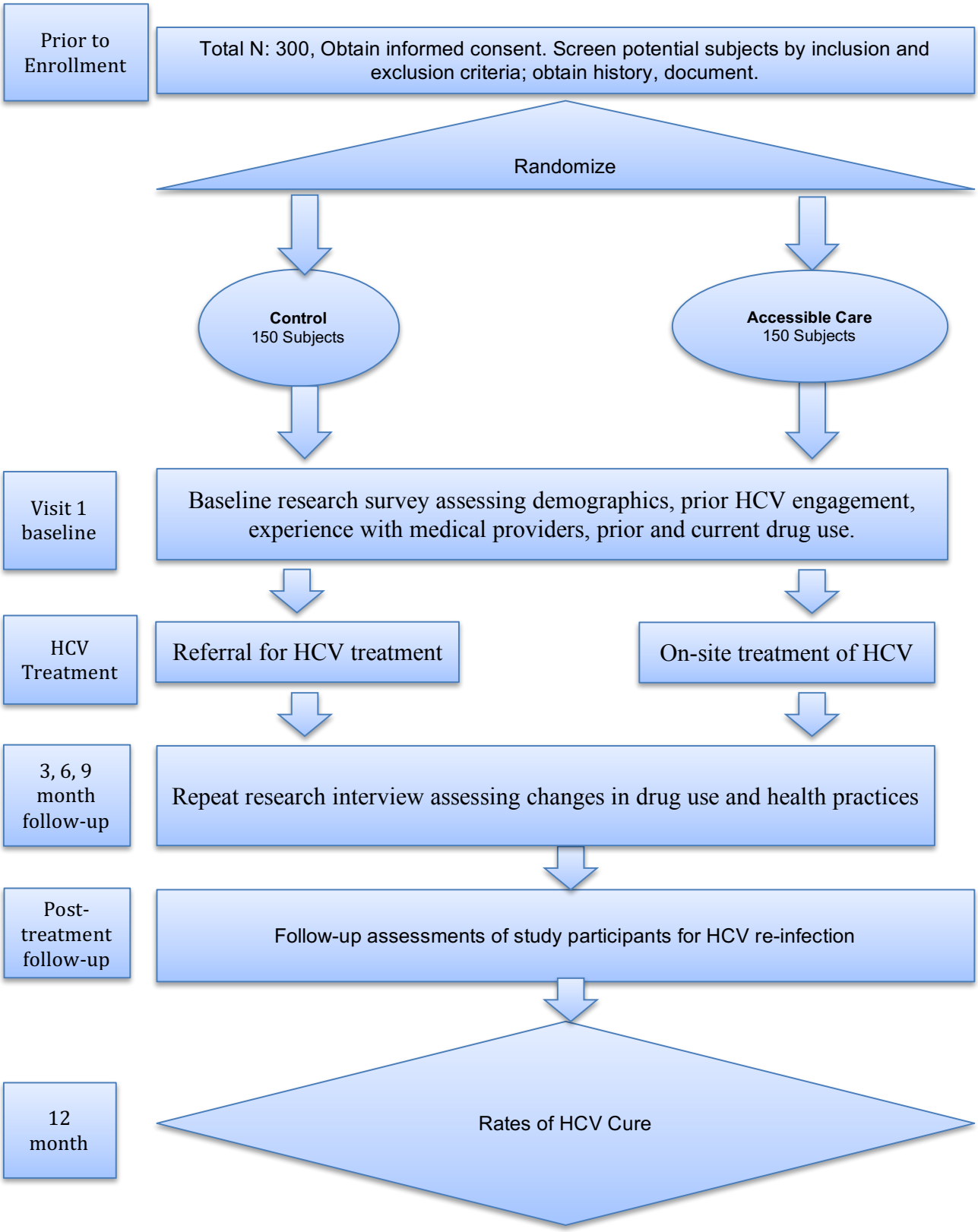
AE	Adverse Event/Adverse Experience
CFR	Code of Federal Regulations
CRF	Case Report Form
CSOC	Clinical Study Oversight Committee
DCC	Data Coordinating Center
DHHS	Department of Health and Human Services
DSMB	Data and Safety Monitoring Board
FFR	Federal Financial Report
FWA	Federalwide Assurance
GCP	Good Clinical Practice
HIPAA	Health Insurance Portability and Accountability Act
ICF	Informed Consent Form
ICH	International Conference on Harmonisation
IRB	Institutional Review Board
ISM	Independent Safety Monitor
MOP	Manual of Procedures
N	Number (typically refers to participants)
NIH	National Institutes of Health
OHRP	Office for Human Research Protections
OHSR	Office of Human Subjects Research
PI	Principal Investigator
QA	Quality Assurance
QC	Quality Control
SAE	Serious Adverse Event/Serious Adverse Experience
SOP	Standard Operating Procedure
US	United States

Protocol Summary

Title	Accessible Care Intervention for Engaging People who Inject Illicit Drugs (PWID) in Hepatitis C Care
Short Title	
Brief Summary	The proposed study will examine the feasibility, acceptability, safety, effectiveness, and cost of an Accessible Care intervention for engaging people who inject illicit drugs (PWID) in hepatitis C care. Accessible Care for PWID is low-threshold care provided in programs designed specifically for PWID where they can comfortably access care without fear of shame or stigma. Accessible Care will be provided by co-locating a hepatitis treatment provider, together with a Hepatitis C Care Coordinator (HCCC), on-site at our collaborating needle exchange program. The proposed study will compare the effectiveness of Accessible Care with Usual Care (referrals to existing services) in facilitating linkage, engagement, and retention of PWID in care for hepatitis C, addiction, and HIV prevention. Our primary outcome is sustained virologic response, which constitutes virologic cure. Substance use and HIV and HCV risk behaviors are secondary outcomes. The Specific Aims of this study are to compare active PWID receiving Accessible Care or Usual Care on the following outcomes: 1. Hepatitis C Outcomes: (1a) Linkage and engagement in hepatitis C care, (1b) Successful hepatitis C treatment, (1c) Safety of hepatitis C treatment, and (1d) Rates of reinfection. 2. Substance use outcomes 3. Reductions in self-reported HIV and HCV risk behaviors. As all-oral regimens become available to patients who do not inject drugs, the substantial health disparities in hepatitis C already evident will become worse, as the haves are cured and the have-nots are not. Data are needed on effective methods to provide successful antiviral therapy to the core population affected by the epidemic, persons who are currently using illicit drugs, so that they, too, may benefit. Treatment can also help end the HCV epidemic by preventing onward transmission, but only if we have effective models for delivering treatment to people actively injecting drugs.
Phase	Clinical study phase 4
Objectives	The proposed study will compare the effectiveness of Accessible Care with Usual Care in facilitating linkage, engagement, and retention of PWID in care for hepatitis C, addiction, and HIV prevention.
Methodology	Open label; Randomized control
Endpoint	Our primary outcome is sustained virologic response (SVR), which constitutes virologic cure. Substance use and HIV and HCV risk behaviors are secondary outcomes.
Study Duration	4 years
Participant Duration	52 to 144 weeks
Duration of IP administration	N/A
Population	500 men and women, age >/= 18 who have injected drugs in the last 90 days.
Study Sites	Lower East Side Harm Reduction Center
Number of participants	500 participants all enrolled at the Lower East Side Harm Reduction Center

Description of Study Agent/Procedure	The research will be investigating a new model of Hepatitis C care delivery, 'Accessible Care'. Accessible Care is low-threshold care provided in programs designed specifically for PWID, in community-based locations where they can comfortably access care without fear of shame or stigma.
Reference Therapy	Accessible Care intervention will be compared to referral of hepatitis C infected patient to existing hepatitis C treatment sites (clinics and hospitals).
Key Procedures	Blood draws that are considered standard of care for hepatitis C treatment will take place as part of the study.
Statistical Analysis	We will compare the frequency of four hepatitis C treatment endpoints in the two arms in an intent-to-treat fashion, in order to evaluate the hypotheses that PWID in the intervention arm will be more likely than those in the control arm to begin, adhere to, complete, and achieve virologic responses to antiviral treatment for hepatitis C. The four endpoints will be defined as follows. Antiviral treatment initiation will be defined as taking the first dose of antiviral medication within 3 months of randomization. Adherence to antiviral treatment will be assessed by self-report and calculated as a percentage of prescribed doses. Treatment completion will be defined as taking the prescribed medications for the entire prescribed treatment duration. Sustained virologic response (SVR) will be defined as testing HCV RNA negative 12 weeks after treatment completion, the standard definition.

Schematic of Study Design



1 Key Roles

NYU:

Benjamin Eckhardt will be involved in the development of survey instrument and will be the lead clinician providing HCV care on-site at Lower East Side Harm Reduction Center. Participants randomized to the 'Accessible Care' arm of the research study will be offered on-site Hepatitis C treatment, with Dr. Benjamin Eckhardt being the primary medical provider. His study-related tasks will include:

1. obtaining a detailed medical history
2. performing a thorough physical examination
3. performing venopuncture to obtain laboratory specimen
4. discussing hepatitis C treatment options
5. prescribing standard of care hepatitis C medication in accordance with national guidelines
6. providing routine follow-up care to participants started on hepatitis C treatment
    - Lab testing will be conducted at the community based research site (Lower East Side Harm Reduction Center) with all labs being sent either to New York Presbyterian-Cornell's Central Lab or Weill Cornell Medicine's Clinical and Translational Science Center. No specimens of any form will be obtained, processed, or analyzed at New York School of Medicine.

Non-NYU

Kristen Marks (Co-PI)
Weill Medical College of Cornell University – Department of Medicine
1300 York Avenue, 4th Floor, New York, NY 10021
markskr@med.cornell.edu
212-746-7602

Pedro Mateu-Gelabert (Co-PI)
CUNY School of Public Health
Pedro.Mateu-Gelabert@sph.cuny.edu

Shashi Kapadia (co-investigator)
Weill Medical College of Cornell University – Department of Medicine
Shk9078@med.cornell.edu

Yesenia Aponte-Melendez (Research Coordinator)
CUNY School of Public Health

Chunki Fong (Biostatistician)
CUNY School of Public Health

Melinda Pai (Research Assistant)
Weill Cornell Medicine

2 Introduction, Background Information and Scientific Rationale

2.1 Background Information and Relevant Literature

The proposed study will examine the feasibility, acceptability, safety, effectiveness, and cost of an Accessible Care intervention for engaging people who inject illicit drugs (PWID) in hepatitis C care. Four times as prevalent in the US as HIV infection, hepatitis C is already the leading cause of liver failure and liver transplantation, and the disease burden and health care costs will continue to rise in the coming decades. The 1.5-2.0 million PWID constitute the core of the hepatitis C epidemic in the United States, with prevalence rates >70% in most studies. New, all-oral antiviral treatment regimens can eradicate HCV in nearly 100% of previously untreated patients. Nonetheless, few studies have reported successful treatment of this infection in active PWID — none with the new all-oral regimens — and they are rarely offered antiviral treatment. As more advantaged populations gain access to the treatments and are cured, health disparities in hepatitis C outcomes will sharpen.

Obstacles to engaging active PWID in care include their competing priorities (e.g., legal, financial, interpersonal, drug-related, housing), more pressing medical or social problems, comorbid psychiatric illness, addiction, fear of stigma, and historically poor relations with health care providers. Other barriers exist at the provider, healthcare system, and structural levels. >

2.2 Name and Description of the Investigational Agent

Accessible Care for PWID is low-threshold care provided in programs designed specifically for PWID, in community-based locations where they can comfortably access care without fear of shame or stigma. In collaboration with community-based organizations providing services to PWID in the South Bronx, East Harlem, and the Lower East Side of Manhattan, we developed an Accessible Care program and found that we could effectively treat both hepatitis C and addiction in a sample of PWID recruited from community-based settings who were actively using illicit drugs. By reducing illicit drug use and providing effective HIV and HCV prevention, the intervention reduced HIV risk behavior as well — a finding supported by a low HCV reinfection rate in follow-up.

The proposed study will compare the effectiveness of Accessible Care with Usual Care in facilitating linkage, engagement, and retention of PWID in care for hepatitis C, addiction, and HIV prevention.

2.2.1 Preclinical Data

N/A

2.2.2 Clinical Data to Date

In a single arm pilot study conducted by our team we treated 53 participants at a community based syringe service program in Washington Heights and found high rates of sustained virologic response of 91%.

2.2.3 Dose Rationale (if applicable)

N/A

2.3 Rationale

PWID are less likely to engage in HCV care through existing models of care delivery. Obstacles to engaging active PWID in care include their competing priorities (e.g., legal, financial, interpersonal, drug-related, housing), more pressing medical or social problems, comorbid psychiatric illness, addiction, fear of stigma, and historically poor relations with health care providers. Other barriers exist at the provider, healthcare system, and structural levels.

2.4 Potential Risks & Benefits

2.4.1 Known Potential Risks

Risk of social harm:
Participants may feel uncomfortable responding to questions about your medical conditions, their feelings, their drug use, or their sexual behaviors. Some of the questions are about topics that may make them feel guilty, anxious, or embarrassed.

Risk of drawing blood:
Drawing participant blood could cause pain, swelling, bruising, light-headedness, or, rarely, infection at the place where your blood was drawn.

Each of these potential risk are low risk, and in our the potential gain outweighs the risk.

2.4.2 Known Potential Benefits

People who inject drugs are the risk group most likely to be infected with HCV, and the least likely to be offered treatment. This study will offer important insights into the feasibility, safety and efficacy of treating active drug users using a co-located model of care designed with their needs in mind. Identifying effective ways to approach HCV treatment in this marginalized population will improve overall health and quality of life and reduce the spread of this disease. Participation in the study may benefit participants by eliminating the hepatitis C virus or halting the progression of this disease. Subjects may also benefit from the discontinuation of illicit drug use through our treatment model and improved health status and quality of life. Serious adverse events related to HCV antiviral treatment are uncommon. Should they occur the close monitoring structure allows early detection and intervention and the timely provision of expert medical care. Given the low risk presented by participation in this study, the risk/benefit ratio is very favorable.

3 Objectives and Purpose

3.1 Primary Objective

The proposed study will compare the effectiveness of Accessible Care with Usual Care in

facilitating linkage, engagement, and retention of PWID in care for hepatitis C, addiction, and HIV prevention.

Hepatitis C Outcomes
Linkage and engagement in hepatitis C care, assessed as (a) stated interest in hepatitis C treatment evaluation, (b) attendance at an initial visit with a hepatitis provider, (c) completion of a medical evaluation for antiviral treatment, and (d) attendance at two visits with a hepatitis treatment provider within 3 months. Successful hepatitis C treatment, defined as (e) beginning antiviral treatment, (f) adherence to antiviral treatment, (g) completion of antiviral treatment, and (h) sustained virologic response, the primary

outcome. We will also describe (i) the reasons for any participants not reaching treatment endpoints (a)–(h) according to staff and participant report, and (i) the costs of the intervention in each arm.
Safety of hepatitis C treatment measured by the frequency of side effects, adverse events, and doselimiting toxicity, since these rates haven't been reported in PWID receiving all-oral regimens.
Rates of reinfection in active PWID who have achieved SVRs with antiviral therapy for hepatitis C. Reinfection is one of the primary reasons cited for withholding antiviral treatment from PWID.

Substance use outcomes
Substance abuse treatment entry and retention in each arm 3, 6, and 9 months after randomization.
Reductions in substance use during follow-up assessed as (a) self-reported frequency of drug injection, and (b) self-reported percentage of days of drug or alcohol use, and (c) urine toxicology.

4 Study Design and Endpoints

4.1 Description of Study Design

The proposed study will evaluate the effectiveness of Accessible Care (AC) for engaging and retaining PWID in care for hepatitis C, as compared with Usual Care (UC). A sample of 300 PWID with chronic hepatitis C will be recruited from the Lower East Side Harm Reduction Center, our community-based partner, and offered enrollment in a longitudinal study in which they will be randomized 1:1 to receive AC or UC. Participants will be given an appointment with a Hepatitis C Care Coordinator (AC) or referrals to existing community resources (UC), according to their study arm. To assure that any observed effects can be attributed to the intervention and not to differences in insurance, transportation, or physician characteristics, study participants in both arms will receive assistance signing up for health insurance (Medicaid); transit fare (MetroCards) as needed for appointments; and access to the same study physicians at the Weill Cornell Medical Center (WCMC) Center for the Study of Hepatitis C.

All patients who choose to receive antiviral treatment and have no contraindications will undergo state-of-the-art antiviral therapy according to standard clinical protocols. Study physicians are committed to caring for people who use drugs without shaming, blaming, or stigmatizing them or withholding care on the basis of arbitrary requirements for abstinence from substance use.

Participants in both arms will be interviewed at baseline and 3, 6, and 9 months after randomization. To assure retention in follow-up and reduce differential attrition, all patients will be seen monthly for a check-in to update contact information, as we have done in previous research. Outreach workers will help retain participants in the study by reminding them of upcoming appointments and searching for those lost to follow-up. Participants in both arms will be asked monthly if they've started antiviral therapy and those receiving antiviral therapy will be interviewed monthly while on therapy to assess adherence and side effects. Patients will receive cash stipend for each study interview or monthly check-in.

Clinical data, including medication start and stop dates and doses, viral RNA levels, other laboratory test results, and adverse events, will be abstracted electronically from the WCMC electronic medical record or by requesting records from other facilities. The effectiveness of AC will be assessed and compared with Usual Care through formal intent-to-treat analyses comparing study endpoints. Semi-structured qualitative interviews will also be conducted with a theoretically sampled group of 60 participants 6 months after randomization, including some who dropped out or did not pursue treatment, to provide contextualized data on how the intervention worked, or didn't, and its strengths and weaknesses. All patients achieving SVR will be followed up with quarterly HCV RNA testing for the duration of the study to detect reinfections. The cost of the intervention in each arm will be estimated as a key component of assessing the feasibility of the interventions. While our program requires intensive effort by intervention staff, we anticipate that that the incremental cost of this effort will be well within the range of the current cost of hepatitis C treatment.

4.2 Study Endpoints

4.2.1 Primary Study Endpoints

We have chosen a series of 5 hepatitis C outcomes that represent the continuum of care — 3 assessing linkage and engagement, and 2 assessing successful treatment. Outcomes will be compared using intent-to-treat analyses, which classify participants lost to follow-up as not having reached any unmeasured endpoint. SVR, the fifth and last of these outcomes, is the primary endpoint; SVR indicates the elimination of HCV infection and the cessation of the hepatitis disease process, and is universally considered the ultimate goal of treatment. Four proximal hepatitis C endpoints have been chosen, however, so that if the intervention is not ultimately successful in achieving SVRs we can examine at what stage the failures occurred. For each comparison, the null hypothesis of no difference between the arms will be assessed using the chi-square test and rejected if $p<0.05$.

Aim 1a. Hepatitis C treatment engagement. We will assess the proportion of patients in each arm who (a) referral to hepatitis C treatment provider, (b) attend an initial visit with a hepatitis treatment provider, and (c) complete a medical evaluation for antiviral treatment, including a history, physical examination, and laboratory evaluation. Proportions with 95% confidence intervals (CIs) calculated using the exact binomial method will be reported. Persons who are lost to follow-up will be considered in each analysis as not having reached the outcome, according to intent-to-treat principles.

Aim 1b. Hepatitis C treatment success. We will compare the frequency of four hepatitis C treatment endpoints in the two arms in an intent-to-treat fashion, in order to evaluate the hypotheses that PWID in the intervention arm will be more likely than those in the control arm to begin treatment, and achieve virologic responses to antiviral treatment for hepatitis C. The two endpoints will be defined as follows. Antiviral treatment initiation will be defined as physically receiving the first dose of antiviral medication (without necessarily having confirmed ingestion). Sustained virologic response (SVR) will be defined as testing HCV RNA negative 12 weeks after treatment completion, the standard definition

Aim 1c. Cost of intervention: The HCCC and the Clinician will log time spent providing services, excluding research activities. Costs will be assigned to staff time based on prevailing national wage rates. Patient time costs will also be estimated based on time spent with staff members and will be valued based on the minimum wage because most patients are likely to be unemployed. We will describe patient-reported health care visits, employment, and incarceration that will be used as inputs to future cost or cost-effectiveness studies.

Aim 1d. Safety: Because concern about side effects has been cited as a reason not to treat PWID for hepatitis C,and because experience with these drugs in PWID has not been reported, we will report prospectively collected data on safety outcomes on all participants who receive antiviral therapy. All treatment-emergent side effects (e.g., fatigue, headache, nausea, insomnia, irritability, anorexia, diarrhea, constipation, etc.) will be tabulated, as will adverse events, including abnormalities in serum bilirubin, liver enzymes, infections, hospitalizations, and deaths), and any adverse effects requiring treatment discontinuation, according to OHRP152 and NIH153 guidelines. We will describe the frequency of side effects, adverse events, and treatment-limiting outcomes, among all study participants who received at least one dose of antiviral medication. If numbers permit, we will compare the rates in the two arms to see whether AC influences perceived side effects.

Aim 1e. Reinfection: We will report reinfection rates in all patients in both arms who achieve SVR using time-toevent methods. If 150 participants initiate antiviral therapy (50% overall) and 120 (80%) of those achieve SVR, with 2%/month attrition (21.5%/yr), we will have 198.3 person-years of follow-up when data collection is concluded, enough for a reasonably robust estimate.

4.2.2 Secondary Study Endpoints

Aim 2: Substance use. We will report rates of addiction treatment entry and retention;

changes in levels of self-reported alcohol and illicit drug consumption; and urine toxicology results. Outcomes will be examined at 3, 6, and 9 months after randomization, to assess the magnitude and durability of intervention effects. Effect sizes and 95% CIs will be reported.

Aim 3: HIV and HCV risk behaviors. We will report changes in frequency of three injection related and three sexual HIV risk behaviors: (a) injection drug use, (b) use of a syringe previously used by another person, and (c) use of any injection equipment (cooker, cotton, mixing water, mixing syringe, rinse water) previously or simultaneously used by another person, (d) condomless vaginal or anal sex, (e) sex with multiple partners (≥ 2 in past 6 months), and (f) sex in exchange for money or drugs. Outcomes will be reported at 3, 6, and 9 months after randomization, to assess the possibility of transient intervention effects.

4.2.3 Exploratory Endpoints

Although not a study aim, we will also report quality of life as an additional outcome. Quality of life will be measured using the HQLQ139 at baseline and 3, 6, and 9 months. Scores at 3, 6, and 9 months will be regressed on baseline scores to examine the effect of the intervention as compared with Usual Care. Effect sizes and 95% CIs will be reported for the effect of each intervention.

5 Study Enrollment and Withdrawal

5.1 Inclusion Criteria

In order to be eligible to participate in this study, an individual must meet all of the following criteria:

Persons will be eligible for HCV and HIV screening if they:
(1) are 18 years or older,
(2) injected heroin, cocaine, or other drugs in the past 30 days.

5.2 Exclusion Criteria

An individual who meets any of the following criteria will be excluded from participation in this study:

(1) Persons already in care for hepatitis C, defined as having had at least 2 visits with a hepatitis treatment provider within the past 6 months, will be excluded.

5.3 Vulnerable Subjects

N/A

5.4 Strategies for Recruitment and Retention

The Lower East Side Harm Reduction Center is a community based syringe exchange programs in New York City. Through funding from the New York City Department of Health 'Check Hep C' program these facilities have been screening syringe exchange participants for hepatitis C. Subjects who have active hepatitis C infection through screening done by the partnering facilities will be referred to the study team for potential enrollment. Study staff will work with syringe program staff to recruit participants. Syringe program staff will refer participants from their program in person to onsite study staff. Recruitment will occur through word of mouth with planned information sessions scheduled at the syringe program's weekly hepatitis C support groups. We will also seek referrals from other organizations serving people who use drugs (methadone maintenance treatment programs, homeless services, harm reduction organizations). In partnership with those organizations, we will engage in active and passive recruitment strategies. Staff at the collaborating organization will engage in active recruitment by identifying potential participants and providing a direct referral to study staff (either by phone or using a referral form). A passive recruitment strategy will be the display of informational flyers at the collaborating sites (see attached flyer). The study flyer will include a brief description of the study, some inclusion criteria and contact information. Additional passive recruitment strategies will include posting and distributing study

flyers in areas where people who use drugs are known to congregate (e.g., parks, near street drug markets).

5.5 Duration of Study Participation

52 to 144 weeks

5.6 Total Number of Participants and Sites

500 participants approached, 300 participants randomized. No participants will be enrolled at NYUMC.

5.7 Participant Withdrawal or Termination

5.7.1 Reasons for Withdrawal or Termination

Participants are free to withdraw from participation in the study at any time upon request. An investigator may terminate participation in the study if:

- Any clinical adverse event (AE), laboratory abnormality, or other medical condition or situation occurs such that continued participation in the study would not be in the best interest of the participant
- The participant meets an exclusion criterion (either newly developed or not previously recognized) that precludes further study participation

5.7.2 Handling of Participant Withdrawals or Termination

We will make every effort must be made to undertake protocol-specified safety follow-up procedures to capture AEs, serious adverse events (SAEs), and unanticipated problems (UPs).

There will be no replacement of participants who withdraw or discontinue early. Data will be analyzed as intention-to-treat.

5.8 Premature Termination or Suspension of Study

This study may be temporarily suspended or prematurely terminated if there is sufficient reasonable cause. Written notification, documenting the reason for study suspension or termination, will be provided by the suspending or terminating party to <investigator, funding agency, the IND/IDE sponsor and regulatory authorities>. If the study is prematurely terminated or suspended, the PI will promptly inform the IRB and will provide the reason(s) for the termination or suspension.
Circumstances that may warrant termination or suspension include, but are not limited to:

- Determination of unexpected, significant, or unacceptable risk to participants
- Demonstration of efficacy that would warrant stopping
- Insufficient compliance to protocol requirements
- Data that are not sufficiently complete and/or evaluable
- Determination of futility

Study may resume once concerns about safety, protocol compliance, data quality are addressed and satisfy the sponsor, IRB and/or FDA.

6 Study Agent (Study drug, device, biologic, vaccine etc.) and/or Procedural Intervention

N/A

7 Study Procedures and Schedule

7.1 Study Procedures/Evaluations

Initial Research Visit (all participants):

1. After signing the consent form, participants will be asked to provide contact information, including your personal telephone number. Also, we will ask participants whether there are friends or family members that we can contact if we have lost contact with you for any reason. No personal health information will be shared with these family or friends. These persons will simply be asked to convey the message that the study team is interested in seeing you. Every month participants will be asked to briefly check in with the study staff, and participants be asked if there are any changes in your contact information.
2. A member of the study team will administer a detailed questionnaire at the time of enrollment into the study. This questionnaire will ask questions about participants' demographics (e.g., age, gender, race), alcohol and drug use history and practices, sexual behavior, and experience with health care.
3. Human Immunodeficiency Virus (HIV) Testing. Participants will have a 10-to 15-minute HIV prevention counseling session with a trained staff member. The session will cover the meaning of results from the HIV test. Participants will also learn about how to reduce your chances of being infected with HIV and other infectious diseases. Participants will get counseling about what the test result means. Participants can get the result of your HIV test within about 20 minutes. Participants will get also get post-test counseling from a trained staff member and referrals to services you may need. If participants already know they have infection with the HIV virus, they may provide results of their HIV test from their medical records instead of doing this test.

At the initial research visit, participants will be randomly assigned to one of these two groups:

Group A: Accessible Care

OR

Group B: Usual Care

If you take part in this study and are assigned to Group A, you will have the following tests and procedures:

Group A-Accessible Care (Hepatitis C Care at Lower East Side Harm Reduction Center) The study will follow participants while receiving, or being offered, treatment for their hepatitis C infection at the Lower East Side Harm Reduction Center. The hepatitis C treatment, and the medications participants may receive for it, are not being tested as part of the study. However, their response to treatment, and the laboratory tests taken as routine usual care during treatment will be used for study purposes.

Research only visits (every 3 mos): Information that will be collected for the study will consist of (1) detailed questionnaires, and (2) one or more extra blood tests. The details of the study are as follows:

1. Questionnaires will be administered every three months for up to 12 months, independent of whether participants receive treatment for your hepatitis C, with questions about their substance use history and practices, sexual practices, and experience with health care. These interviews can be conducted at the research site, in-person at a different location, or over the telephone.
2. Human Immunodeficiency Virus (HIV) Testing as described above will be offered at a research visit every 6 months to those participants who previously tested negative for HIV.

3. If participants' Hepatitis C is cured they will continue to be followed for up to 144 weeks after treatment completion for the duration of the study.

Hepatitis Care and Treatment:

4. Participants will be scheduled to see a hepatitis C medical doctor at your harm reduction facility (Lower East Side Harm Reduction). If a participant decides to attend the hepatitis C medical evaluation, a study doctors will evaluate them to find out whether you would benefit from treatment for hepatitis C. The doctor will ask participants questions, examine them, give them information, and answer their questions about hepatitis C, about treatment for hepatitis C, and about the risks and benefits of being treated. The purpose of the medical evaluation is to decide whether participants need treatment for your hepatitis C and what the best treatment would be. Participants will receive a standard medical evaluation to assess your Hepatitis C treatment needs.
5. At the medical evaluation, about 20mL (4teaspoons) of blood will also be drawn by one of the other research staff members, and sent to New York Presbyterian Hospital. The blood will be tested to assess participants' health and liver. A small percentage of the blood drawn will be stored at the Weill Cornell Medical College Clinical and Translational Science Center for future testing of characteristics of your hepatitis C virus.
6. We will schedule participants to come back in 2 weeks to find out the results of your blood tests. Participants and their hepatitis C doctor will work together to make an informed decision about whether participants will take medication used to treat hepatitis C. The doctor will explain the risks and benefits of taking any medicines before you take them. The medications the doctor will prescribe are the current best standard of HCV treatment available. If the doctor recommends that the participant take these medications, participants will be free to decide whether or not to take them.
7. If participants take the medication for hepatitis C, they will get appointments to come back to pick up their medication. Hepatitis C medications prescriptions will be sent to specialty pharmacies, and when obtained, delivery of medication will be to the harm reduction facility or patients residence if novel coronavirus is an issue.
8. If participants begin treatment for hepatitis C, standard blood tests for monitoring the treatment will be performed by a members of the research staff (or commercial lab testing centres if novel coronavirus is an issue), at weeks 2, 4 and 12 of treatment, and 4 and 12 weeks after the end of treatment. In addition, an extra two teaspoons of blood may be drawn at each of these visits for research purposes and sent for storage at Cornell's Clinical and Translational Science Center. These samples may be tested to look for signs of multiple concurrent hepatitis C infections, and help to decipher treatment failure from re-infection in participants who do not achieve cure of their hepatitis C.
9. If participants start the medications used to treat hepatitis C and want to stop them before their treatment is finished, they are free to do so and will not be penalized in any way, although this could limit the success of hepatitis C treatment. Participants will be encouraged to continue with the study questionnaires every three months.
10. Within 6 months of enrolling in the study, participants will have a one-on-one meeting with a hepatitis C study coordinator to review harm reduction practices. This discussion will include discussions on prevention of hepatitis C transmission and re-infection, ways to engage in safe injection practices and avoid cross-contamination of injection equipment while injecting with others.
11. Data from participants' clinical medical records will be entered into our research database during the course of your treatment by a members of the research staff. These data include, but are not limited to, hepatitis C genotype, hepatitis C viral load, fibrosure results(looking for signs of cirrhosis), HIV antibody, sustained virologic response (defined as no detectable hepatitis C virus 12 weeks after completing therapy), and any side effects or adverse effects you experience during therapy

If participants agree to take part in this study and are assigned to Group B, participants will have the following tests and procedures:

Group B –Usual Care Group (Hepatitis Care at usual locations in the community): If assigned to this group, participants will participate in research visits but not receive hepatitis care or treatment at the Lower East Side Harm Reduction Center as part of the study. Participants can obtain care and treatment for hepatitis C at the usual locations in the community.

Research Visits (every 3 mos): Information that will be collected for the study will consist of (1) detailed questionnaires, and (2) one or more extra blood tests. The details of the study are as follows:

1. Questionnaires will be administered every three months for up to 12 months, independent of whether participants receive treatment for your hepatitis C, with questions about their demographics (e.g., age, gender, race), their alcohol and drug use history and practices, sexual practices and experience with health care.
2. One teaspoon of your blood will be drawn and sent to New York Presbyterian Hospital –Weill Cornell Translation Science Center where it will be processed and stored for potential future testing of characteristics of your Hepatitis C virus.
3. Human Immunodeficiency Virus (HIV) testing as described above will be offered at a research visit every 6 months to those participants who previously tested negative for HIV.

Hepatitis Care and Treatment:

4. Participants will be referred to a hepatitis C case manager (funded through the New York City Department of Health Check Hep C Program), on site at their harm reduction facility (Lower East Side Harm Reduction Center), who will assist participants with referral for hepatitis C care within the community.
5. If participants start treatment for hepatitis C during their time in the study, we will ask participants to give us permission to talk with their hepatitis C doctor so we can have access to their medical records and monitor how they are responding to treatment.
6. If participants achieve a sustained virologic response after completing hepatitis C treatment, which means that the treatment was successful, participants will be given an appointment to come back every three months to complete a study interview and be tested for hepatitis C, for up to 144 weeks after treatment completion, to find out whether they are still negative, or to see whether they get re-infected.

QUALITATIVE INTERVIEWS During the study, we may ask participants to take part in an interview about their experiences related to hepatitis C treatment. This will last about 60-90-minutes. If participants choose to participate, the interview will be digitally audio-recorded. If participants are selected for this interview we will ask participants about: health care and hepatitis C-related healthcare experiences, alcohol and drug use, injection risk behaviors and sexual practices. We will ask participants how these changed, if they did, during their taking part in the study.

7.2 Concomitant Medications, Treatments, and Procedures

N/A

7.3 Justification for Sensitive Procedures

N/A

7.4 Prohibited Medications, Treatments, and Procedures

N/A

7.5 Prophylactic Medications, Treatments, and Procedures

N/A

7.6 Rescue Medications, Treatments, and Procedures

N/A

7.7 Participant Access to Study Agent at Study Closure

N/A – finite course of treatment.

8 Assessment of Safety

8.1 Specification of Safety Parameters

We anticipate that providing HCV care and treatment on site at a community syringe exchange center will allow access to treatment for greater numbers of people who inject drugs (PWID). Treatment on this study will include FDA-approved standard of care regimens with excellent safety profile; however limited data exists on the use of these agents in PWID. While experts have little concern for drug-drug interactions between most DAAs and illicit drugs, we have chosen to monitor HCV Treatment-related SAEs, Hospitalizations and Deaths related to Overdose, and Overall Deaths as safety endpoints that would trigger review of the study. Other on treatment side effects will also be captured and described, but will not impact conduct of the study and thus will not be reported to DSMB. Currently, HCV cure rates exceed 90% with currently available all oral DAA regimens in clinical trials and recent clinical cohorts regardless of HCV genotype; however little is known about treatment efficacy and safety in active drug users as these patients are typically excluded from clinical trials. One clinical trial of a modern era DAA regimen was conducted in 301 persons receiving opioid agonist therapy (OAT) (Merck C-EDGE Co-STAR) and provides some safety and efficacy data relevant to our study. It did not exclude patients who were actively using drugs of potential abuse, and more than 50% of patients had at least one urine drug screen positive for potential drugs of abuse. The study randomized patients to the fixed dose combination of elbasvir/grazoprevir or placebo, so that safety could be carefully ascertained in this patient population perceived as being high risk for unrelated adverse events. Those that received placebo were subsequently treated open label. The primary efficacy outcome showed an SVR 12 of 91.5% in the immediate treatment group and 89.5% in the delayed treatment group. Positive urine drug screens did not affect adherence or efficacy. 18 patients had recurrent viremia and 5 were due to probable reinfection. The safety profile was similar between treatment and placebo with rare SAEs (3.5% in treated, 4% in placebo); however, only 1 SAE in each group was considered treatment-related. The high efficacy and relative safety of this study of patients on OAT, many of who also used drugs of potential abuse, is reassuring that HCV treatment may be safely delivered to our study population.

8.1.1 Definition of Adverse Events (AE)

An ***adverse event*** (AE) is any symptom, sign, illness or experience that develops or worsens in severity during the course of the study. Intercurrent illnesses or injuries should be regarded as adverse events. Abnormal results of diagnostic procedures are considered to be adverse events if the abnormality:

- results in study withdrawal
- is associated with a serious adverse event
- is associated with clinical signs or symptoms
- leads to additional treatment or to further diagnostic tests
- is considered by the investigator to be of clinical significance

8.1.2 Definition of Serious Adverse Events (SAE)

Serious Adverse Event

Adverse events are classified as serious or non-serious. A ***serious adverse event*** is any AE that is:

- fatal

- life-threatening
- requires or prolongs hospital stay
- results in persistent or significant disability or incapacity
- a congenital anomaly or birth defect
- an important medical event

Important medical events are those that may not be immediately life threatening, but are clearly of major clinical significance. They may jeopardize the subject, and may require intervention to prevent one of the other serious outcomes noted above. For example, drug overdose or abuse, a seizure that did not result in in-patient hospitalization, or intensive treatment of bronchospasm in an emergency department would typically be considered serious.

All adverse events that do not meet any of the criteria for serious should be regarded as ***non-serious adverse events***.

8.1.3 Definition of Unanticipated Problems (UP)

Unanticipated Problems Involving Risk to Subjects or Others
Any incident, experience, or outcome that meets all of the following criteria:

- Unexpected in nature, severity, or frequency (i.e. not described in study-related documents such as the IRB-approved protocol or consent form, the investigators brochure, etc)
- Related or possibly related to participation in the research (i.e. 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)
- Suggests that the research places subjects or others at greater risk of harm (including physical, psychological, economic, or social harm).

8.2 Classification of an Adverse Event

8.2.1 Severity of Event

For AEs not included in the protocol defined grading system, the following guidelines will be used to describe severity.

- **Mild** – Events require minimal or no treatment and do not interfere with the participant's daily activities.
- **Moderate** – Events result in a low level of inconvenience or concern with the therapeutic measures. Moderate events may cause some interference with functioning.
- **Severe** – Events interrupt a participant's usual daily activity and may require systemic drug therapy or other treatment. Severe events are usually potentially life-threatening or incapacitating.

8.2.2 Relationship to Study Agent

For all collected AEs, the clinician who examines and evaluates the participant will determine the AE's causality based on temporal relationship and his/her clinical judgment. The degree of certainty about causality will be graded using the categories below.

- ***Definitely Related*** *– There is clear evidence to suggest a causal relationship, and other possible contributing factors can be ruled out. The clinical event, including an abnormal laboratory test result, occurs in a plausible time relationship to drug administration and cannot be explained by concurrent disease or other drugs or chemicals. The response to withdrawal of the drug (dechallenge) should be clinically plausible. The event must be pharmacologically or phenomenologically definitive, with use of a satisfactory rechallenge procedure if necessary.*
- ***Probably Related*** *– There is evidence to suggest a causal relationship, and the influence of other factors is unlikely. The clinical event, including an abnormal laboratory test result, occurs within a reasonable time after administration of the drug, is unlikely to be attributed to concurrent disease or other drugs or chemicals, and follows a clinically reasonable response on withdrawal (dechallenge). Rechallenge information is not required to fulfill this definition.*
- ***Possibly Related*** *– There is some evidence to suggest a causal relationship (e.g., the event occurred within a reasonable time after administration of the trial medication). However, other factors may have contributed to the event (e.g., the participant's clinical condition, other concomitant events). Although an AE may rate only as "possibly related" soon after discovery, it can be flagged as requiring more information and later be upgraded to "probably related" or "definitely related," as appropriate.*
- ***Unlikely to be related*** *– A clinical event, including an abnormal laboratory test result, whose temporal relationship to drug administration makes a causal relationship improbable (e.g., the event did not occur within a reasonable time after administration of the trial medication) and in which other drugs or chemicals or underlying disease provides plausible explanations (e.g., the participant's clinical condition, other concomitant treatments).*
- ***Not Related*** *– The AE is completely independent of study drug administration, and/or evidence exists that the event is definitely related to another etiology. There must be an alternative, definitive etiology documented by the clinician.*

8.2.3 Expectedness

Benjamin Eckhardt will be responsible for determining whether an AE is expected or unexpected. An AE will be considered unexpected if the nature, severity, or frequency of the event is not consistent with the risk information previously described for the study agent.

8.3 Time Period and Frequency for Event Assessment and Follow-Up

The occurrence of an AE or SAE may come to the attention of study personnel during study visits and interviews of a study participant presenting for medical care, or upon review by a study monitor. All AEs including local and systemic reactions not meeting the criteria for SAEs will be captured on the appropriate RF. Information to be collected includes event description, time of onset, clinician's assessment of severity, relationship to study product (assessed only by those with the training and authority to make a diagnosis), and time of resolution/stabilization of the event. All AEs occurring while on study must be documented appropriately regardless of relationship. All AEs will be followed to adequate resolution.

Any medical condition that is present at the time that the participant is screened will be considered as baseline and not reported as an AE. However, if the study participant's condition deteriorates at any time during the study, it will be recorded as an AE. UPs will be recorded in the data collection system throughout the study.

Changes in the severity of an AE will be documented to allow an assessment of the duration of the event at each level of severity to be performed. AEs characterized as intermittent require documentation of onset and duration of each episode.

The PI will record all reportable events with start dates occurring any time after informed consent is obtained until 7 (for non-serious AEs) or 30 days (for SAEs) after the last day of study participation. At each study visit, the investigator will inquire about the occurrence of AE/SAEs since the last visit. Events will be followed for outcome information until resolution or stabilization.

All unresolved adverse events should be followed by the investigator until the events are resolved, the subject is lost to follow-up, or the adverse event is otherwise explained. At the last scheduled visit, the investigator should instruct each subject to report any subsequent event(s) that the subject, or the subject's personal physician, believes might reasonably be related to participation in this study. The investigator should notify the study sponsor of any death or adverse event occurring at any time after a subject has discontinued or terminated study participation that may reasonably be related to this study. The sponsor should also be notified if the investigator should become aware of the development of cancer or of a congenital anomaly in a subsequently conceived offspring of a subject that has participated in this study.

8.4 Reporting Procedures – Notifying the IRB

8.4.1 Adverse Event Reporting

Immediately report any harm experienced by a participant or other individual, whether occurring to a subject enrolled related to the human research procedure(s), and/or intervention(s)when ALL of the following three (3) conditions are met:

1. The harm is "unexpected" when its specificity and severity are not accurately reflected in the WCM consent document, Investigator's Brochure (if applicable), or package insert (if applicable); AND

2. The harm is "related" or "possibly related", where there is a reasonable possibility that the harm may have been caused by the research procedure(s), or intervention(s) AND

3. The harm suggests that the research places WCM subjects at greater risk of harm (including physical, psychological, economic or social harm) than was previously known or recognized.

If ALL of the three (3) conditions are met, submit the Immediate Report within 7 calendar days of PI awareness.

At the time of IRB Continuing Review, an Adverse Event Reporting Cumulative Table will be submitted listing adverse events from the study site that are both expected and unexpected and for which ANY of the following apply:

1. Severe or medically significant, but not immediately life-threatening; hospitalization or prolongation of hospitalization indicated; disabling; limiting self care activities of daily living (Grade 3)*

2. Life-threatening consequences; urgent intervention indicated (Grade 4)

3. Death related AE (Grade 5) Serious Adverse Event Reporting

8.5 Safety Oversight

It is the responsibility of the Principal Investigator to oversee the safety of the study at his/her site. This safety monitoring will include careful assessment and appropriate reporting of adverse events as noted above, as well as the construction and implementation of a site data and safety-monitoring plan. Medical monitoring will include a regular assessment of the number and type of serious adverse events.

Safety oversight will be under the direction of a Weill Cornell-based DSMB composed of individuals with the appropriate expertise, including hepatitis C and substance use disorder. The DSMB will meet at least semiannually to assess safety and efficacy data on each arm of the study. The DSMB will operate under the rules of an approved charter that will be written and reviewed at the organizational meeting of the DSMB. At this time, each data element that the DSMB needs to assess will be clearly defined. The DSMB will provide its input to the study sponsor (NIDA).

9 Statistical Considerations

9.1 Statistical and Analytical Plans (SAP)

We will examine a series of study outcomes in both study arms in order to evaluate the effectiveness of the Accessible Care (AC) intervention as compared with Usual Care (UC). Our three Aims are to compare hepatitis treatment, substance use, and HIV and HCV prevention outcomes in the two arms in order to answer three fundamental questions about the AC intervention: (1) Is it sufficiently safe and effective to allow active PWID in appreciable numbers to be successfully treated for hepatitis C? (2) Does it reduce substance use? (3) Does it reduce HIV and HCV risk behaviors? We will assess a multiplicity of outcome measures in order to fully describe the experience of participants in each arm.

9.2 Statistical Hypotheses

Specific Aim 1: Hepatitis C Outcomes.

Hepatitis C treatment engagement. We will assess the proportion of patients in each arm who (a) referred to a hepatitis C treatment provider, (b) attend an initial visit with a hepatitis treatment provider, and (c) complete a medical evaluation for antiviral treatment, including a history, physical examination, and laboratory evaluation. Proportions with 95% confidence intervals (CIs) calculated using the exact binomial method will be reported. Persons who are lost to follow-up will be considered in each analysis as not having reached the outcome, according to intent-to-treat principles.

Hepatitis C treatment success. We will compare the frequency of two hepatitis C treatment endpoints in the two arms in an intent-to-treat fashion, in order to evaluate the hypotheses that PWID in the intervention arm will be more likely than those in the control arm to begin treatment and achieve virologic responses to antiviral treatment for hepatitis C. The two endpoints will be defined as follows. Antiviral treatment initiation will be defined as physically receiving the first dose of antiviral medication. Sustained virologic response (SVR) will be defined as testing HCV RNA negative 12+ weeks after treatment completion.

Cost of intervention: The HCCC and the Clinician will log time spent providing services, excluding research activities. Costs will be assigned to staff time based on prevailing national wage rates. Patient time costs will also be estimated based on time spent with staff members and will be valued based on the minimum wage because most patients are likely to be unemployed. We will describe patient-reported health care visits, employment, and incarceration that will be used as inputs to future cost or cost-effectiveness studies.

Reinfection: We will report reinfection rates in all patients in both arms who achieve SVR using time-toevent methods. If 150 participants initiate antiviral therapy (50% overall) and 120 (80%) of those achieve SVR, with 2%/month attrition (21.5%/yr), we will have 198.3 person-years of follow-up when data collection is concluded, enough for a reasonably robust estimate.

Specific Aim 2: Substance use. We will report rates of addiction treatment entry and retention; changes in levels of self-reported alcohol and illicit drug consumption; and urine toxicology results. Outcomes will be examined at 3, 6, and 9 months after randomization, to assess the magnitude and durability of intervention effects. Effect sizes and 95% CIs will be reported.

Specific Aim 3: HIV and HCV risk behaviors. We will report changes in frequency of three injection related and three sexual HIV risk behaviors: (a) injection drug use, (b) use of a syringe previously used by another person, and (c) use of any injection equipment (cooker, cotton, mixing water, mixing syringe, rinse water) previously or simultaneously used by another person, (d) condomless vaginal or anal sex, (e) sex with multiple partners (≥ 2 in past 6 months), and (f) sex in exchange for money or drugs. Outcomes

will be reported at 3, 6, and 9 months after randomization, to assess the possibility of transient intervention effects.

Subgroup Analyses. We will conduct exploratory analyses of group assignment effects on study outcomes with 95% confidence intervals in the following subgroups that we hypothesize may differ in their ability to benefit from the AC intervention: (1) men and women (2) older and younger than sample median (3) homeless and housed (4) cocaine use and none (5) daily and less frequent illicit drug injection (6) heavy alcohol use (≥5 drinks/day) and less or none (7) health care utilization in past 6 months and none (8) psychiatric diagnosis and none. In the event of statistically significant interactions we will report treatment group assignment effects in subgroups only.

9.3 Analysis Datasets

Outcomes will be compared using intent-to-treat analyses

9.4 Sample Size

Using standard methods for power calculations and α=.05, a randomized trial comparing two arms with 150 participants in each arm will have 80% power to detect the differences in proportions of study endpoints in the two arms shown in Figure 3. This power will be sufficient to detect meaningful differences between the study arms and achieve our study aims. For example, we will have 80% power to detect a difference if 66% of participants initiate antiviral therapy in an intervention arm and 50% in the control arm do. Differences between the arms of 20% or more in any outcome will be detectable (see Figure 3). These are clinically meaningful differences and are conservative estimates of our anticipated effect sizes. sert Text>

9.5 Measures to Minimize Bias

As described above, participants will be randomized after conducting baseline survey to either the Accessible Care or Usual Care arms. If a participant withdrawals from the study, no replacement will be made.

The study is not blinded.

10 Source Documents and Access to Source Data/Documents

Source data is all information, original records of clinical findings, observations, or other activities in a clinical trial necessary for the reconstruction and evaluation of the trial. Source data are contained in source documents. Examples of these original documents, and data records include: hospital records, clinical and office charts, laboratory notes, memoranda, subjects' diaries or evaluation checklists, pharmacy dispensing records, recorded data from automated instruments, copies or transcriptions certified after verification as being accurate and complete, microfiches, photographic negatives, microfilm or magnetic media, x-rays, subject files, and records kept at the pharmacy, at the laboratories, and at medico-technical departments involved in the clinical trial. It is acceptable to use CRFs as source documents. If this is the case, it should be stated in this section what data will be collected on CRFs and what data will be collected from other sources.

The study case report form (CRF) is the primary data collection instrument for the study. All data requested on the CRF must be recorded. All missing data must be explained. If a space on the CRF is left blank because the procedure was not done or the question was not asked, write "N/D". If the item is not applicable to the individual case, write "N/A". All entries should be printed legibly in black ink. If any entry error has been made, to correct such an error, draw a single straight line through the incorrect entry and enter the correct data above it. All such changes must be initialed and dated. DO NOT ERASE OR

WHITE OUT ERRORS. For clarification of illegible or uncertain entries, print the clarification above the item, then initial and date it.

Access to study records will be limited to IRB-approved members of the study team. The investigator will permit study-related monitoring, audits, and inspections by the IRB/EC, the sponsor, government regulatory bodies, and University compliance and quality assurance groups of all study related documents (e.g. source documents, regulatory documents, data collection instruments, study data etc.). The investigator will ensure the capability for inspections of applicable study-related facilities (e.g. pharmacy, diagnostic laboratory, etc.).

Participation as an investigator in this study implies acceptance of potential inspection by government regulatory authorities and applicable University compliance and quality assurance offices.

11 Ethics/Protection of Human Subjects

11.1 Ethical Standard

The investigator will ensure that this study is conducted in full conformity with Regulations for the Protection of Human Subjects of Research codified in 45 CFR Part 46, 21 CFR Part 50, 21 CFR Part 56, and/or the ICH E6.

11.2 Institutional Review Board

The protocol, informed consent form(s), recruitment materials, and all participant materials will be submitted to the IRB for review and approval. Approval of both the protocol and the consent form must be obtained before any participant is enrolled. Any amendment to the protocol will require review and approval by the IRB before the changes are implemented to the study. All changes to the consent form will be IRB approved; a determination will be made regarding whether previously consented participants need to be re-consented.

11.3 Informed Consent Process

11.3.1 Consent/Assent and Other Informational Documents Provided to Participants

Consent forms describing in detail the study agent, study procedures, and risks are given to the participant and written documentation of informed consent is required prior to starting intervention/administering study product. The following consent materials are submitted with this protocol.

- Screening Consent
- Accessible Care Consent

11.3.2 Consent Procedures and Documentation

Informed consent is a process that is initiated prior to the individual's agreeing to participate in the study and continues throughout the individual's study participation. Extensive discussion of risks and possible benefits of participation will be provided to the participants and their families. Consent forms will be IRB-approved and the participant will be asked to read and review the document. The investigator will explain the research study to the participant and answer any questions that may arise. All participants will receive a verbal explanation in terms suited to their comprehension of the purposes, procedures, and potential

risks of the study and of their rights as research participants. Participants will have the opportunity to carefully review the written consent form and ask questions prior to signing. The participants should have the opportunity to discuss the study with their surrogates or think about it prior to agreeing to participate. The participant will sign the informed consent document prior to any procedures being done specifically for the study. The participants may withdraw consent at any time throughout the course of the trial. A copy of the signed informed consent document will be given to the participants for their records. The rights and welfare of the participants will be protected by emphasizing to them that the quality of their medical care will not be adversely affected if they decline to participate in this study.

A copy of the signed informed consent document will be stored in the subject's research record. The consent process, including the name of the individual obtaining consent, will be thoroughly documented in the subject's research record. Any alteration to the standard consent process (e.g. use of a translator, consent from a legally authorized representative, consent document presented orally, etc.) and the justification for such alteration will likewise be documented.

11.4 Participant and Data Confidentiality

Information about study subjects will be kept confidential and managed according to the requirements of the Health Insurance Portability and Accountability Act of 1996 (HIPAA). Those regulations require a signed subject authorization informing the subject of the following:

- What protected health information (PHI) will be collected from subjects in this study
- Who will have access to that information and why
- Who will use or disclose that information
- The rights of a research subject to revoke their authorization for use of their PHI.

In the event that a subject revokes authorization to collect or use PHI, the investigator, by regulation, retains the ability to use all information collected prior to the revocation of subject authorization. For subjects that have revoked authorization to collect or use PHI, attempts should be made to obtain permission to collect at least vital status (i.e. that the subject is alive) at the end of their scheduled study period.

Participant confidentiality is strictly held in trust by the participating investigators, their staff, and the sponsor(s) and their agents. This confidentiality is extended to cover testing of biological samples and genetic tests in addition to the clinical information relating to participants. Therefore, the study protocol, documentation, data, and all other information generated will be held in strict confidence. No information concerning the study or the data will be released to any unauthorized third party without prior written approval of the sponsor.

The study monitor, other authorized representatives of the sponsor, representatives of the IRB or pharmaceutical company supplying study product may inspect all documents and records required to be maintained by the investigator, including but not limited to, medical records (office, clinic, or hospital) and pharmacy records for the participants in this study. The clinical study site will permit access to such records.

The study participant's contact information will be securely stored at each clinical site for internal use during the study. At the end of the study, all records will continue to be kept in a secure location for as long a period as dictated by local IRB and Institutional regulations.

Study participant research data, which is for purposes of statistical analysis and scientific reporting, will be transmitted to and stored at NYU Langone Medical Center. This will not include the participant's contact or identifying information. Rather, individual participants and their research data will be identified by a unique study identification number. The study data entry and study management systems used by clinical sites and by NYU Langone Medical Center research staff will be secured and password protected.

At the end of the study, all study databases will be de-identified and archived at the NYU Langone Medical Center.

11.4.1 Research Use of Stored Human Samples, Specimens, or Data

- Intended Use: Samples and data collected under this protocol may be used to study the heterogeneity of hepatitis C virus within our population, and other viral characteristics. No genetic testing will be performed.
- Storage: Access to stored samples will be limited using stored plasma. Samples and data will be stored using codes assigned by the investigators. Data will be kept in password-protected computers. Only investigators will have access to the samples and data.
- Tracking: Data will be tracked using de-identified participants codes.
    - Disposition at the completion of the study: All stored samples will be sent to a Weill Cornell Clinical and Translational Science Center for Storage. Study participants who request destruction of samples will be notified of compliance with such request and all supporting details will be maintained for tracking.

11.5 Future Use of Stored Specimens

Data collected for this study will be analyzed and stored at the Weill Cornell Medicine (clinical data) and the National Development and Research Institutes (behavioral data). After the study is completed, the de-identified, archived data will be transmitted to and stored at the National Development and Research Institute, under the supervision of Pedro Mateu-Gelabert, for use by other researchers including those outside of the study. Permission to transmit data to the data repository will be included in the informed consent.

With the participant's approval and as approved by local IRs, de-identified biological samples will be stored at the Weill Cornell Clinical and Translational Science Center. These samples could be used for research into the causes of hepatitis C, its complications and other conditions for which individuals with hepatitis C are at increased risk, and to improve treatment. The Weill Cornell Clinical and Translational Science Center will also be provided with a code-link that will allow linking the biological specimens with the phenotypic data from each participant, maintaining the masking of the identity of the participant.

During the conduct of the study, an individual participant can choose to withdraw consent to have biological specimens stored for future research. However, withdrawal of consent with regard to biosample storage will not be possible after the study is completed.

When the study is completed, access to study data and/or samples will be provided through the Weill Cornell Clinical and Translational Science Center.

12 Data Handling and Record Keeping

12.1 Data Collection and Management Responsibilities

Data collection is the responsibility of the clinical trial staff at the site under the supervision of the site PI. The investigator is responsible for ensuring the accuracy, completeness, legibility, and timeliness of the data reported.

All source documents should be completed in a neat, legible manner to ensure accurate interpretation of data. Black ink is required to ensure clarity of reproduced copies. When making changes or corrections,

cross out the original entry with a single line, and initial and date the change. DO NOT ERASE, OVERWRITE, OR USE CORRECTION FLUID OR TAPE ON THE ORIGINAL.

Copies of the electronic CRF (eCRF) will be provided for use as source documents and maintained for recording data for each participant enrolled in the study. Data reported in the eCRF derived from source documents should be consistent with the source documents or the discrepancies should be explained and captured in a progress note and maintained in the participant's official electronic study record.

Clinical data (including AEs, concomitant medications, and expected adverse reactions data) and clinical laboratory data will be entered into ONA, a 21 CFR Part 11-compliant data capture system provided by the National Development and Research Institute. The data system includes password protection and internal quality checks, such as automatic range checks, to identify data that appear inconsistent, incomplete, or inaccurate. Clinical data will be entered directly from the source documents.

12.2 Study Records Retention

Study documents will be retained for the longer of 3 years after close-out, 5 years after final reporting/publication, or 2 years after the last approval of a marketing application is approved for the drug for the indication for which it is being investigated or 2 years after the investigation is discontinued and FDA is notified if no application is to be filed or if the application has not been approved for such indication. No records will be destroyed without the written consent of the sponsor, if applicable. It is the responsibility of the sponsor to inform the investigator when these documents no longer need to be retained.

12.3 Protocol Deviations

A protocol deviation is any noncompliance with the clinical trial protocol, GCP, or Manual of Procedures (MOP) requirements. The noncompliance may be either on the part of the participant, the investigator, or the study site staff. As a result of deviations, corrective actions are to be developed by the site and implemented promptly.

These practices are consistent with ICH E6:

- 4.5 Compliance with Protocol, sections 4.5.1, 4.5.2, and 4.5.3
- 5.1 Quality Assurance and Quality Control, section 5.1.1
- 5.20 Noncompliance, sections 5.20.1, and 5.20.2.

It is the responsibility of the site PI/study staff to use continuous vigilance to identify and report deviations within five working days of identification of the protocol deviation, or within five working days of the scheduled protocol-required activity.

All protocol deviations must be addressed in study source documents, and reported to NIDA Program Official.

Protocol deviations must be reported to the local IRB per their guidelines. The site PI/study staff is responsible for knowing and adhering to their IRB requirements. Further details about the handling of protocol deviations will be included in the MOP.

12.4 Publication and Data Sharing Policy

This study will comply with the NIH Public Access Policy, which ensures that the public has access to the published results of NIH funded research. It requires scientists to submit final peer-reviewed journal

manuscripts that arise from NIH funds to the digital archive PubMed Central upon acceptance for publication.

The International Committee of Medical Journal Editors (ICMJE) member journals have adopted a clinical trials registration policy as a condition for publication. The ICMJE defines a clinical trial as any research project that prospectively assigns human subjects to intervention or concurrent comparison or control groups to study the cause-and-effect relationship between a medical intervention and a health outcome. Medical interventions include drugs, surgical procedures, devices, behavioral treatments, process-of-care changes, and the like. Health outcomes include any biomedical or health-related measures obtained in patients or participants, including pharmacokinetic measures and adverse events. The ICMJE policy, and the Section 801 of the Food and Drug Administration Amendments Act of 2007, requires that all clinical trials be registered in a public trials registry such as ClinicalTrials.gov, which is sponsored by the National Library of Medicine. Other biomedical journals are considering adopting similar policies. For interventional clinical trials performed under NIH IC grants and cooperative agreements, it is the grantee's responsibility to register the trial in an acceptable registry, so the research results may be considered for publication in ICMJE member journals. The ICMJE does not review specific studies to determine whether registration is necessary; instead, the committee recommends that researchers who have questions about the need to register err on the side of registration or consult the editorial office of the journal in which they wish to publish.

FDAAA mandates that a "responsible party" (i.e., the sponsor or designated principal investigator) register and report results of certain "applicable clinical trials":

- Trials of Drugs and Biologics: Controlled, clinical investigations, other than Phase I investigations of a product subject to FDA regulation;
- Trials of Devices: Controlled trials with health outcomes of a product subject to FDA regulation (other than small feasibility studies) and pediatric postmarket surveillance studies.
- NIH grantees must take specific steps to ensure compliance with NIH implementation of FDAAA.

13 Study Finances

13.1 Funding Source

National Institute on Drug Abuse

13.2 Costs to the Participant

None

13.3 Participant Reimbursements or Payments

Participants will receive cash compensation for completing the research questionnaires (and, if applicable, providing blood) that are a part of this study, of which there will be at least four. The first research visit is the longest and is anticipated to take between 60-90 minutes. The subsequent research visits should take between 60 and 75 minutes. Participants will not be compensated for seeing the care coordinator, attending medical visits, or undergoing hepatitis C treatment. Participants will be compensated for each of the research visits which include questionnaire and, if applicable, drawing blood. The compensation schedule is as follows: $60 for first research visit; $50 for the second and third research visit (approximately at 3 and 6 months of first research visit); $60 for the forth research visit (approximately at 9 months of first research visit/interview); and $70 for the fifth research Page 8 of 37 10/31/17 10:51 AM visit (approximately at 12 months of first research visit/interview). $40 for subsequent research visits, if any. $50 for qualitative interview if the participant is asked and agrees to participate. $5 for each monthly check-in visit These compensations will be received in cash at the study visit.

Participants will be compensated $20 for referral of a new participant. Participates will be eligible for this compensation regardless of whether the new participant enrolls in the study.

14 Conflict of Interest Policy

The independence of this study from any actual or perceived influence, such as by the pharmaceutical industry, is critical. Therefore any actual conflict of interest of persons who have a role in the design, conduct, analysis, publication, or any aspect of this trial will be disclosed and managed. Furthermore, persons who have a perceived conflict of interest will be required to have such conflicts managed in a way that is appropriate to their participation in the trial. The study leadership in conjunction with the NIDA has established policies and procedures for all study group members to disclose all conflicts of interest and will establish a mechanism for the management of all reported dualities of interest.

Any investigator who has a conflict of interest with this study (patent ownership, royalties, or financial gain greater than the minimum allowable by their institution, etc.) must have the conflict reviewed by the NYU Langone Conflict of Interest Management Unit (CIMU) with a Committee-sanctioned conflict management plan that has been reviewed and approved by the study sponsor prior to participation in this study. All NYULMC investigators will follow the applicable conflict of interest policies.

15 Attachments

These documents are relevant to the protocol, but they are not considered part of the protocol. They are stored and modified separately. As such, modifications to these documents do not require protocol amendments.