Patient-Centered Models of HCV Care for People Who Inject Drugs
The HERO Study: Hepatitis C Real Options

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Protocol Co-Chairs: Alain Litwin, MD, Kimberly Page, Ph.D., MPH

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STATEMENT OF COMPLIANCE

The study will be carried out in accordance with Good Clinical Practice (GCP) as required by the following:

- United States (US) Code of Federal Regulations (CFR) applicable to clinical studies (45 CFR Part 46; 21 CFR Part 50, 21 CFR Part 56, and 21 CFR Part 312)
- International Conference of Harmonisation (ICH) E6; 62 Federal Register 25691 (1997)
- Patient-Centered Outcomes Research Initiatives Clinical Terms of Award

All key personnel (all individuals responsible for the design and conduct of this study) have completed Human Subjects Protection Training.

SIGNATURE PAGE

The signatures below constitute the approval of this protocol and appendices, and provide the necessary assurances that this trial will be conducted according to all stipulations of the protocol, including all statements regarding confidentiality, and according to local legal and regulatory requirements and applicable US federal regulations and ICH guidelines.

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LIST OF ABBREVIATIONS

Ab	Antibody
AASLD	American Association for the Study of Liver Diseases
ACTG	AIDS Clinical Trials Group
AE	Adverse Event/Adverse Experience
AIDS	Acquired Immune Deficiency Syndrome
ALT	Alanine Aminotransferase
APRI	AST to Platelet Ratio Index
ASI	Addiction Severity Index
AST	Aspartate Aminotransferase
AUDIT	Alcohol Use Disorders Identification Test
CHC	Community Health Center
CBO	Community-Based Organization
CD4	Cluster of Differentiation 4
CDC	Centers for Disease Control and Prevention
CI	Confidence Interval
CITI	Collaborative Institutional Training Initiative
CFR	Code of Federal Regulations
Co-I	Co-Investigator
CRC	Clinical Research Center
CRF	Case Report Form
CT	Computed Tomography
DAA	Direct-acting Antiviral Agent
DOH	Department of Health
DOT	Directly Observed Therapy
DSM	Data and Safety Monitoring
EASL	European Association for the Study of the Liver
eCRF	Electronic Case Report Form
eDOT	Electronic Directly Observed Therapy
EDTA	Ethylenediaminetetraacetic Acid
ETR	End of Treatment Response
FDA	Food and Drug Administration, DHHS
FDC	Fixed Dose Combination
FIB	Fibrosis
FQHC	Federally Qualified Health Center
FWA	Federalwide Assurance
GAD	Generalized Anxiety Disorder
GCP	Good Clinical Practice
HAART	Highly Active Anti-Retroviral Therapy

HBsAg	Hepatitis B Surface Antigen
HBV	Hepatitis B Virus
HCC	Hepatocellular Carcinoma
HCV	Hepatitis C Virus
HERO	Hepatitis C Real Options
HgB	Hemoglobin
HIPAA	Health Insurance Portability and Accountability Act
HIV	Human Immunodeficiency Virus
HRC	Human Rights Campaign
HU	Harvard University
ICF	Informed Consent Form
ICH	International Conference on Harmonisation
ID	Identification
IDSA	Infectious Diseases Society of America
IEC	Independent or Institutional Ethics Committee
IFN	Interferon
IMB	Information-Motivation-Behavioral
INHSU	International Network of Hepatitis in Substance Users
IOM	Institute of Medicine
IRB	Institutional Review Board
IU	International Units
JHU	The Johns Hopkins University
LSAB	Local Stakeholder Advisory Board
MARS	Medication Assisted Recovery Services
mDOT	Modified Directly Observed Therapy
mg	Milligram
mL	Milliliter
MMC	Montefiore Medical Center
MOP	Manual of Procedures
MRI	Magnetic Resonance Imaging
MSM	Men who have Sex with Men
N	Number (Typically Refers to Subjects)
NAMA	National Alliance for Medication Assisted Recovery
NATAP	National AIDS Treatment Advocacy Project
NIH	National Institutes of Health, DHHS
NSAB	National Stakeholder Advisory Board
NVHR	National Viral Hepatitis Roundtable
NYCDOH	New York City Department of Health
NYCDOHMH	New York City Department of Health and Mental Hygiene
OAT	Opiate Agonist Treatment

OHRP	Office for Human Research Protections
OR	Odds Ratio
OTP	Opioid Treatment Program
PCORI	Patient-Centered Outcomes Research Institute
PD	Protocol Deviation
PHQ	Patient Health Questionnaire
PI	Principal Investigator
PN	Patient Navigator
POC	Point of Care
PWID	People Who Inject Drugs
PY	Person-Years
RA	Research Assistant
RAV	Resistance-associated Variant
RCT	Randomized Control Trial
REDCap	Research Electronic Data Capture
RNA	Ribonucleic Acid
SAE	Serious Adverse Event/Serious Adverse Experience
SAS	Statistical Analysis System
SD	Standard Deviation
SDCC	Statistical and Data Coordinating Center
SMS	Short Message Service
SOP	Standard Operating Procedure
SVR	Sustained Virologic Response
TAG	The Advocacy Group
TAU	Treatment as Usual
UCSF	University of California San Francisco
UNM HSC	University of New Mexico Health Science Center
URI	University of Rhode Island
US	United States
UT	Urine Toxicology
UW	University of Washington
VAS	Visual Analogue Scale
VL	Viral Load
WHO	World Health Organization
WVU	West Virginia University

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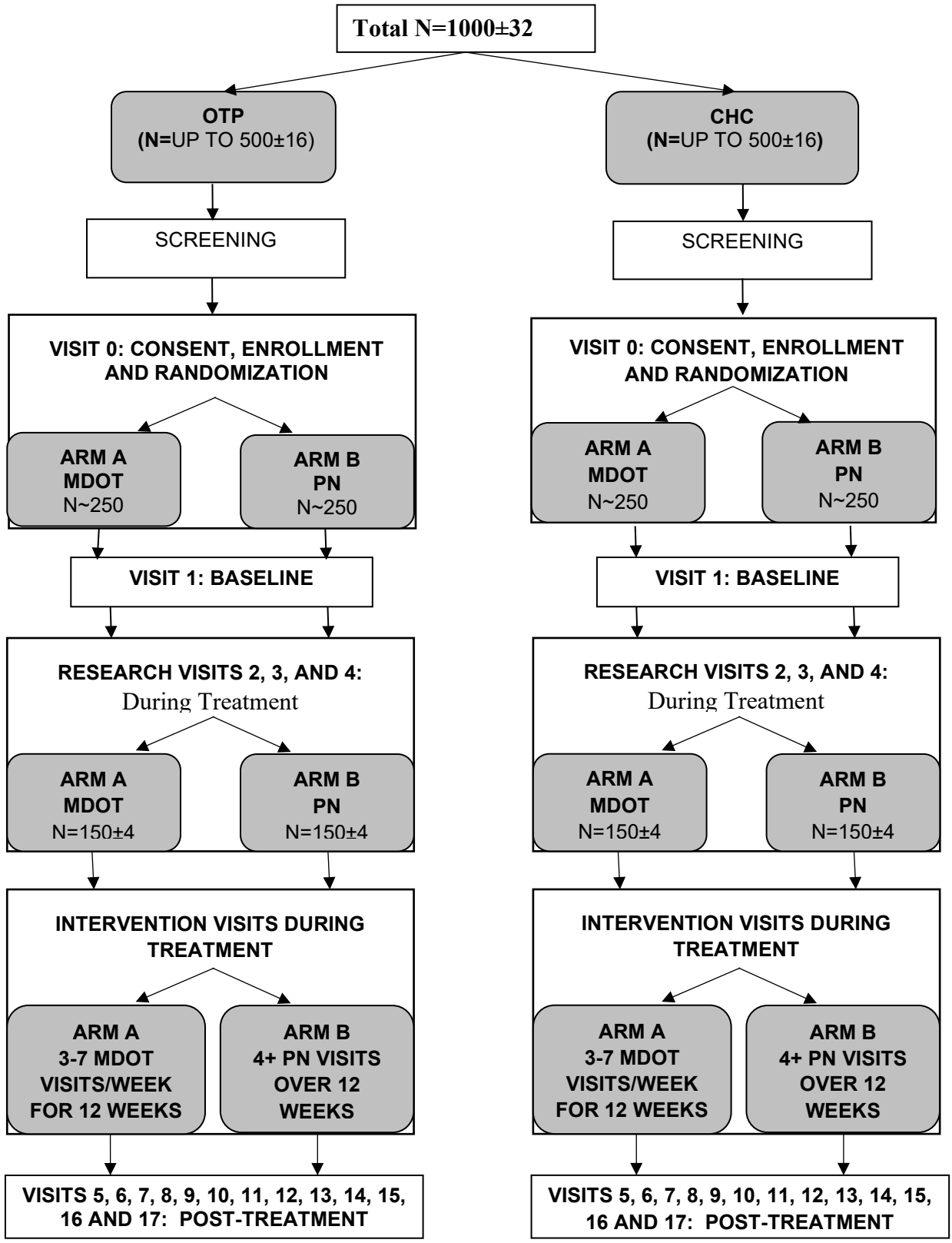
Figure 1: Schematic of Study Design



PROTOCOL SUMMARY

Title:	Patient-Centered Models of HCV Care for People Who Inject Drugs
Design:	Two arm study evaluating modified directly observed therapy (mDOT) versus patient navigator (PN) to deliver HCV treatment to PWID in two health settings: (1) opioid treatment program (OTP), (2) community health center (CHC) -Sites in eight cities (16 programs) Total number of subjects: Up to 1000 subjects will be enrolled and randomized with an expected 600 participants initiating treatment. <u>Participants: 600 subjects on treatment</u> Arm A: (1) OTP, N=150; (2) CHC, N=150 Arm B: (1) OTP, N=150; (2) CHC, N=150
Population:	Adults of any gender with current Hepatitis C Virus (HCV) infection, people with recent active injection drug use, 18 – 70 years old.
Number of Sites:	Eight Sites (Montefiore Medical Center, New York; West Virginia University, Morgantown; University of Washington, Seattle; University of Rhode Island, Providence; University of California San Francisco; The Johns Hopkins University, Baltimore; University of New Mexico, Albuquerque)
Study Duration:	Approximately 6 years
Subject Participation Duration:	Up to 180 weeks: up to 12 weeks of pre-treatment evaluation, 12 weeks of treatment, 12 weeks of follow-up to determine Sustained Virologic Response (SVR) 12, and 144 weeks of follow-up to determine long-term SVR and reinfection
Description of Intervention:	Participants will be randomized to one of two treatment

	model arms: A: mDOT or B: PN, at one of two clinical sites: 1) opioid treatment program (OTP) or (2) community health center (CHC) setting.
Objectives:	1. To determine whether SVR-12 rates are higher among those randomized to mDOT compared to those randomized to PN, among People Who Inject Drugs (PWID) treated at opioid treatment program (OTP) and community health centers (CHC). 2. We will also examine the following outcomes overall, and by randomization arm (mDOT vs. PN): (1) HCV treatment initiation (2) Adherence (3) Treatment completion (4) Drug resistance (5) HCV reinfection 3. To examine factors associated with key study outcomes (treatment initiation, adherence, SVR, drug resistance and HCV reinfection) using quantitative and qualitative methods.
Estimated Date of Completion:	2022

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2 Background Information and Scientific Rationale

2.1 Background Information

HCV epidemic in people who inject drugs (PWID)

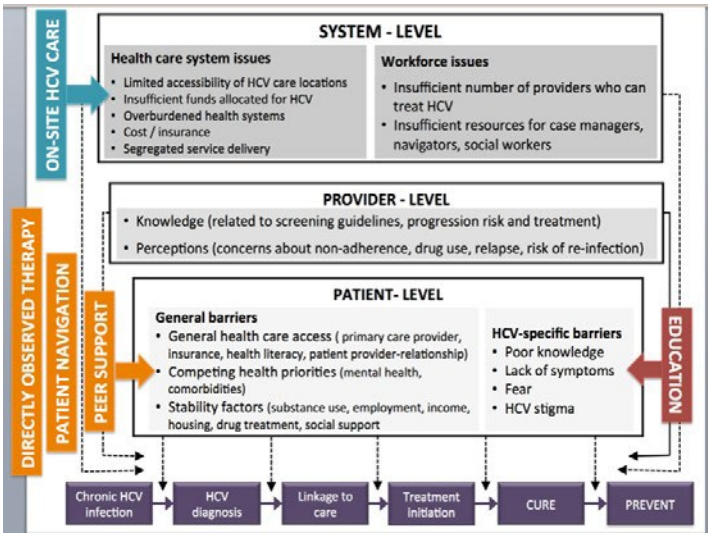
PWID have the highest incidence and prevalence of HCV in the U.S. and globally [1]. In the U.S. an estimated 43% of current or former PWID aged 40-65 years have chronic HCV [2]. Prevalence of HCV varies by age and duration of injecting, but meta-analyses show that in developed countries, including the U.S., mean cumulative incidence was over 20%, and prevalence was 72% in PWID with a history of 10 year of injecting [2]. The Centers for Disease Control and Prevention (CDC) estimates at least 30,000 new HCV infections per year [3], predominantly among PWID, with a 44% increase in the number of acute cases from 2010 to 2011 [4]. This increase has been associated with an expanding PWID population, especially in non-urban areas across the U.S. [5], and has been related in part to increases in prescription opioids, followed by related transitions to injection drug use [6, 7]. Addressing methods to optimize access to curative HCV treatment in PWID is a priority given their role in the growing HCV epidemic in the U.S. HCV causes up to 15,000 deaths annually, and is the leading cause of liver transplantation in the U.S. [8-10]. Treatment effectiveness among PWID is crucial because PWID remain the leading risk group for HCV infection [11]. PWID have the highest prevalence and incidence of HCV in the U.S., yet HCV treatment is rarely provided to PWID. In two systematic reviews of interferon-based treatment for PWIDs, overall SVR was 56%, and response rates were comparable to large RCTs [12, 13]. International guidelines from the American Association for the Study of Liver Diseases (AASLD)/ Infectious Diseases Society of America (IDSA), European Association for the Study of the Liver (EASL), International Network of Hepatitis in Substance Users (INHSU), and the World Health Organization (WHO) all recommend treatment for HCV infection among PWID [14-17]. With significant scale up of HCV treatment of PWID, overall HCV prevalence could be reduced by up to 75% within 15 years [18]. Nevertheless, few data exist on direct-acting antiviral agents (DAAs) treatment outcomes in PWID, and therefore PWID are often not eligible to receive DAAs.

HCV treatment uptake among PWIDs is limited by multiple barriers

Hepatitis C treatment uptake among PWID has been limited by multiple interrelated barriers at the level of the patient, the provider and the system (Figure 2) [19, 20]. Patient-level barriers included poor knowledge related to HCV and treatment as well as the absence of symptoms, which often results in a low perceived need for treatment. These issues are compounded by general barriers to health care access (e.g., having insurance, a primary care provider), competing comorbidities, which may require more

immediate attention as well as factors which impede stability including unemployment, unstable housing, lack of transportation, incarceration and ongoing substance use [21-25]. Providers are often unwilling to prescribe HCV treatment to even former PWID because of concerns related to ongoing substance use, low adherence and the potential risk of reinfection [20, 25].

Figure 2: Barriers to Treatment



Some studies have suggested that physicians have suboptimal knowledge regarding HCV and its treatment which can impact which patients get tested, referred and who initiate treatment [20, 26]. A major structural barrier is the cost of the medications and the associated monitoring. But beyond cost, additional structural barriers include insufficient locations where HCV testing can be performed and where treatment can be delivered [20, 27]. There is also a dearth of providers who can treat HCV and patient navigators dedicated to spearheading HCV-infected PWID and others through treatment. Finally, HCV care has historically been delivered in specialist settings which means it is segregated from other services that PWID utilize including primary care, opiate substitution and HIV care.

Efficacy of new HCV regimens for HCV-infected patients

New direct-acting antiviral agents (DAAs) are efficacious in >95% of treatment-naïve patients [14]. The interferon-free DAA fixed dose combination of ledipasvir 90 mg and sofosbuvir 400 mg once daily for 12 weeks is associated with SVR rates of >95% in genotype-1 infected patients [14], and is associated with fewer side effects than previous regimens: fatigue 13% - 18%, headache 11% - 17%, and nausea 6% - 9%. The interferon-free DAA fixed-dose regimen of sofosbuvir 400 mg once-daily (nucleotide polymerase) and velpatasvir 100 mg once-daily (NS5A inhibitor) has demonstrated high efficacy (95-96% SVR12) with a treatment duration of 12 weeks in treatment-naïve patients with HCV genotypes 1-6 [28], and was approved for use by the Food and Drug Administration (FDA) on June 28, 2016. The availability of a simplified IFN-free DAA-based once-daily regimen of sofosbuvir/velpatasvir may further enhance the capacity to scale-up HCV treatment among PWID. A pan-genotypic regimen can help increase access for PWID by eliminating the need for genotypic testing prior to treatment. Therefore, fixed-dose sofosbuvir/velpatasvir will now be used for this study.

PWID excluded from HCV DAA clinical trials

PWID have been excluded from many clinical trials evaluating the efficacy of DAAs. A systematic evaluation of exclusion criteria concerning drug and alcohol use in DAA-based HCV treatment trials for Human Immunodeficiency Virus (HIV)/HCV co-infected persons performed by searching the clinicaltrials.gov website of the U.S. National Library of Medicine and National Institutes of Health (NIH) for all available trials through May 2013 [29] identified eighteen clinical trials, involving 9 DAAs (protease, polymerase and NS5A inhibitors). Nine trials (50%) excluded individuals with either current or prior alcohol, "substance," or "drug" use. In a majority of these trials (78%), exclusion was also based upon site investigators' perceptions of suitability to participate in the trial. Developing consistent, evidence-based criteria concerning substance use will permit greater, more equitable access to DAA trials for the HCV monoinfected and HIV/HCV co-infected populations. Exclusion of important subgroups such as PWID from clinical trials has a direct effect on policy and payer's willingness to provide medications for PWID. The National Association for Medicaid Directors endorsed the University of Oregon report entitled, "Sofosbuvir for the treatment of hepatitis C and evaluation of the 2014 AASLD Treatment Guidelines" which concluded (due to lack of DAA data in PWID) that sofosbuvir-based treatment should be excluded from people who have used drugs and alcohol over the last 12 months.

Medicaid restrictions of DAAs for PWIDs

The high price of DAAs and high demand has also led payers to institute restrictions on their access, although by law Medicaid programs are entitled to a rebate of at least 23% [30, 31]. In the U.S., a disproportionate number of people living with HCV are of low-income [32, 33]. Most PWID are eligible for HCV therapy reimbursement through Medicaid, the jointly funded federal/state partnership that provides health insurance for low-income people meeting the program's eligibility criteria. Each state has wide discretion in administering its own Medicaid program. A systematic evaluation of State Medicaid policies for HCV treatment with sofosbuvir in the United States [34] by searching State Medicaid websites between June 23 and December 7, 2014 found that overall, 42 states (82%) had publicly available information regarding sofosbuvir Medicaid reimbursement criteria. Of these, 88% (n=37) include drug and/or alcohol use in their sofosbuvir eligibility criteria, with 50% requiring a period of abstinence. The majority of states require that patients be abstinent from drug and alcohol for 6 months (n=11), while others require abstinence periods of 1 month (n=2), 3 months (n=5) and 12 months (n=2). The majority of states (n=27, 64%) require urine drug screening prior to treatment to assess drug and/or alcohol use, with only 6 (14%) requiring testing specifically for those with previous drug/alcohol abuse.

Rather than recommending exclusion of PWID, AASLD/IDSA guidelines list PWID as a priority group due to potential treatment as prevention benefit [14]. HCV treatment for PWID is cost-effective, particularly when the prevention benefits are considered [35]. Nevertheless, PWID in the U.S. are systematically denied access to DAAs.

Direct-acting antiviral HCV agents and resistance

HCV NS5A resistance-associated variants (RAVs) can emerge following unsuccessful treatment with an NS5A-inhibitor containing regimen as they have relatively low barriers to resistance [36]. RAVS with reduced drug susceptibility are also observed in treatment-naïve patients. Patients who did not achieve SVR in Gilead studies evaluating direct-acting antiviral regimens including ledipasvir (but not sofosbuvir) were enrolled in a 3-year registry trial. NS5A RAVs were measured at positions 24, 28, 30, 31, 32, 58, and 93 because they confer >2.5 reduced susceptibility to ledipasvir in-vitro. At baseline, 16% of patients (12/76) of patients treated with ledipasvir had NS5A RAVs. At virologic failure, almost all (99%; 72/73) of patients had NS5A RAVs. Moreover, 86% of these patients still had NS5A RAVs at follow-up week 96 [37]. NS5A mutations seen in monotherapy with velpatasvir include those measured at positions 24, 28, 30, 31, 32, 58, 92, and 93. Cross-resistance is observed to all NS5A inhibitors [38]. NS5A inhibitor-resistant viruses appear to persist for years after treatment failure, and the time needed to clear resistant variants is unknown. Therefore, resistant viruses associated with decreased response to antiviral treatment may be transmitted to other PWID.

HCV reinfection among PWID

Reinfection is a potential problem and a barrier to treatment among PWID [23]. Data collected to date, principally in PWID who have received interferon-based treatments, show reinfection is low: 5.2/100 person years (py) for those who report injection drug use after treatment, and less (3.2/100 py) for those who do not report ongoing injection drug use [39, 40]. However, recent reports have noted higher rates of reinfection after interferon-based treatments in prisoners (8/100 py), HIV/HCV Men who have Sex with Men (MSM) (24/100 py), and PWID who relapse to drug use with longer follow-up (30/100 py). [41, 42]

Prospective studies assessing HCV reinfection PWID who spontaneously cleared infection [43, 44] show that to accurately capture reinfection events, genotyping and viral sequencing is necessary to distinguish reinfection from intercalation. Without these tests, estimates of reinfection incidence were significantly overestimated. Testing interval also has an impact on detection of reinfection. In PWID who clear infection spontaneously, testing intervals less frequent than every three months resulted in substantial (by up to 66%) underestimation of reinfection rate [45]. A caveat here is that these estimates are from patients who spontaneously clear the virus, and who have

been shown to have a high likelihood of re-clearance of subsequent infections [44, 46, 47], and immunological responses to reinfection may differ in those with treatment induced clearance. Systematic testing (every 3 months after SVR12 in our proposed study) to assess the presence of HCV RNA will be essential to accurately determine reinfection events. There is little to no data on reinfection rates in the era of DAAs.

2.2 Scientific Rationale

HCV treatment delivered in primary care settings

The number of HCV-infected patients who need treatment far exceeds the availability of specialists, who are often concentrated in academic medical centers, making access to care difficult [48, 49]. When referred to specialty care, HCV patients may feel stigmatized by specialist care settings that often exclude PWID from treatment [50-52]. Given the simplicity and efficacy of new HCV medications, there is an unparalleled opportunity to treat PWID within medical settings that they are already accessing, such as Federally Qualified Health Centers (FQHCs). Several studies have also shown that PWID are effectively treated for HCV in primary care settings [53-55]. Primary care clinics, such as FQHCs, are abundant throughout the U.S. and serve populations at high risk for HCV; studies show an HCV prevalence rate of approximately 8% in FQHCs, almost 5x greater than the general population [56, 57]. There are 1200 FQHCs nationwide, delivering care to 20,000,000 low-income, underserved patients [58]. These individuals, who frequently have minimal education, high unemployment, and live in urban areas, also have high rates of substance use and dependence [59, 60]. Of 6.4 million PWIDs nationwide [59], the majority is not enrolled in substance use disorder treatment, and instead seeks medical care in clinics such as FQHCs [61-64]. Increased rates of HCV treatment have been found in community-based primary care clinics when primary care-based HCV treatment is combined with close collaboration between the HCV medical provider and an HCV patient navigator. This favorably impacts the HCV Care Cascade as seen in the figures below comparing the cascade in the same community-based clinic with and without a primary care based HCV program. [65]

Figure 3: FQHCs in the US

Figure 5: HCV Care Cascade without Primary Care

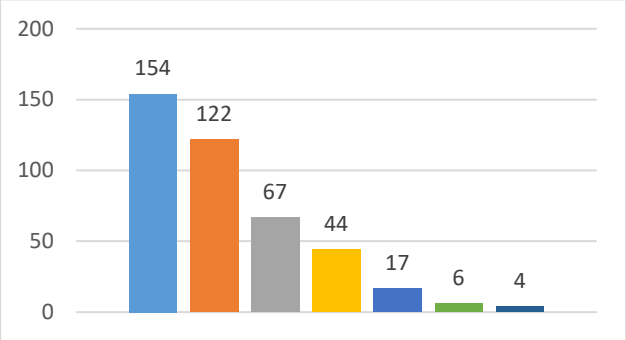
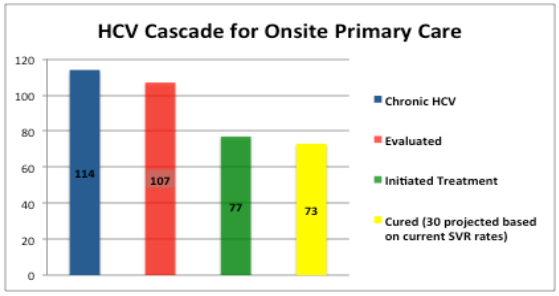


Figure 4: HCV Care Cascade with Onsite Primary Care



Evidence-based interventions to enhance assessment, treatment, and adherence in the chronic hepatitis C continuum

With the availability of DAAs with rates of SVR reaching 95%, evidence-based strategies are urgently needed to achieve real-world effectiveness in challenging patient populations such as PWID. Using Institute Of Medicine guidelines, a systematic review of evidence-based interventions from PubMED, Medline, Google Scholar, EmBASE, and PsychInfo bibliographic databases and citation indices [16] identified evidence-based interventions to enhance HCV assessment, treatment, and adherence in 4 categories: 1) diagnosis; 2) linkage to care; 3) pre-therapeutic evaluation or treatment initiation; or 4) treatment adherence. Several interventions introduced on-site HCV care with patients in previously established opiate agonist treatment programs and showed comparable rates of uptake and SVR to non-PWID populations [66-71].

Common to all of these interventions is a multidisciplinary approach that combines medical and addiction treatment with intensive social support [13]. Similarly, primary care settings represent key opportunities for HCV care linkage interventions, often within clinics that have engaged PWID. These studies demonstrated that patients with ongoing drug use and psychiatric comorbidity can be effectively linked to care and treated within these settings [54, 55, 69, 72-74]. Peer-driven interventions including weekly support groups have demonstrated high uptake of HCV treatment and SVR rates among PWIDs [75-77]. Additional studies are needed to measure the impact of peer-driven interventions [78, 79] in the eras of DAAs.

When PWID are surveyed to assess HCV treatment knowledge and barriers to treatment initiation [22], interest [80, 81], and willingness to receive treatment [82], treatment-naïve patients were more willing to enter HCV treatment program if they perceived themselves at risk for cirrhosis or liver cancer [81] or had more knowledge about HCV [82]. A randomized control trial (RCT) of patient navigation intervention consisting of motivational interviewing, education, and case management was

associated with increased HCV clinic visit attendance among patients in methadone maintenance [83]. With the simplicity of treatment with newer DAAs (one pill daily), treatment has moved towards primary care venues [84].

The 2015 INSHU HCV Clinical Guidelines for PWID [15] recommends that: (I) Models of HCV care integrated within addiction treatment and primary care health centers, as well as prisons, allow successful pre-therapeutic assessment (Class I, Level B); II) Peer-driven interventions delivered within opiate substitution treatment settings may lead to higher rates of treatment initiation (Class IIa, Level C); and (III) Care coordination in conjunction with behavioral interventions can increase likelihood of PWID being evaluated and initiating treatment (Class I, Level B). Though on-site multidisciplinary models of care have demonstrated good outcomes for PWID, optimal models of care must be studied [85].

Directly Observed Therapy

Similar to the implementation of directly administered antiretroviral therapy, or directly observed therapy (DOT) for HIV [86, 87], several interventions involved the provision of HCV treatment as DOT [88]. By using a modified DOT approach (mDOT) to observe only the morning dose of ribavirin or weekly injections of interferon, HCV treatment was successfully delivered in opiate agonist treatment programs [68, 69, 89], prison settings [90], and community health centers [75]. Another study provided ribavirin as once-daily DOT, demonstrating extremely high rates of SVR among patients stably maintained on opioid substitution therapy [91].

RCT of directly observed HAART in methadone-maintained patients

In an RCT of DOT with Highly Active Anti-Retroviral Therapy (HAART) in HIV-infected drug users in methadone clinics seventy-seven participants were randomized to a 24-week DOT intervention or treatment as usual (TAU), with 86% study retention at 24 weeks. Participants randomized to DOT (v. TAU) had greater adherence (mean adherence: 86% v. 56%, $p<0.0001$) and VL decreased by 0.52 log10 copies/ml in the DOT group while it remained stable in the TAU group ($p<0.01$). More DOT than TAU participants had undetectable viral load (71% vs. 44%, $p=0.03$) [86]. Active drug use decreased adherence, but the negative impact of drug use on adherence was eliminated by DOT [92]. By 3 months after DOT ended, differences in both adherence and viral load between DOT and TAU had extinguished [93]. These data demonstrate that DOT is associated with improved HIV virological outcomes among methadone-maintained patients, including active drug users, and that it should be continued long-term for durable effect. In several other HIV studies, treatment adherence and virological outcomes are improved among PWID when DOT is administered at methadone clinics and in community settings [94, 95].

Study of HCV treatment in methadone-maintained patients

In 2003, a study within a methadone maintenance treatment program included directly-administered weekly interferon in addition to screening, assessment of treatment eligibility, psychiatric services, and on-site antiviral therapy [96]. Of 73 patients, most were Latino (67%) or African-American (12%), nearly half (49%) had used illicit substances in the 6 months before initiating treatment, 32% were HIV-infected, and current psychiatric illness was common (67%). Most (86%) completed 12 weeks of HCV treatment and 45% achieved SVR, including 40% of genotype- 1 patients. Though 30% used illicit drugs during HCV treatment, there was no association between illicit drug use and virological outcomes. These results demonstrate that PWID with complex medical and psychiatric comorbidities can be effectively treated for HCV with co-located on-site care.

However, it is unknown which interventions (on-site care v. DOT injections) contributed to the observed outcomes [70, 96, 97]. In 2008 a pilot RCT of modified DOT (mDOT), extended the DOT strategy to the oral medication ribavirin. This trial (n=80) was designed to test the efficacy of 2 versions of mDOT [89]. The primary objective was to determine whether enhanced DOT with both interferon (IFN) plus ribavirin is more efficacious than standard DOT with weekly provider-administered IFN and self-administered ribavirin for improving adherence. Significant differences in pill count adherence between the treatment arms were observed (88% in mDOT arm vs. 77% in the treatment as usual, or TAU arm, p=0.02) [98]. In addition, 81% of mDOT subjects achieved ≥ 80% adherence v. 53% in the TAU arm (p=0.09). Only 16% discontinued treatment, and among genotype-1 infected patients, 55% achieved SVR (half active drug users) [94].

In 2009, treatment for genotype-1 patients in the study was changed to include DAAs (telaprevir or boceprevir) in combination with pegylated interferon and ribavirin. Of the first 50 patients treated with DAAs (either telaprevir or boceprevir in combination with pegylated interferon and ribavirin), 62% achieved SVR despite high rates of recent drug use prior to treatment (52%), ongoing drug use during treatment (45%) and psychiatric comorbidity (86%) [98].

Since January 2014, sofosbuvir-based regimens have been implemented in 115 methadone-maintained PWID including 51 genotype-1 patients with highly efficacious, all-oral regimens of sofosbuvir in combination with simeprevir (n=29) OR fixed-dose sofosbuvir in combination with ledipasvir (n=24). To date, almost all patients (98%) are either undetectable or have HCV VL<15 International Units (IU)/ml. Among 31 who have completed treatment, 13 have achieved an SVR12, 15 have an end of treatment response (ETR) and are awaiting SVR12 determination, 2 are awaiting ETR

determination, and 1 had a relapse after ETR. Twenty patients remain on treatment, and all are either undetectable (n=13), have HCV Viral Load (VL) <15 IU/ml (n=3) at week 4, or have not yet reached week 4 (n=4). No patients have discontinued treatment.

Models of Patient Navigation

First used with cancer patients, the principal goal of patient navigation is to assist patients to move through the medical care system. There are four principal roles of PNs: 1) coordinating treatment; 2) health education and promotion; 3) assisting patients to overcome personal barriers; and 4) providing psychosocial support. In a multi-site U.S. study, PNs assisting HIV-positive individuals resulted in higher adherence to medical care appointments and a significant increase in those achieving an undetectable viral load [99]. HCV models of care integrating PNs within substance use disorder treatment and community health centers have been widely implemented in several states, including New York [100, 101]. PN models integrating peer support through on-site support groups have led to high rates of treatment uptake and SVR in methadone maintenance treatment patients including those using drugs, and peers have led to improved outcomes in several other chronic diseases [102, 103]. PN models with integrated peer support may improve patient-centered outcomes such as self-efficacy, shame and stigma. However, the best model of care for treating HCV in PWID is unknown, as is which model is most acceptable to patients. Despite availability of highly efficacious regimens, PWID face more barriers to treatment than ever, due to continued concerns from providers regarding poor adherence and reinfection, and restrictions from payers due to lack of data with new DAAs [104].

2.3 Potential Risks and Benefits

Potential Risks

The risks of the study include:

1) Inconvenience of attending research visits, 2) discomfort associated with research interviews, 3) venipuncture, 4) discomfort associated with directly observed medication administration or with a patient navigator, and 5) confidentiality issues associated with research encounters. These risks will be discussed with potential participants during the informed consent process. The alternative of not participating in the study will be discussed with participants during the informed consent process.

Inconvenience of attending research visits: This study requires that participants participate in face-to-face encounters with the research staff at visits 0, 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, and 17 over a period of 42-45 months.

Inconvenience of study participants attending research visits will be addressed by 1) reimbursement for time spent in research encounters ($20 for each research visit and $5 for each returned weekly blister pack), 2) conducting assessments on-site in participants' OTPs, when allowed by the OTP, or 3) conducting assessments at community research sites which may be more conveniently located for participants that reside nearby. Additionally, participants will be informed by the research staff during the informed consent process that they can choose to withdraw from the study at any point. We will also provide rest and refreshment breaks during visits.

Discomfort associated with research interviews: Surveys will assess health status, substance use, psychiatric symptoms, stigma, shame, medication adherence and other sensitive subjects. It is possible that survey questions could be uncomfortable for participants. Participants will be told that they may choose to stop the interview or withdraw from the study if they find the questions troubling.

Discomfort associated with directly observed therapy or patient navigator: Participants may feel uncomfortable with receiving mDOT or with a patient navigator. There may be discomfort with the additional level of scrutiny or interaction associated with these models of care.

Confidentiality issues in research encounters: The risk of study participation includes possible loss of confidentiality. Risks to privacy and confidentiality exist with all human research. Because this project focuses on people who inject drugs, confidentiality is a major concern. The study will be collecting personal information from participants to facilitate follow up, and will be asking questions about sensitive data including illicit drug use and alcohol use, mental health, and health status. Subjects will be assigned a unique study identification number which will be used on case report forms (CRFs), and specimens collected for laboratory analyses. No samples or data will be labeled with the subject's name. The key to subjects' names will be accessible only to the study co-principal investigators, and hard-copies and electronic copies of data will be stored in secured locations.

Venipuncture: The risk from venipuncture is minimal but may include anxiety, pain, bruising, and infection.

Potential Benefits

Participants assigned to the mDOT or PN arms of this study may benefit by achieving high levels of treatment initiation, adherence and improved HCV outcomes. Participants will receive access to medications that are often denied by payers and providers to PWID. The patient-centered models of HCV care (mDOT

and PN) may also provide a mechanism for rapid identification of potential adverse medication effects, and this may result in fewer adverse events, decreased morbidity from HCV, and improved psychosocial functioning. Given the low risk presented by participation in this study and the high potential for direct benefit of cure if the participant completes HCV treatment, the risk/benefit ratio is very favorable.

3 Study Objectives

3.1 Primary Objective

To determine whether SVR-12 rates are higher among those randomized to mDOT compared to those randomized to PN, among PWID treated for HCV at OTPs and community health centers.

3.2 Secondary Objective 1

To examine the following outcomes overall and by randomization arm (mDOT compared to PN) among PWID treated at OTPs and community health centers:

(i) Treatment initiation: whether a higher proportion of participants in the PN arm initiate treatment compared to mDOT arm;
(ii) Adherence (≥80% of prescribed medication taken): whether a higher proportion of those in the mDOT arm are adherent compared to PN arm;
(iii) Treatment completion (finishing 100% of prescribed 12-week course): whether a higher proportion of participants in the mDOT arm complete treatment compared to PN arm;
(iv) Drug resistance: whether the proportion who develop drug resistance is higher in the PN arm compared to mDOT arm;
(v) Reinfection: whether (a) rate (incidence), and the (b) proportion who become reinfected with HCV is higher in the PN arm compared to mDOT arm;

Comparisons will be performed to determine the proportion of subjects in each arm who: a) initiate treatment; b) adhere to antiviral treatment; c) complete antiviral treatment; d) attain SVR (cure); e) develop drug resistance; f) reinfection. We will also conduct time to event analyses to examine drug resistance and reinfection outcomes. Subgroup analyses will be performed to assess differences in outcomes among those randomized to PN vs. mDOT in specific sub-populations.

3.3 Secondary Objective 2

To examine factors associated with key study outcomes (treatment initiation, adherence, SVR, drug resistance and HCV reinfection) using quantitative and qualitative methods.

Quantitative methods: We will examine associations between psychosocial factors such as homelessness, co-morbid mental illness, poor social support, and high

levels of shame and stigma, with key study outcomes described above. It is hypothesized that these psychosocial variables are associated with lower rates of adherence and SVR in the PN arm, but not the mDOT arm; and associated with lower rates of treatment initiation in the mDOT arm, but not the PN arm.

Qualitative methods: Qualitative methods will be used to conduct an interview study focusing on pragmatic concerns and experiences of key stakeholders. Two key groups of stakeholders, patients and patient navigators, will be interviewed regarding the barriers and facilitators to successful treatment uptake. In the patient group, up to 15 patients from each site will be recruited. Recruitment will be of both successful and unsuccessful participants along the pathway to care and use structured comparisons to understand differences between those who have benefited from the intervention and those who have not. In years 1-2 of the project period, preliminary results of these analyses will be used for formative evaluation purposes, feeding back results to study leaders in order to help improve/adapt study features and make the interventions more patient centered. In years 3-6 of the project, the data will contribute to the mixed methods summative evaluation to understand barriers and facilitators to program success. Protocol and implementation details for qualitative methods are detailed in the Implementation Study Protocol (Appendix 3).

4 Study Design

Overview of study approach

This is a multi-site national study (8 U.S. cities), where up to 1000 HCV-infected PWIDs (injecting illicit substances within 3 months of screening) will be randomized to either PN plus weekly or biweekly blister pack dispensation versus mDOT. Among patients who go on to initiate HCV treatment (n=600 targeted) with a once-daily combination regimen of fixed-dose sofosbuvir/velpatasvir, a comparison will be conducted of the proportion of patients in each arm who: (a) optimally adhere (≥80%), (b) complete treatment, (c) achieve SVR, and (d) develop resistance. The primary outcome will be SVR. The 8 sites offer geographic and policy diversity: New York City, Baltimore, Providence, Boston, Morgantown, Seattle, San Francisco, and Albuquerque.

Participants will be recruited from diverse venues: OTPs, community health centers, syringe exchange programs, community-based organizations, homeless programs, and cohorts established by research studies. The clinical sites will determine eligibility based on clinical records, or on-site testing including HCV tests (anti-HCV and HCV viremia). Study participants will be screened, consented and enrolled on-site at OTP and non-OTP settings. There will be differences in linkage, engagement and outreach at each site. These procedures will be documented in site specific operating manuals.

Patients will be randomized to one of two models of care: patient navigation (PN) vs. modified directly observed treatment (mDOT). Patients enrolled from OTPs who are receiving methadone and randomized to mDOT will receive doses of once daily medication at the same time as they receive methadone. Patients enrolled from community health settings and randomized to mDOT may receive observed doses through use of miDOT (emocha Mobile Health, Inc.), a mobile health app on a smartphone, or at the CHC. Subjects randomized to PN will receive a standardized PN intervention. Sites also have the option to offer all subjects optional additional support through a peer-led support group.

Participants will be followed for up to 180 weeks: 12 weeks of pre-treatment evaluation, 12 weeks of treatment, 12 weeks of follow-up to determine SVR12, and 144 weeks of follow-up to determine long-term SVR and reinfection. Data sources will include clinical lab and imaging results from medical records, blood tests (HCV viral load during long-term follow-up and resistance assays), urine toxicology, questionnaires, electronic monitors for assessing adherence, and interviews.

5 Study Population

Participants will be recruited from a diverse national patient population from at least 16 health centers in 8 states- all with on-site HCV care (8 OTPs and 8 community health centers – **Table 1**). Target enrollment is up to 1000 PWID (to target 600 PWID initiating treatment) with the following characteristics (**Table 2**): Caucasian (55%), Latino (21%), and African American (20%), male (61%), and mean age of 44 years; 28% will be HIV/HCV co-infected. Within the 8 OTPs, there is a potential pool of 4790 mono-infected and 510 co-infected patients. Within the 8 community health centers, there is a potential participant pool of 2809 mono-infected and 1433 co-infected patients. Community enrollment has a pool of >4000 HCV-infected clients in the community. With over 13,000 HCV-infected patients, target enrollment is 1000 PWID. Eligibility for HCV treatment will be determined by subjects' on-site medical care providers, as part of routine clinical care.

Table 1: HCV-infected Patients at OTPs and Community Health Centers

City, State	OTP	#HCV	#HIV/HCV	Community Health Center	#HCV	#HIV/HCV
Bronx, NY	Melrose Wellness Center	1500	250	Comprehensive Health Care Center	400	60
Providence, RI	CODAC Behavioral Health Services	750	25	Miriam Hospital Brown Infectious Diseases Center	50	400
Albuquerque, NM	UNM ASAP	720	25	Truman Health Services	20	200
San Francisco, CA	Ward 93 Opiate Treatment Outpatient Program	325	70	PHP Ward 86 and Tom Waddell Urban Health Clinic	100	213
Boston, MA	Bay Cove Human Services	150	10	MGH and CCHI	300	100
Baltimore, MD	Reach Health Services	300	60	Comprehensive Care Practice	1000	100
Seattle, WA	Evergreen Treatment Services	700	50	Harborview Adult Medicine	884	250
Morgantown, WV	Valley Alliance Treatment Services	345	20	Milan Puskar Health Right	110	20
Total		4790	510		2809	1433

Table 2: Demographic, Clinical, and Psychosocial Characteristics of HCV-infected Patients

State	NY	MA	RI	WV	WA	NM	CA	MD	Total
Age (mean)	49.0	40.5	55.0	30.0	40.0	41.5	48.0	46.5	43.9
Gender									
Male	62% (78)	68% (85)	41% (51)	55% (69)	63% (78)	70% (88)	82% (102)	50% (63)	61% (614)
Ethnicity									
Latino	65% (81)	13% (16)	15% (19)	0% (0)	5% (6)	52% (65)	17% (21)	1% (1)	21% (213)
Race/ethnicity									
Caucasian	20% (25)	73% (91)	37% (46)	98% (118)	62% (78)	76% (95)	50% (63)	25% (31)	55% (546)
African-Am	25% (31)	20% (25)	31% (39)	2% (1)	24% (30)	3% (4)	25% (31)	75% (65)	20% (196)
Native-Am	0% (0)	1% (1)	11% (14)	0% (0)	2% (3)	9% (11)	1% (3)	0% (0)	3% (32)
Asian	0% (0)	1% (1)	0% (0)	0% (0)	2% (3)	1% (1)	4% (5)	0% (0)	1% (13)
Other	55% (69)	5% (6)	21% (26)	2% (3)	10% (13)	11% (14)	20% (25)	0% (0)	21% (211)
Cirrhosis	34% (43)	15% (19)	45% (56)	7.5% (9)	15% (19)	33% (41)	14% (18)	5% (6)	21% (211)
HIV-infected	20% (25)	13% (16)	50% (62)	2.0% (3)	5% (6)	47% (59)	70% (88)	13% (16)	28% (336)
Unstably housed	20% (25)	35% (44)	11% (14)	13% (16)	28% (35)	25% (31)	60% (75)	15% (19)	26% (261)
Psych	75% (94)	67% (84)	63% (78)	45% (54)	60% (75)	35% (44)	71% (89)	25% (31)	55% (549)

The participants in the proposed trial will be 1000 patients recruited from 8 cities: Bronx (Montefiore Medical Center), Baltimore (John Hopkins University), Providence (The University of Rhode Island), Boston (Harvard School of Medicine), Morgantown (West Virginia University), San Francisco (UCSF), Albuquerque (University of New Mexico), and Seattle (University of Washington).

5.1 Inclusion Criteria

Inclusion criteria that must be met before enrollment:

- Current HCV infection (HCV viremic)
- HCV Viral load test from any time
- Must have had the following tests performed in the past 12 months: AST, ALT, platelets
- Actively injecting drugs (any substance within 3 months of screening)
- Not previously treated with HCV direct-acting antiviral medications
- Age 18 – 70
- Willing to receive HCV treatment with sofosbuvir/velpatasvir
- Willing to be randomized to either PN vs mDOT
- If receiving methadone, be attending or be willing to attend OTP a minimum of 5 times per week

- Able to provide informed consent
- English or Spanish fluency

5.2 Exclusion Criteria

Exclusion criteria will include:

- Pregnant or breast feeding
- Hepatocellular carcinoma

5.3 Re-Screening

Subjects can be rescreened if they fail screening. Participants can be rescreened only one time following first screen failure.

5.4 Randomization

Up to 1000 patients will be recruited, with patients randomized to PN or mDOT in a 1:1 ratio (500 subjects in each group) in variable block sizes of 2-6 via central, computer-generated randomization provided by the UNM Statistical and Data Coordinating Center (SDCC). Randomization will occur in blocks to ensure comparison groups of approximately equal size. Given that the intervention will not be blinded, block size will vary to prevent anticipation of treatment arm assignment.

Two special randomization strategies (stratification and blocking) will be used to avert imbalances in prognostic factors or treatment settings, and to ensure comparison groups of approximately equal size. Participants will be stratified by 3 factors: city, OTP vs. community health center and stage of liver disease (cirrhosis v. no cirrhosis).

In addition, adaptive re-weighting of random allocation in a pseudo urn randomization fashion will be made when N~300 has been enrolled to balance the sample size between mDOT and PN arms. Specifically, as we hypothesize that number of randomized subjects who will initiate treatment will be larger in the PN arm, unbalancing between arms is likely to occur during the course of the study. Of note, therefore, a randomized subject will not necessary be a clinical treatment subject but will be included in the comparison of treatment initiation.

To adjust for this potential unbalance, we will adjust randomization based on observed allocation ratio at the middle of trial if the overall allocation difference is greater than 5% (i.e., <47.5% vs. 52.5%).

Storage and dispensing of random allocation codes will be made in a centralized fashion. The UNM SDCC will generate and store the codes for all sites and types of clinics, and will be embedded into the Research and Electronic Data Capture (REDCap) data management system in the backend so that the identification of a treatment assignment will be ready and immediate without contacting the coordinating center when requested through the REDCap electronic request form by a responsible research staff at the sites whenever a new eligible participant is enrolled. The UNM SDCC will also be responsible for conducting re-weighted randomization, if necessary, at the middle of the trial.

Randomization will occur at enrollment, however research staff will wait until after the baseline assessments have been conducted to reveal the randomization to the participant, to avoid bias during baseline data collection.

5.5 Withdrawal

Reasons for Withdrawal
Subjects may withdraw or be withdrawn for any of the reasons given below. The reason for withdrawal will be recorded on a CRF.

In accordance with the current revision of the Declaration of Helsinki (amended October 2000, with additional footnotes added 2002 and 2004) and any other applicable regulations, a subject has the right to withdraw from the study at any time and for any reason and is not obliged to give his or her reasons for doing so. The Investigator may withdraw the subject at any time in the best interests of the subject's health and well-being. In addition, the subject may withdraw/be withdrawn for any of the following reasons:

- Administrative decision by the Investigator.
- Ineligibility (either arising during the study or retrospective, having been overlooked at screening).
- Significant protocol deviation.
- Subject non-compliance with study requirements.

6 Investigational Interventions

This is multi-site national study (8 U.S. cities), where up to 1000 HCV-infected PWIDs (injecting illicit substances within the last 3 months) will be randomized to either PN plus blister pack dispensation (weekly or every other week) versus mDOT.

6.1 modified Directly Observed Treatment

6.1.1 OTP Setting

Observation of HCV medication administration will be linked to methadone visits among patients receiving methadone. The schedule of five days per week will be considered modified DOT (mDOT). Participants enrolled in the mDOT arm through the OTP who are not taking methadone, but another version of opioid agonist treatment (OAT), such as buprenorphine, will follow the mDOT protocol for community health center participants.

Method of observation: Subjects in the mDOT arm will receive: 1) 5 directly observed doses per week (from a blister pack) at the same time as they receive methadone, and 2) take-home doses packaged in blister packs for self-administration on other days. In addition, the observing staff will: (i) notify clinicians when doses are declined or missed and (ii) refer subjects to clinicians as necessary.

Administration of Medication: Medications will be packed in labeled blister packs. For participants who are receiving methadone and attending clinic 5 days/week, medication will be kept at the clinic where research/clinical staff will observe them taking the medications. Participants will also receive take-home doses packaged in blister packs for the days that they are not observed at the methadone clinic. Blister packs will be returned to research staff at the next research visit.

Each time a subject misses an observed dose, there should be an assessment by the observer: the observer will ask whether the patient missed that day's dose, took a rescue dose, or took medication from another source.

Rescue Doses: Each participant will receive a container labeled with the contents, containing up to two doses of HCV treatment medication. In the event the participant misses the opportunity to take an observed dose at the OTP, they can take one of the rescue doses instead. This container will be either a pill case or a container specified by the local site. When the participant presents to the program for the next observed dose, the prior missed dose will be given to the participant to replace the rescue dose that was taken for any future events.

Record keeping: Each time a subject misses an observed dose, there should be an assessment by the observer: the observer will ask whether the patient missed that day's dose, took a rescue dose, or took medication from another source.

Staff that observe the participant taking their medication will log the information on a standardized log. Adherence will be measured with standardized forms each week by Study Coordinators and will include pill counts of blister packs.

Participants that choose to leave the OTP during treatment will have the potential to remain in the study by being transferred to the Community Health Center.

6.1.2 Community Health Center Setting

This intervention is considered modified DOT (mDOT) since between 3-7 weekly doses will be directly observed.

Method of Observation: All observed doses will be observed using electronic DOT (eDOT), via the mobile health smartphone app miDOT (developed by emocha Mobile Health, Inc.). Participants will be provided with a smartphone that is pre-loaded with a data/minutes plan and the miDOT app. Research staff will train the participant on how to use the app. Using the app, participants will take a video of themselves taking their HCV medication, then upload the video to the database maintained by emocha. Research staff will review these videos. On the day of medication pick-up, research staff will be available to provide technical assistance with that day’s video.

If a participant loses the study-provided phone or is otherwise unable/unwilling to use the miDOT app, participants will receive mDOT three times per week at the CHC by clinic/research staff. The remaining doses will be taken by the participant outside of the clinic.

Dispensing of Medication: Participants participating in mDOT will receive their medications in weekly blister packs once a week. Participants will return blister packs (with or without any remaining medication) at their next research visit. If the participant is not using the emocha miDOT app, their medication will be packaged in weekly blister packs and the participant will receive three observed doses at the clinic by clinical or research staff. The blister pack will remain with staff during the week until the participant has received their last observed dose for the week. The participant will then receive the blister pack with remaining doses to take home as unobserved doses. For any unobserved doses during the week prior to their final observed dose of the week, the participant will pop out the pill from the blister pack and take it home in a labeled pill case.

Research or clinic staff will: (i) notify clinicians when doses were declined or not observed and (ii) refer subjects to clinicians as necessary.

Rescue Doses: Each participant will receive a container, labeled with the contents, containing up to two doses of HCV treatment medication. In the event the participant misses the opportunity to take an observed dose at the OTP, he/she can take one of the rescue doses instead. This container will be either a pill case or a container specified by the local site. When the participant presents to the program for the next observed dose, the prior missed dose will be given to the participant to replace the rescue dose that was taken for any future events.

Record keeping: Research staff will review the miDOT videos, and record the date and time that the dose was taken. For participants not utilizing miDOT, clinic or research staff will observe the participant taking their medication and log the information on a standardized log. Adherence will be measured with standardized forms each week by Study Coordinators and will include pill counts.

Adherence will be measured and logged with standardized forms each week by research staff and will include pill counts of blister packs.

6.2 Patient Navigation

The study will follow a PN model developed by New York City Department of Health (DOH) in collaboration with Montefiore Medical Center and the community. HCV PNs have the following functions: 1) coordination of treatment; 2) health education and promotion; 3) assisting patients to overcome barriers; and 4) psychosocial support. Additional support may be offered through optional weekly peer-led support group (see below Section 6.3). Details of the PN protocol and materials are in the Patient Navigator Manual. Implementation of the PN protocol will differ by site based on the structure of the PN groups. Sites will document site-specific procedures in their operating manuals.

<u>Packing of Pills for Patient Navigation Arm</u>
For the PN arm pills will be packed in two-week blister packs and dispensed every other week. If participant is having difficulty with adherence on the biweekly schedule, the provider will assess changing the dispensing to weekly, and document the reasons for changing. No doses will be observed so even if patient is coming to the clinic weekly and picking up medications, all doses will be self-administered.

6.3 Education and Peer Support

Optional Peer Support - Weekly Support Groups:
Peer support groups may be available at all sites for all participants, depending on local factors. Peer support groups will provide support and education covering the following topics: natural history, goals of treatment, treatment regimen and side effects, adherence (including strategies), drug and alcohol abuse, and transmission / reinfection. Support groups will receive HCV support group materials developed by Project Inform, Montefiore Medical Center, and HCV Mentor and Support Group; each group will be guided by local advisory boards based on local patient preferences and barriers. Availability, structure and frequency of peer support and education will differ by site. Sites will document available peer support and education resources, structure and attendance in a site log.

7 Study Procedures/Evaluations

7.1 Clinical Evaluations

Individual medical records will be reviewed to evaluate HCV-related labs and dates performed (HCV viral load, genotype and subtype, FIB-4 (AST, ALT, and Platelets), total bilirubin, albumin, prothrombin time, FibroSURE (if available), Fibroscan/liver biopsy (if available), abdominal imaging results (ultrasound/MRI) if available, and other medical history including the most recent HIV test.

To determine presence of cirrhosis, all subjects will have a FIB-4 biomarker test calculated at enrollment (obtained by chart review). If FIB-4>3.25, the patient is considered to have advanced cirrhosis. If available, results of fibroscan, liver biopsy or imaging study (ultrasound/CT/MRI c/w cirrhosis) will be used for stratification instead of FIB-4.

Psychiatric status will be assessed in all participants using structured instruments, including: 1) PHQ-9 to assess for depression and 2) the GAD-7 to assess for anxiety. Suicidal ideation will trigger a psychiatric referral.

7.2 Laboratory Evaluations

HCV Viremia: Blood for HCV viral loads will be sent directly to Quest Diagnostics. Twenty mL of blood will be collected at visits 5, 6, 7, 8, 9, 10, 11, 12,13, 14, 15, 16 and 17 for HCV viremia testing and archiving. Specimens will be identified only by study ID number or bar-code, and will also be labeled with the name of the research study, the date and time of collection, and the specimen number. Each site will send blood samples directly to Quest. Results which will be entered into the study data system.

Resistance testing: For subjects who fail to achieve SVR or show evidence of reinfection, NS5A/NS5B resistance testing will be performed on the baseline, and either treatment failure visit (unscheduled) or Visit 5 specimens. The second time point will be determined by when treatment failure is first identified. The specimen for “treatment failure visit” will be used if the subject fails treatment during the 12 weeks of treatment, and the specimen for “Visit 5” will be used if the subject fails treatment after the treatment period. All specimens for resistance testing will be shipped to Montefiore CRC, and banked. Batched runs for resistance testing will be run at Monogram.

Biorepository specimen: Blood specimens will be collected at research visits 1, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16 and 17. At Visit 1, twenty mL of blood will be drawn and

stored locally until sent to the study biorepository. A biorepository will be established at Prima Health-Upstate for archiving stored blood for future studies. At all other visits, twenty mL of blood will be drawn and sent to Quest for HCV VL testing and temporary archiving before being sent to Prisma Health-Upstate's Biorepository.

Toxicology: Urine toxicology tests (American Bio Medica Corporation RapidTox Point of Care (POC) test) will be performed at research visits 1, 2, 3, 4, 5, 7, 9, 11, 13, 15, and 17. At these research visits, the RA will ask subjects to provide a urine specimen, unobserved, in a private bathroom. Collection containers and biohazard bags will be available to the study staff from the commercial laboratory. Specimens will be labeled with the name of the research study, the date and time of collection, and the specimen number; no names or other identifying information will be used. The specimen number will be generated using the subject's study ID number, the letters UT (to denote urine toxicology test), and the visit number. The RA will perform the point of care test (results back in 5 minutes). Urine will be tested for multiple substances: amphetamines, barbiturate, benzodiazepine, buprenorphine, cocaine, marijuana, methadone, methamphetamine, opiates, and oxycodone. Results will be recorded in REDCap. Urine toxicology results are confidential and will only be used for study purposes, not recorded in the participant's clinical record.

7.3 Non-Clinical Evaluations

Participant surveys: At baseline and every research visit, participants will answer surveys administered by the research assistants who will either record the responses directly into the REDCap database or onto a paper form, then entered into the REDCap database after the research visit is finished.

Medical record: HCV viral load will be obtained when possible by chart review. Information on treatment interruptions and discontinuation will be obtained from medical records.

Adherence by electronic monitors (Med-ic®) and self-report:

Adherence to medications dispensed in electronic blister packs will be measured by electronic compliance monitoring for blistered medications with an attached Med-ic® device. Med-ic® is an innovative stick-on paper label for medication blisters that provides a disposable method to measure adherence (117). Med-ic® packages yield 99.6% event accuracy (time of dose removal correctly recorded within ±2 minutes). This technology will allow tracking of medication usage from weekly blister packs prepared by the local pharmacists. Blister packs will be pre-fitted with labels and electronic tags.

In the PN arm, subjects will receive their HCV medication from the medical staff, packaged in 7-14 day blister packs, either weekly or every other week (standard), depending upon the determination of the provider after discussion with the participant. Used blister packs will be returned at research visits for downloading adherence data.

In the mDOT arm, subjects (enrolled in the OTP) will take observed doses at the OTP. The date and time of the dose will be recorded in the mDOT log. Seven-day blister packs containing weekend take-home doses (1-2 doses/week) will be provided on either Friday or Saturday. Blister packs will be collected at each research visit.

Subjects (enrolled in the community health center) will be offered mDOT 7 times a week via a smartphone application, miDOT. Alternatively, mDOT will occur 3 times a week at the community health center observed by the clinic/research staff. If the mDOT is administered at the community health center, dosing logs will be maintained by staff. If receiving miDOT (virtual DOT), subjects will be seen once a week in the clinic and receive one observed dose each week – observed by both clinic/research staff and the miDOT application. Subjects will be provided with 7-day blister packs for all of their doses.

Pill counts will also be performed by counting remaining doses in blister packs. Self-reported adherence will be measured using a single-item visual analogue scale (VAS) which has been shown to correlate well with both pill counts and virological outcomes in HIV-infected patients taking HAART [105, 106].

8 Study Schedule

Participants will be followed for up to 180 weeks: Up to 8 weeks (±4 weeks) of pre-treatment evaluation, 12 weeks of treatment, 12 weeks of follow-up to determine SVR12, and 144 weeks of follow-up post SVR12 to determine long-term SVR and reinfection.

8.1 Screening and Enrollment

8.1.1 Screening

Potential participants will be identified through two possible means: chart reviews of existing patients at the clinics and by community-based outreach and screening. Eligible participants should be enrolled within one month of screening. If enrollment does not occur within one month, eligibility should be reassessed.

8.1.1.a. Screening with Chart Reviews

Prior to conducting chart reviews of existing patients at the OTP and community clinics, sites will obtain a *Waiver of HIPAA authorization for screening/recruitment purposes.* Once this waiver is obtained, charts of potential participants will be reviewed to determine if the patient is eligible for participation.

- The following will be reviewed through Chart Review Part 1:
    - HCV Antibody (ever)
    - HCV viral load (ever)
    - HCV genotype/subtype (ever)
    - AST/ ALT and platelets in the past 12 months (for FIB-4 fibrosis estimation),
    - Imaging if available to rule out hepatocellular carcinoma if the participant has advance cirrhosis/fibrosis (abdominal ultrasound/CT scan with contrast, or MRI with contrast)
    - Confirm that the person has not previously received DAAs
    - **Document Study eligibility on CRF**

If subject is deemed eligible via “Chart Review Part 1”, then “Eligibility Screener” should be conducted.

8.1.1.b. Community-Based Screening

Participants may also be recruited through community-based outreach and screening. Potential participants will be identified through an eligibility screening tool. If they meet basic eligibility criteria – e.g. HCV positive, recent injection drug use – determine if they are currently seeing a provider.

- If they have an HCV provider:
    - Get a release of information to contact the provider
    - Obtain clinical records from the provider
    - **Extract data to assess eligibility (same as listed in 8.1.1.a), documenting on Chart Review Part 1.**
    - **Document Study eligibility on CRF**
- If they do not have an HCV provider:
    - Refer to an HCV provider at the community health center or OTP
    - Get a release of information
    - **Once the clinical record has been started, extract data to assess eligibility as listed in 8.1.1.a, documenting on Chart Review Part 1.**
    - **Document Study eligibility on CRF**

8.1.2 Visit 0: Eligibility confirmation, Consent and Enrollment Visit

A research assistant will meet with the potential participant in a private room in OTP, community health center, or other research location to confirm eligibility and obtain consent. Depending upon the time the participant has available and their state, this visit may be combined with Baseline Visit.

- Discuss study procedures, risks and benefits of study participation
- Obtain written signed consent for:
    1) Clinical trial participation;
    2) Study staff to use protected health information from clinic records;
    3) Study staff to disclose protected health information in event of clinical need
    4) staff to track any hospitalizations or emergency events

- Administer the sociodemographic instrument.
- Participant will be randomized to the DOT or PN arm (stratified, blocked) generated by DCC at UNM HSC. Wait until after baseline assessments have been completed before revealing randomization status to the participant.
- If the Baseline Visit is not taking place at this time, schedule the Baseline Visit within two weeks of enrollment.
- Treatment initiation should begin within twelve weeks of enrollment

8.2 Visit 1: Baseline Visit

The baseline visit should occur within two weeks of enrollment and prior to treatment initiation. This visit will assess for several different factors including HCV clinical factors, potential mediating variables based on the information-motivation-behavioral (IMB) model, potential moderators, and additional psychosocial factors hypothesized to predict adherence, using the following research assistant administered instruments, in this order:

- Modified ASI – Baseline (assess drug use)
- Behavior risk assessment (assesses injection behaviors)
- AUDIT-C (assess alcohol use)
- Substance Use Treatment (assess past and present experience with treatment)
- PHQ-9 (assess depression)
- GAD-7 (assess anxiety)
- EQ-5D with added pain question (assess quality of life)
- Stigma scale
- Shame scale
- Health efficacy
- Medical Outcomes Social Support Scale

The baseline visit will also include specimen collection:

- Urine for POC drug screening
- Collect 20 mL of whole blood in EDTA tubes for archiving.

Additional services will be provided:

- Counseling on avoidance of HCV transmission and HIV infection will be conducted.
- Information on drug treatment and needle exchange programs will be provided, and other referrals as needed.

At this visit, after all baseline instruments have been administered, research staff will inform the participant about their randomly assigned treatment delivery arm.

8.3 Treatment Initiation

Treatment initiation will occur after the baseline visit, within 12 weeks of enrollment, and as determined by the clinician. Prior to initiating treatment, the clinician must complete the provider checklist.

If treatment initiation does not begin within 12 weeks of enrollment, the participant will be withdrawn from the study.

8.4 Chart Review Part 2

Chart Review Part 2 should be completed at 12 weeks after enrollment regardless of if the participant initiates treatment. The following information should be collected:

- Pregnancy status
- Total bilirubin
- Albumin
- Prothrombin time
- HBV status
- HAV status
- Fibrosure, Fibroscan, liver biopsy (if available)
- Problem list diagnoses:
  - Cirrhosis
  - Psychiatric
  - Medical
- Imaging if advanced fibrosis/cirrhosis to rule out hepatocellular carcinoma (abdominal ultrasound/CT scan with contrast, or MRI with contrast)
- Reason why patient did not initiate treatment (if applicable)
- HCV Viral load
- HCV Genotype/subtype
- FIB-4 score
- Child-Pugh score
- ALT and AST levels
- Platelets
- HIV status
- HIV Viral load (if applicable)
- HIV CD4 count (if applicable)

8.5 Treatment (follow-up) visits:

During treatment participants will have research visits and either mDOT visits or PN visits. Research visits will be the same for all participants, regardless of assigned treatment arm. Participants will be contacted by research staff regarding their first treatment visit by phone or in person and briefed on the visit and what to expect.

8.5.1 Treatment Research Visits

8.5.1.a Visit 2: week 4 of treatment, ± 7 days

Research staff will assess for factors of interest by administering the following questionnaires:

- Modified ASI – Follow-up (assess drug use)
- Behavior risk assessment (assesses injection behaviors)
- Substance Use Treatment (assess past and present experience with treatment)
- Visual Analogue Scale (assess adherence)

Review medical chart and record the following information:

- HCV viremia
- Child-Pugh score to assess hepatic decompensation (if available)
- HIV viral load and CD4 count (if applicable)
- FIB-4 score (if available)

Collect the following specimens:

- Urine for POC drug screening

Provide the following services:

- Counseling on avoidance of HCV transmission and HIV infection.
- Information on drug treatment and needle exchange programs, and other referrals as needed

8.5.1.b Visit 3: week 8 of treatment, ± 7 days

Research staff will assess for factors of interest by administering the following questionnaires:

- Modified ASI – follow-up (assess drug use)
- Substance Use Treatment (assess past and present experience with treatment)
- Visual Analogue Scale (assess adherence)

Review medical chart and record the following information:

- HCV viremia
- Child-Pugh score to assess hepatic decompensation (if available)
- HIV viral load and CD4 count (if applicable)
- FIB-4 score (if available)

Collect the following specimens:

- Urine for POC drug screening

Provide the following services:

- Counseling on avoidance of HCV transmission and HIV infection.
- Information on drug treatment and needle exchange programs, and other referrals as needed

8.5.1.c Visit 4: week 12 of treatment, ± 7 days

Research staff will assess for factors of interest by administering the following questionnaires:

- Modified ASI – follow-up (assesses drug use)
- Behavior risk assessment (assesses injection behaviors)
- AUDIT-C (assesses for alcohol use)
- Substance Use Treatment (assess past and present experience with treatment)
- PHQ-9 (assesses for depression)
- GAD-7 (assesses for anxiety)
- EQ-5D with added pain question (assesses quality of life)
- Health efficacy
- Medical Outcomes Social Support Scale (assesses social support)
- Visual Analogue Scale (assess adherence)
- ONLY FOR THOSE IN PN ARM: Brief Revised Working Alliance Inventory (assesses rapport with PN)

Review medical chart and record the following information:

- HCV viremia

- Child-Pugh score to assess hepatic decompensation (if available)
- HIV viral load and CD4 count (if applicable)
- FIB-4 score (if available)

Collect the following specimens:

- Urine for POC drug screening

Provide the following services:

- Counseling on avoidance of HCV transmission and HIV infection.
- Information on drug treatment and needle exchange programs, and other referrals as needed

8.6 Post-treatment (follow-up) visits

Follow-up visits are scheduled in reference to the treatment start date.

8.6.1 Visit 5: week 24, ±14 days

Research staff will assess for factors of interest by administering the following questionnaires:

- Modified socio-demographic survey (assess for any changes in housing, income)
- Modified ASI – follow-up (assesses for drug use)
- Behavioral risk questionnaire (assesses injection behaviors)
- AUDIT-C (assesses alcohol use)
- Substance Use Treatment (assess past and present experience with treatment)
- PHQ-9 (assesses for depression)
- GAD-7 (assesses for anxiety)
- EQ-5D with added pain question (assesses quality of life)

Review medical chart and record the following information:

- HCV viremia
- FIB-4 score (if available)

Collect the following samples:

- Urine for POC drug screening
- Collect 20 mL of whole blood in EDTA tubes to send to Quest Diagnostics for HCV viremia testing and for archiving.

Provide the following services:

- Counseling on avoidance of HCV transmission and HIV infection.
- Information on drug treatment and needle exchange programs, and other referrals as needed

8.6.2 Visit 6: week 36, ± 14 days

Research staff will assess for factors of interest by administering the following questionnaires:

- Behavioral risk assessment (assesses injection behaviors)
- Shame scale (assesses shame)

Collect the following samples:

- Collect 20 mL of whole blood in EDTA tubes to send to Quest Diagnostics for HCV viremia testing and for archiving.

Provide the following services:

- Counseling on avoidance of HCV transmission and HIV infection.
- Information on drug treatment and needle exchange programs, and other referrals as needed

8.46.3 Visit 7: week 48, ± 14 days

Research staff will assess for factors of interest by administering the following questionnaires:

- Behavioral risk assessment (assesses injection behaviors)
- AUDIT-C (assesses alcohol use)
- Substance Use Treatment (assess past and present experience with treatment)
- PHQ-9 (assesses for depression)
- GAD-7 (assesses for anxiety)
- EQ-5D with added pain question (assesses quality of life)
- Medical Outcomes Social Support Scale (assesses social support)

Collect the following samples:

- Urine for POC drug screening
- Collect 20 mL of whole blood in EDTA tubes to send to Quest Diagnostics for HCV viremia testing and for archiving.

Provide the following services:

- Counseling on avoidance of HCV transmission and HIV infection.
- Information on drug treatment and needle exchange programs, and other referrals as needed

8.6.4 Visit 8: week 60, ± 14 days

Research staff will assess for factors of interest by administering the following questionnaires:

- Behavioral risk assessment (assesses injection behaviors)

Collect the following samples:

- Collect 20 mL of whole blood in EDTA tubes to send to Quest Diagnostics for HCV viremia testing and for archiving.

Provide the following services:

- Counseling on avoidance of HCV transmission and HIV infection.
- Information on drug treatment and needle exchange programs, and other referrals as needed

8.6.5 Visit 9: week 72, ± 14 days

Research staff will assess for factors of interest by administering the following questionnaires:

- Modified socio-demographic survey (assess for any changes in housing, income)
- Modified ASI – follow-up (assesses drug use)
- Behavioral risk questionnaire (assesses injection behaviors)
- AUDIT-C (assesses alcohol use)

Collect the following samples:

- Urine for POC drug screening
- Collect 20 mL of whole blood in EDTA tubes to send to Quest Diagnostics for HCV viremia testing and for archiving.

Provide the following services:

- Counseling on avoidance of HCV transmission and HIV infection.
- Information on drug treatment and needle exchange programs, and other referrals as needed

8.6.6 Visit 10: week 84, ± 14 days

Research staff will assess for factors of interest by administering the following questionnaires:

- Behavioral risk assessment (assesses injection behaviors)

Collect the following samples:

- Collect 20 mL of whole blood in EDTA tubes to send to Quest Diagnostics for HCV viremia testing and for archiving.

Provide the following services:

- Counseling on avoidance of HCV transmission and HIV infection.
- Information on drug treatment and needle exchange programs, and other referrals as needed

8.6.7 Visit 11: week 96, ± 14 days

Research staff will assess for factors of interest by administering the following questionnaires:

- Behavioral risk assessment (assesses injection behaviors)
- AUDIT-C (assesses alcohol use)

Collect the following samples:

- Urine for POC drug screening
- Collect 20 mL of whole blood in EDTA tubes to send to Quest Diagnostics for HCV viremia testing and for archiving.

Provide the following services:

- Counseling on avoidance of HCV transmission and HIV infection
- Information on drug treatment and needle exchange programs, and other referrals as needed

8.6.8 Visit 12: week 108, ± 14 days

Research staff will assess for factors of interest by administering the following questionnaires:

- Behavioral risk assessment (assesses injection behaviors)

Collect the following samples:

- Collect 20 mL of whole blood in EDTA tubes to send to Quest Diagnostics for HCV viremia testing and for archiving.

Provide the following services:

- Counseling on avoidance of HCV transmission and HIV infection.
- Information on drug treatment and needle exchange programs, and other referrals as needed

8.6.9 Visit 13: week 120, ± 14 days

Research staff will assess for factors of interest by administering the following questionnaires:

- Modified socio-demographic survey (assess for any changes in housing, income)
- Modified ASI – follow-up (assesses for drug use)
- Behavioral risk questionnaire (assesses injection behaviors)
- AUDIT-C (assesses alcohol use)
- Substance Use Treatment (assess past and present experience with treatment)
- PHQ-9 (assesses for depression)
- GAD-7 (assesses for anxiety)
- EQ-5D with added pain question (assesses quality of life)
- Shame Scale (assesses for shame associated with HCV infection)
- Medical Outcomes Social Support Scale (assesses for social support)

Collect the following samples:

- Urine for POC drug screening
- Collect 20 mL of whole blood in EDTA tubes to send to Quest Diagnostics for HCV viremia testing and for archiving.

Provide the following services:

- Counseling on avoidance of HCV transmission and HIV infection.
- Information on drug treatment and needle exchange programs, and other referrals as needed

The original HERO protocol involved a total of 13 research visits over a 30-month period. On May 2019, participants were offered the opportunity to participate in an extended follow-up period involving 4 additional research visits over a 12-month period. Participants were invited to participate in the protocol extension period (12 months). Participants were informed of all the procedures in the additional 4 visits. Only

participants who agreed to participate and signed the informed consent were enrolled in the additional visits.

8.6.10 Visit 14: week 132, ± 14 days

Research staff will assess for factors of interest by administering the following questionnaires:

- Behavioral risk assessment (assesses injection behaviors)

Collect the following samples:

- Collect 20 mL of whole blood in EDTA tubes to send to Quest Diagnostics for HCV viremia testing and for archiving.

Provide the following services:

- Counseling on avoidance of HCV transmission and HIV infection.
- Information on drug treatment and needle exchange programs, and other referrals as needed

8.46.11 Visit 15: week 144, ± 14 days

Research staff will assess for factors of interest by administering the following questionnaires:

- Behavioral risk assessment (assesses injection behaviors)
- AUDIT-C (assesses alcohol use)

Collect the following samples:

- Urine for POC drug screening
- Collect 20 mL of whole blood in EDTA tubes to send to Quest Diagnostics for HCV viremia testing and for archiving.

Provide the following services:

- Counseling on avoidance of HCV transmission and HIV infection
- Information on drug treatment and needle exchange programs, and other referrals as needed

8.6.12 Visit 16: week 156, ± 14 days

Research staff will assess for factors of interest by administering the following questionnaires:

- Behavioral risk assessment (assesses injection behaviors)

Collect the following samples:

- Collect 20 mL of whole blood in EDTA tubes to send to Quest Diagnostics for HCV viremia testing and for archiving.

Provide the following services:

- Counseling on avoidance of HCV transmission and HIV infection.
- Information on drug treatment and needle exchange programs, and other referrals as needed

8.6.13 Visit 17: week 168, ± 14 days (Exit interview)

Research staff will assess for factors of interest by administering the following questionnaires:

- Modified socio-demographic survey (assess for any changes in housing, income)
- Modified ASI – follow-up (assesses for drug use)
- Behavioral risk questionnaire (assesses injection behaviors)
- AUDIT-C (assesses alcohol use)
- Substance Use Treatment (assess past and present experience with treatment)
- PHQ-9 (assesses for depression)
- GAD-7 (assesses for anxiety)
- EQ-5D with added pain question (assesses quality of life)
- Shame Scale (assesses for shame associated with HCV infection)
- Medical Outcomes Social Support Scale (assesses for social support)

Collect the following samples:

- Urine for POC drug screening
- Collect 20 mL of whole blood in EDTA tubes to send to Quest Diagnostics for HCV viremia testing and for archiving.

Provide the following services:

- Counseling on avoidance of HCV transmission and HIV infection.
- Information on drug treatment and needle exchange programs, and other referrals as needed

Research staff will thank the participant for participating in the study.

8.7 Unscheduled Visits

Unscheduled visits may occur at any time during the study. They may occur for the following reasons:

(1) For operational reasons, e.g., a subject may request to reschedule, or to ask questions;

(2) For SAE related reasons. When interim contacts or visits are completed in response to subject reports of SAEs, study staff will assess the reported event and refer the subject to appropriate medical care. All SAEs will be evaluated and reported as required (Section 9.4);

(3) If a subject presents to the study site after having missed a scheduled visit (e.g., in response to locator/tracking efforts) on a day that does not fall within a scheduled visit window;

(4) For other reasons at subject request. All interim contacts and visits will be documented in subjects' study records and on applicable data collection forms.

(5) If a subject fails HCV treatment. This visit will be solely for collection of 20 mL of blood to be processed and archived by local labs for resistance testing.

8.8 Patient Navigator Encounters

Participants assigned to the PN arm will be scheduled for a minimum of 4 encounters with the PN, 3 of which must be conducted in-person and 1 of which can be conducted either in-person or remotely (via phone, e-mail or text) .These four minimum encounters include: 1) Enrollment, Assessment and Referrals; 2) Treatment Readiness (in-person); 3) Treatment Adherence Check-in (remotely via text, call or e-mail); and 4) After Treatment (in-person). Additional contacts may occur more frequently and via different methods (e.g.: phone calls, texts) depending upon the needs of the participant. PN contacts are described in more depth in the PN Protocol.

8.7.1 Initial Visit (Required)

The initial visit will take place prior to the participant beginning treatment.

- The PN will use the *Health Promotion Guide* modules I and II to complete the first page of the Patient Navigation Form (Sections: Intake, Self-Reported History, Assessment and Referrals)
- Based on the outcome of the Assessment, the PN and participant will develop a Patient Navigation Care Plan together.
- Referrals for supportive services will be provided
- Additional visits to complete the assessments, referrals and health promotion may be conducted as needed (optional).

8.7.2 Treatment Readiness Encounter (Required)

In the treatment readiness encounter, the PN and participant will develop a treatment plan for the participant, incorporating input from the provider, including the provider in the encounter if possible.
Using *Health Promotion Guide Module* III:

- The PN will provide treatment readiness information and counseling
- The PN and participant will discuss the frequency and method of PN encounters to support adherence through the course of treatment. Frequency may change during treatment depending on the needs of the participant (for example, if the participant has unexpected side effects, or trouble remembering to take medications as prescribed, adherence support could be increased).
- The PN and participant will complete the *Treatment Planning Form*, after receiving input from the provider.

8.7.3 Treatment Adherence Encounter (3 days post treatment initiation - Required)

The PN is required to contact the participant three days (2-5 days is acceptable) after he/she starts treatment to address any side effects the patient may be experiencing, ask if any doses have been missed, and intervene to improve adherence. This encounter can occur in-person or could be a remote encounter (phone, email, text) depending upon participant need.

- Based on the outcome of this check-in, the PN will update the Treatment Planning form with any changes to the treatment adherence support frequency and method, and then contact the patient as agreed upon for the duration of the treatment.
- The method and frequency of treatment adherence support can be adjusted as needed through the course of treatment.

8.7.4 Treatment Period Encounters (Weeks 1-11) (Recommended)

Weekly adherence check-ins during the course of treatment are recommended. These check-ins could occur in-person or remotely via phone call, text or email. If weekly contact is not appropriate for the participant, the treatment adherence encounters should occur at the frequency agreed upon by the provider, PN and participant and documented in the *Treatment Plan*.

- The treatment adherence encounters should be documented using the *Care Coordination Log*

- The PN will provide referrals to services in which the participant is interested.

8.7.5 After Treatment Encounter (Week 12 of treatment) (Required)

At the final required encounter after treatment, the PN will use the Health Promotion Guide Module IV to:

- Ensure the patient is aware of future clinical monitoring requirements.
- Provide reinfection prevention information, resources and support.
- Discharge or transition patient to an appropriate supportive program, provide referrals
- The PN has an ***option*** to work with the participant after treatment to support reinfection prevention, for up to six months (optional).

8.9 mDOT Visits

OTP: Participants assigned to the mDOT arm in the OTP will have a minimum of 5 observed doses per week by clinic or research staff. Each observed dose will be recorded on the dose log, then entered into the study database.

Community Health Center: Participants assigned to the mDOT arm in the CHC will have one observed dose by clinic or research staff per week when they pick up their medication. Other doses will be observied as described in section 6.1.2. All observed doses will be recorded on the mDOT log (Adherence Calendar) and entered into the study database.

9 Safety Reporting and Safety Assessment Monitoring

9.1 Data and Safety Monitoring Plan.

The PI (Dr. Litwin) will be responsible for monitoring the safety and efficacy of this study, executing the Data and Safety Monitoring (DSM) plan, and complying with the reporting requirements. The PI will provide a summary of the DSM report to PCORI on an annual basis as part of the progress report. The DSM report will include the participants' sociodemographic characteristics, a summary of Severe Adverse Events (SAEs), any actions or changes with respect to the protocol, and any quality assurance or regulatory issues that occurred during the past year. The DSM report to PCORI will also include, when available, the results of any efficacy data analysis conducted.

9.2 Data monitoring plan

Because the intervention is very low risk and is highly integrated within usual clinical care, the main element of the monitoring plan will be continuous, close monitoring by study staff and investigators, with prompt identification and reporting of adverse events (AEs).

9.3 Data Confidentiality

Each participating site will maintain appropriate medical and research records for this trial, in compliance with ICH E6, Section 4.9 and regulatory and institutional requirements for the protection of confidentiality of subjects. Forms for use as source documents will be derived from the electronic case report forms (eCRFs) and be provided by the Statistical and Data Coordinating Center (SDCC). Source documents will only be accessible by study staff and all research records will be kept in a locked filed cabinet in the research office of the PI.

Medical records are stored in locked rooms in each clinic, or in password protected computer files. The RA with assistance from the Co-I/PI will review the charts. Prior to starting the chart review process, research staff will complete online training in patient-oriented research, including confidentiality, and will receive further training in confidentiality and the chart review protocol from the PI.

9.4 Serious Adverse Events

An adverse event will be considered serious when the outcome is:

- Death
- Life-threatening
- Hospitalization (initial or prolonged)
- Disability or permanent damage
- Congenital Anomaly/Birth Defect
- Required intervention to prevent permanent impairment or damage (devices)
- Other serious important medical event

SAEs will be systematically assessed at each of the research visits. Any SAE will be reported according to the IRB requirements of the institution that the participant is enrolled through. The initial SAE report will be followed by submission of a completed SAE report to Einstein. In the event that a research subject either withdraws from the study or the investigator decides to discontinue a patient due to a SAE, the patient will be monitored by the investigator via ongoing status assessment until: (1) a resolution is reached, i.e., the problem requiring hospitalization has resolved or stabilized with no further changes expected, (2) the SAE is determined to be clearly unrelated to the study intervention, or (3) the SAE results in death. Outcome of SAEs will be periodically reported to PCORI. A summary of the SAEs that occurred during the previous year will be included in the annual progress report. Subjects enrolled in this study will be prescribed FDA-approved antiviral medications as part of standard clinical care. The study involves randomization to the mode of administration of the antiviral medications. For each SAE, the site investigator will determine if the SAE was related to the study. A second opinion will obtained if needed from a PI at a different clinical site.

10 Stakeholder Engagement

This project was conceptualized and designed with the active participation of patients, researchers and other stakeholders from its inception. Patient engagement, including individuals who have or are currently injecting and have HCV, or have been cured from HCV, has been actively fostered in study planning at each local site. Because this project brings together patients and providers representing a diverse geography and policy, patients and other stakeholders will continue to be actively and formally involved in the planning, design and execution of the study at two levels – locally and nationally.

At the local level, each research site will form a Local Stakeholder Advisory Board (LSAB) which consists of a Primary Investigator, 1-3 patients (termed Co-Investigators) and local representatives from participating venues such as OTPs, community health centers, syringe exchange programs, community-based organizations (CBOs), public health boards/departments, HCV providers, and homeless programs. Site PIs, in consultation with OTP and community treatment site leadership have identified patients to serve on the local Stakeholder Advisory Board.

The LSAB will meet on a quarterly basis to allow discussion of study implementation, recruitment, participant tracking, intervention delivery, and outcome assessment. The board will provide technical assistance and guidance to the research sites.

At the second level, a National Stakeholder Advisory Board (NSAB) will be convened, consisting of the local site PI and a local representative as well as representatives from national partners such as CDC (lead governmental organization); professional policy, educational, and advocacy organizations - TAG, NATAP, HRC, Hepatitis Support and Mentor Group, Project Inform, Hepatitis Education Project, NVHR; professional patient organizations - NAMA and Medication-Assisted Recovery Services (MARS); governmental organizations - NYSDOHMH and NYCDOH; industry – Gilead, Quest, Monogram, and Orasure. Other partners will be recruited, such as Medicaid payers based on recommendations elicited in the initial convocation of the group. The National Stakeholder Advisory Board will meet on a quarterly basis in Year 1 to review the project design, ensure the project will answer questions in alignment with stakeholder priorities, and provide guidance on dissemination planning from the outset. In years 2-4 the NSAB will meet on a quarterly basis to monitor progress to date, address difficulties with study implementation, recruitment, intervention or outcome assessment, and discuss strategies for communicating results to the wider community and all interested stakeholder groups. In Year 5 the NSAB will meet quarterly to review results and guide dissemination activities.

11 Statistical Considerations

11.1 Independent Parallel Analysis

To assure reproducibility of statistical analysis results, two independent statisticians, Dr. Herbert Davis at UNM and Dr. Moonseong Heo at Einstein, will adhere as closely as possible to the analytical plans detailed below. They will analyze the primary outcome, the 12-week sustained viral response (SVR), independently in a blinded and parallel manner, and compare their results. If their results are substantially different beyond a tolerable variation, then the two statisticians will examine each other's analytic strategy and software codes to reach a consensus. Final results will be produced upon agreement of the two statisticians. Investigators will not be involved in this process, and more importantly, data analysis will not be guided or influenced by the indications of results. Each aspect of data analysis such as cleaning, analysis, and output will be logged and archived for review. Whenever possible, the two statisticians will follow the procedure for other outcome analysis (see 11.3 below) as well.

11.2 Definition of Study Subjects

The study subjects for the primary and secondary outcomes are who: 1) meet the inclusion and exclusion criteria (sections 5.1 and 5.2); 2) sign the consent form; 3) are randomized; and 4) initiate treatments, i.e., intake at least one dose of the medicine. As we do not anticipate that all randomized subjects will initiate treatments, a randomized subject will not necessarily be a study subject for primary analysis and beyond. However, depending on secondary or other study questions such as comparison of treatment initiations, all randomized subjects will serve as an analytic sample.

11.3 Study Hypotheses

SVR: Among subjects who initiate HCV treatment, rate of SVR will be higher in the mDOT vs. PN arm. We hypothesize that SVR rate will be 80% in PN arm.

Treatment initiation rate: A higher proportion of patients in the PN arm will initiate treatment compared to the mDOT arm, which is expected to have 60% treatment initiation rate.

Adherence rate: Patients in the mDOT arm will have higher adherence rate, compared to the PN arm which is expected to have 80% adherence rate.

Treatment completion rate: Patients in the mDOT arm will have higher treatment completion rate, compared to the PN arm, which is expected to have 80% completion rate.

Detectable resistance: Patients in the PN arm will have higher resistance rate, compared to the mDOT arm. We hypothesize that the majority (65%) of patients who fail to achieve SVR will develop detectable resistance, yielding an overall 10% resistance rate.

Reinfection rate: The hypothesis is that there will be a minimum 5% reinfection rate based on meta-analysis of reinfection rates in patients treated with IFN-based regimens.

11.4 Sample Size Determination

Sample size N=300 per arm, or a total of N=600, was determined based on feasibility of recruitment from all sites during the study period. Power analysis for each hypothesis below is conservatively conducted based on a reduced sample size (N= 270 per arm, or N=540 in total) after considering 10% attrition rates. The target power is 80% with a two-sided significance level of 0.05. To this end, minimally detectable effect sizes and widths of 95% confidence intervals were computed with those parameters and the sample size after attrition.

11.5 Primary Analytic Principle

The intention-to-treat principle will be used as the primary analytic principle, which pertains more to a real-world situation. That is, once a treatment was randomly assigned to a participant, the participant's treatment identity will not change in the analysis even if s/he changes to the other model of care during the trial period or did not take the assigned treatment. Other analytic strategies such as per protocol or as-treated analyses will also be applied to examine robustness of effectiveness of mDOT vs. PN.

11.6 Preliminary Data Analysis

First, the distributions of all variables will be examined using graphical or descriptive statistics to identify any values out of range. When identified, out of range values will be found in the original record, compared and corrected if needed. Second, although by the stratified randomization design, each arm will equally be distributed across city, clinical site (OTP and CHC) and stage of liver disease (cirrhosis vs. no cirrhosis), the

success of randomization will be checked as a way of checking key assumptions by comparing the PN and mDOT groups on key variables, such as age, gender, ethnicity, race, viral load, subtype, psychiatric history, drug use type, and social support. Continuous variables will be compared between arms using the t-tests or Mann-Whitney tests, and categorical variables will be compared using chi-square or Fisher's exact tests.

Variables that are not equally distributed, albeit expected to be rare, will be included in multivariate models to control for their potential cofounding effects. When necessary, normal assumptions will be checked for continuous variables by applying a formal Kolmogorov-Smirnov test, and if violated, Box-Cox transformations will be considered. All preliminary statistical analysis and beyond will be conducted using SAS v9.3.

11.7 Missing data analysis

In order to not compromise internal or external validity of our study results, every effort will be made to minimize missing data that could occur due to missed visits or subject attrition. A maximum 10% subject attrition rate is anticipated during the first 24-week intervention period considering a real-world situation that withstands a tight control. However, the missing outcome data rates will depend on the outcome definition whereas most analyses will use baseline characteristics as covariates that will thus have negligible missing data rate.

The primary analysis will be based on available data without missing data imputation; however, we will conduct variety of missing data imputation methods for sensitivity analyses. Depending on the clinical nature of outcome, worst scenario imputation or, if deemed more relevant, mean imputation methods will be considered. In addition, fully specific conditional specification multiple imputation methods will also be applied, which are applicable to non-ignorable missing data.

Characteristics of patients who are lost to follow-up will be compared to those that remain in the study to assess the degree of any selection bias due to attrition, and the analysis results of the different types of imputed missing data will be compared to the primary analysis results. In particular, variability of the coefficients of primary predictors across the different imputation methods will be assessed to evaluate robustness of the findings. If the changes in the coefficients are greater than 15% from those of the primary analysis, we will limit the generalizability, internal and external validity of our findings, which we nevertheless do not believe will occur if attrition rates are less than 25%.

11.8 Heterogeneity of mDOT or PN effects

The mDOT or PN effects depending on outcome (see Aim 1 hypotheses) will be assessed for each subgroup stratified various factors (e.g., clinic setting, demographic, or clinical), which are specified below, and will be compared across the subgroup strata. Forest plots will be produced to show graphically the differences or contrasts in effect sizes across all subgroups. Formal tests will follow via testing significance of pertinent interaction terms with the mDOT or PN arm indicator in statistical models.

11.9 Mediated mDOT or PN effects

Mediator analysis will be conducted to identify potential mediators between mDOT/PN effect and each of the five outcomes. A mediator will be a variable whose value changes or occurs between the baseline and the end of the study; for example, reduced stigma and shame, extent of peer support, changes in social support, and increased self-efficacy. The potential mediating effects will be assessed by differences in mDOT or PN effect sizes depending on outcome between with and without a potential mediator variable in statistical models. Their significance will be tested following the Baron and Kenny mediation test principle.

11.10 Analytic plan for Primary and Secondary outcomes: SVR, Treatment initiation rate, Adherence rate, and Treatment completion rate

Study Hypotheses:

SVR: Among subjects who initiate HCV treatment, rate of SVR will be higher in the mDOT vs. PN arm. We hypothesize that SVR rate will be 80% in PN arm.

Treatment initiation rate: A higher proportion of patients in the PN arm will initiate treatment compared to the mDOT arm, which is expected to have 60% treatment initiation rate.

Adherence rate: Patients in the mDOT arm will have higher adherence rate, compared to the PN arm which is expected to have 80% adherence rate.

Treatment completion rate. Patients in the mDOT arm will have higher treatment completion rate, compared to the PN arm, which is expected to have 80% completion rate.

Statistical Model

Multivariable logistic regressions will be applied to test the overall effectiveness of mDOT or PN on the five binary outcomes (success vs. failure) with the SVR rate as the primary outcome. The arm indicator will be the predictor for each outcome. With respect to adherence outcome in particular, repeatedly measured adherence will be analyzed (using 6 post-baseline time points and adherence as a continuous measure) applying a mixed effects linear model to test if the two arms are significantly different. This model accounts for within-subject longitudinal outcome correlation by taking the subject-level intercept as random. All models will include potential confounding variables that are significantly different between the two arms; the sites will be included as a covariate as well. Likewise, mixed effects logistic regression will also be applied to test the significance of PN and DOT on repeatedly-measured undetectable HCV VL throughout the intervention period, adjusting for substance use in addition to other confounding variables. Changes in illicit drug use will be analyzed using urine toxicology data from each visit, counting the "person-month" as a unit of analysis, and analyzing the percentage of person-months that are positive for use of illicit drugs during the study period using a t-test or Mann-Whitney test.

Power analysis: Minimally detectable effect sizes

SVR: Considering the base 80% SVR rate of in PN arm, a minimum of 9% difference between the two arms will be detected (i.e., 89% vs. 80%, Odds Ratio (OR)=2.1) in a multivariable logistic regression model in which confounding variables will explain 10% of variation in the predictor variable. This study posits that a >9% difference in SVR between the PN and mDOT groups will be clinically significant based on studies that showed that SVR in treatment naive patients was >90% [14].

Mixed effects logistic regression models for the undetectable HCV load will be able to detect even smaller percent point difference since they will utilize repeated measures for each subject no matter how large within-subject outcome correlations will be.

Treatment initiation rate: With anticipated 60% treatment initiation rate in the mDOT arm, a minimum of 7% difference will be detectable (i.e., 60% vs. 67%, OR=0.74) in any outcome in a multivariable logistic regression model in which confounding variables will explain 10% of variation in the predictor variable. Note that sample size for this analysis will be N=1000, the total number of randomized participants.

Adherence rate: With expected 80% adherence rate in the PN arm, a minimum of 9% difference in adherence rates between the 2 arms will be detectable (i.e., 89% vs. 80%, OR=2.1) in a multivariable logistic regression model. Per the repeatedly measured continuous adherence percentage outcome, mixed effects linear models will be able to detect standardized effect sizes (mean difference divided by a pooled Standard

Deviation (SD)) greater than 0.2 irrespective of magnitudes of within-subject outcome correlations overt time. In a previous DOT study, a standardized effect size of mDOT vs. TAU was estimated to be 0.6.

Treatment completion rate. Under the expected 80% completion rate in the PN arm, a minimum of 9% difference in completion rates between the two arms will be detectable (i.e., 89% (mDOT) vs. 80% (PN), OR=2.1).

Subgroup Heterogeneity Analyses

To assess heterogeneity of mDOT or PN effects, additional analyses will be conducted to evaluate whether the mDOT effect varies by variety of subgroups stratified by the following characteristics: OTP (50%) vs. CHC (50%); Males (70%) vs. Females (30%); Patients using illicit drugs during treatment (65%) vs. those not using illicit drugs (35%); HIV/HCV coinfected (28%) vs. HCV mono-infected (72%); Cirrhosis (21%) vs. non-cirrhosis (79%); African American / Latino (41%) vs. Caucasian (59%); Marginally housed (26%) vs. stably housed (74%); Comorbid mental illness (55%) vs. no mental illness (45%); and Peer-support (70%) vs. no peer-support (30%). Initially, subgroups will be defined based on the above factors and estimates of treatment effect will be obtained separately in each subgroup using the methods described above. The significance of any heterogeneous mDOT or PN effects across these factors will be formally tested by testing significance of corresponding interaction terms with the mDOT or PN arm indicator. In addition, we will also conduct within-arm subgroup analyses to identify factors that are associated with outcomes within arms. For example, one test would be if increased social support will be associated with higher treatment initiation within the PN arm.

Power analysis for subgroup analysis: For the subgroup analysis, the minimally detectable effect size will depend on the sample size of subgroups. However, assuming that a subgroup has 50% of the total sample, i.e., N=270, and that a base outcome rate is 80% (e.g., SVR), then ≥12% difference will be detected using a Chi-square test. The minimally detectable standardized effect size for continuous outcome will be 0.3. This power analysis also applies to detect binary or continuous factors associated with outcome from within-arm subgroups analyses since the sample size of each arm will be N=270 after attritions. For the subgroups with smaller sample size, the minimally detectable effects sizes, binary or continuous, will be larger. For example, for some of our subgroups will be as small as 20% (or, N= 108) of the sample (e.g. HIV/HCV coinfected), minimum effect sizes are larger at ≥17% for SVR and 0.5 standardized effect size for continuous variables.

11.11 Analytic plan for Resistance and Reinfection Rates

Study Hypotheses:
Detectable resistance: Patients in the PN arm will have higher resistance rate, compared to the mDOT arm. We hypothesize that the majority (65%) of patients who fail to achieve SVR will develop detectable resistance, yielding an overall 10% resistance rate.

Reinfection rate: The hypothesis is that there will be a minimum 5% reinfection rate based on meta-analysis of reinfection rates in patients treated with IFN-based regimens.

Statistical Model

The precision of proportion of participants who develop resistance or reinfection will be determined with 95% confidence intervals (CIs) calculated using exact binomial methods. To identify factors associated with resistance or reinfection, we will conduct bivariate analysis using (exact) logistic regressions for both continuous and dummy-coded categorical variables. A series of bivariate analyses will be followed by a multivariable logistic regression that includes all factors significant in the bivariate analysis at a two-sided 0.05 significance level. All analyses will be separately conduced for each of resistance and reinfection outcomes. For the examination of association between resistance and adherence in particular, a multivariable logistic regression will also be applied in which overall adherence will be the primary predictor in the presence of other factors identified in the bivariate logistic regression analysis. In all multivariable analysis, the mDOT arm indicator will be included for adjusting purpose.

Power analysis

With a total of N=540 after attrition, the expected 95% confidence intervals are (7.7%, 12.8%) and (3.5% and 7.2%) for the resistance and reinfection rates, respectively, For the bivariate analysis, any binary variable with odds-ratio (OR) ≥1.8 (or 7% vs. 14.4%) for resistance and OR > 3.3 (or 2.5% vs. 7.8%) for reinfection will be identified with >80% power; and any continuous variable with OR>1.6 and OR>2.1 per 1 SD unit changes will be detected for resistance and reinfection, respectively. In the multivariable analysis, binary variables with OR > 2.5 (7% vs. 16.2%) and OR > 4.0 (2.5% vs. 9.3%) and continuous variables with OR 1.8 and OR>2.5 per 1 SD unit change will be detected for resistance and reinfection, respectively, with>80% power, expecting that as large as 30% of variation of each variable will be explained by the other variables in the models for aim 2 analyses. Likewise, for detecting association between a continuous

adherence rate and resistance, OR ≥1.8 per 1 SD unit change will be detected with > 80% power.

11.12 Analytic plan for Aim 3

11.12.1 Patient Navigator (PN) Stakeholder Qualitative Study.

Recruitment. 10-15 PNs will be recruited in Year 1 including at least one navigator from each site. Data will be utilized as part of a formative evaluation, with the goal of identifying emerging barriers to program success and facilitating problem solving [107].

Data collection. After participating in an informed consent process, navigators from each of the project sites will be interviewed by telephone. Study staff have considerable experience with telephone interviews [108, 109]. Thirty-minute semi-structured interviews will be conducted focusing on navigator experiences and perceptions of the intervention, with particular focus on gaining the perspectives of these front line workers into barriers to successful patient outcomes.

Analysis. Interviews will be recorded and transcribed. Data will be analyzed using Miller and Crabtree's "Editing" approach [110]. The Qualitative Team (Drs. Karasz, McKee, and RA) will create a preliminary coding scheme, which is then revised in iterative fashion as it is applied to new subsets of the data. When the coding scheme is judged to be adequate by the team, the entire data set will be coded in NVivo, a qualitative data analysis program that facilitates the rapid organization and retrieval of thematically related data [109, 111, 112]. Themes related to successes and failures, and sources of stress and satisfaction will be summarized. Data summaries will be presented to the NSAB to discuss implications, identify emerging problems, and brainstorm solutions.

11.12.2 The Patient Stakeholder Qualitative Study.

The focus of the Patient Stakeholder Study, conducted in Years 2-5, will be to understand barriers to successful outcomes along the pathway to care, including: the lack of treatment uptake, poor adherence (< 80%), failure to achieve SVR, development of drug resistance, and HCV reinfection. By contrast to the Navigator study, the Patient Stakeholder Study incorporates a comparative design. With the goal of identifying barriers to successful treatment, structured comparisons will be made between successful and unsuccessful patients at each stage along the pathway to care.

Recruitment. At the *treatment uptake stage*, a sample of 10 patients who successfully initiated treatment will be recruited and interviewed, and a similar group of patients who did not. Similarly, we will recruit patients who adhered/did not adhere, achieved SVR/did not adhere; and who became re-infected/remained HCV free.

Data Collection. Patients will be recruited and interviewed by telephone. An interview guide will be developed that focuses on potential barriers and facilitators to successful treatment participation, including perceptions of the intervention, perceived need for treatment, relationships with staff, and experiences with medication. The guide will include questions on contextual barriers to successful participation such as economic, social, and psychological stressors, as well as facilitators such as social support and other resources.

Data Analysis. Data analysis will proceed in two steps. The first step entails the standard data analysis approach described above. In a second step, the analysis team will make structured comparisons across successful and unsuccessful patients, searching for patterns in the data that reveal core differences across groups and provide insight into why some patients are able to succeed with treatment and some are not. In Year 2, data from these comparative analyses will be summarized and presented to the Stakeholder team, with the goal of improving the capacity of intervention team to provide patient-centered care and better meet patient needs. Data collected in later years of the project will be used as part of a summative evaluation, to understand the successes and failures of the intervention with the goal of increasing scientific knowledge and improving the effectiveness of future interventions.

11.12.3 Quantitative Analysis

The proposed mDOT and PN interventions are guided by Fisher's IMB model [113-115]. The IMB model asserts that information, motivation, and behavioral skills are fundamental determinants of adherence [113]. The IMB model further specifies that personal and situational characteristics, such as poor psychologic health, substance use, unstable housing, or inadequate access to medical care, may moderate these relationships and impact adherence [113]. In extreme cases, strong negative effects on adherence are expected, and interventions aimed at improving information and motivation may not be effective without adjuvant support. Both interventions - mDOT and PN - focus on enhancing information, motivation, and behavioral skills, and provide adjuvant support to lessen negative impacts of moderating factors. While primarily operating on behavioral skills, the mDOT intervention also enhances both information and motivation (through support from nurses and outreach workers). The PN intervention addresses information (through education), motivation (through PN and peer support), and behavioral skills (PN and peer-led skill-building sessions).

IMB model mediator analysis. The analysis will examine if mDOT vs. PN adherence, for example, will be mediated by IMB components. Specifically, IMB model mediators of

adherence will be assessed at baseline, and during the intervention, and will use as the observed values of IMB mediators changes in those variables from the baseline to the intervention period. The indirect effects of IMB mediators will be tested by assessing changes in coefficients of the intervention effect (PN or mDOT) with and without IMB component(s) in mixed effects models. Confidence intervals of the mediated effects will be calculated by bootstrapping, and mediation assumed if confidence intervals do not include zero.

12 Data Handling/Record Keeping/Source Documents

The principal investigator at each site is responsible for ensuring the accuracy, completeness, legibility, and timeliness of the data reported.

Forms for use as source documents will be derived from the electronic case report forms (eCRFs) and provided by the SDCC to the sites to record and maintain data for each subject enrolled in the study. All source documents should be completed in a neat, legible manner to ensure accurate interpretation of data. Black or blue ink is required to ensure clarity of reproduced copies. When making a change or correction, the original entry should be crossed out with a single line, and the change should be initialed and dated. Do not erase, overwrite, or use correction fluid or tape on the original. Data entry, media/tools and data management platform are described in detail in a Data Management Plan.

Data reported in the eCRF should be consistent with the source documents or the discrepancies should be documented.

12.1 Source Documents and Access to Source Documents

Each participating site will maintain appropriate medical and research records for this trial, in compliance with ICH E6, Section 4.9 and regulatory and institutional requirements for the protection of confidentiality of subjects. Forms for use as source documents will be derived from the eCRFs and be provided by the Statistical and Data Coordinating Center (SDCC). Source documents will only be accessible by study staff and all research records will be kept in a locked filed cabinet in the research office of the PI.

These medical records are stored in locked rooms in each clinic, or in password protected computer files. The RA with assistance from the Co-I/PI will review the charts. Prior to starting the chart review process, research staff will complete online training in patient-oriented research, including confidentiality, and will receive further training in confidentiality and the chart review protocol from the PI.

12.2 Data Management Responsibilities

Data collection is the responsibility of the clinical trial staff at the site under the supervision of the site principal investigator. During the study, the investigator must maintain complete and accurate documentation for the study. All source documents

and laboratory reports must be reviewed by the clinical team and data entry staff, who will ensure that they are accurate and complete. Serious adverse events must be reviewed by the site principal investigator or designee.

The Biostatistics group at the UNM Division of Epidemiology, Biostatistics and Preventive Medicine will serve as the Statistical and Data Coordinating Center (SDCC) for this study, and will be responsible for data management, quality review, analysis, and reporting of the study data.

12.3 Data Capture Methods

Sources of data will include: blood and urine tests, participant interviews, medical charts, direct observation of staff and PNs, and electronic adherence monitors. Information from participant interviews will be either directly entered into an electronic data capture system, or will be recorded on paper, then entered. In-person research interview data will be recorded on paper or computer-based data collection instruments. All HCV VL load, HCV resistance assays, urine tests, and adherence data will be measured by electronic monitors.

12.4 Types of Data

This study will collect quantitative and qualitative information. Quantitative data will be collected from 1) subject interviews; 2) blood specimens for HCV viral load and resistance assays; 3) urine toxicology test at each research visit; 4) electronic monitors for assessing adherence; 5) clinic records for methadone or buprenorphine dose, clinical tests and medical history. Qualitative data will be collected from patients and staff interviews (qualitative aim).

12.5 Timing/Reports

- Each site will enter accrual and study data from source forms into the study database maintained by the SDCC within 7 days of collection.
- The UNM SDCC will provide weekly accrual, and enrollment reports by site and overall. Reports will include information on treatment initiation, study exiting and loss to follow up.
- The UNM SDCC will maintain a “Consort” log of trial progress.

12.6 Study Records Retention

The UNM SDCC will store and secure all quantitative data. The Research Informatics Core of the Montefiore Medical Center will store all qualitative data. A patient-level de-

identified copy of the final datasets will be available in electronic form for investigators willing to sign a data use agreement with provisions for protecting patients from any attempts to de-identify the data, as well as that any findings derived from the data would be made public within nine months of the end of the final funding year or by earlier request, to PCORI and other relevant parties. Documentation will accompany the final data sets that enables others in the research community to utilize the data for additional/secondary analysis. Data may be shared electronically or via file-transfer protocols and will be provided in a SAS or STATA datafile for quantitative data, and original transcriptions for qualitative data obtained through interviews and focus groups. Syntax files from SAS or STATA used for quantitative analyses will be archived and can also be made available.

The link between the subject and the research study will be destroyed 5 years after the end of the study.

13 Quality Assurance

There will be three levels of data quality assurance:

First, at each site there will be trained research staff (either the project director or research associate) who will be responsible for complete and accurate data collection and entry of source data into the UNM DCU. The designated research staff at each hub will undergo training in all aspects of the clinical protocol, with refresher training once per year.

Secondly, the UNM SDCC will have a central data quality coordinator who will: (1) provide training for site-based personnel; (2) perform periodic monitoring and audits of the data collected including source (clinical records and laboratory) and entered (site-based) to ensure consistent and accurate records.

Third, the UNM SDCC will have a data manager who will be responsible for receiving, reviewing and cleaning all of the study data. The data manager will be responsible for regular collation of all incoming data from study sites, maintenance of recruitment, enrollment and accrual records, generation of weekly accrual reports, and conducting basic analyses for reports and papers. S/he will ensure secure data storage of verified and documented data, audit trails for data changes, and ensure back-up systems are working.

PROCESS AND FIDELITY ASSESSMENT: All patient navigators and outreach workers will be trained by the New York City Department of Health and Mental Hygiene (NYC DOHMH), and NYC DOHMH will provide technical assistance to project directors and other staff during the study period. To assess fidelity, local Project Directors will observe local project staff to ensure that patient navigation protocols are appropriately delivered. Feedback will be provided with retraining and reassessment when indicated. In addition, Montefiore site visit protocols will include observation of local staff delivering patient navigation and DOT protocols.

14 Ethics/Protection of Human Subjects

14.1 Ethical Standard/Declaration of Helsinki

The investigator(s) will ensure that this study is conducted in full conformity with principles of the Belmont Report: Ethical Principles and Guidelines for the Protection of Human Subjects of Research of the National Commission for the Protection of Human Subjects of Biomedical and Behavioral Research (April 18, 1979) and codified in 45 CFR 46, 21 CFR 50 and 56, and ICH E6; 62 Federal Regulations 25691 (1997), if applicable. The investigator's Institution will hold a current Federal-wide Assurance (FWA) issued by the Office for Human Research Protections (OHRP) for federally funded research.

14.2 Institutional Review Board

Each participating institution will provide for the review and approval of the study protocol and the associated informed consent documents, by an appropriate ethics review committee or Institutional Review Board (IRB) listed on their Federal Wide Assurance. Any amendments to the protocol or informed consent materials must also be approved before they are placed into use unless change is for the safety of the subject. Only those IRB members who are independent of the investigators and the sponsor should provide an opinion on study related matters. Verification of IRB approval of the protocol and the written informed consent will be transmitted by the investigator or designee prior to the shipment of medication. No deviations from or changes to the protocol will be initiated without prior approval of an appropriate amendment unless change is for the safety of the subject.

14.3 Informed Consent Process

The written informed consent document will embody the elements of informed consent as described in the Declaration of Helsinki and will adhere to the ICH Harmonised Tripartite Guideline for Good Clinical Practice. Informed consent should be implemented before any protocol-specified procedures or interventions are carried out. Informed consent will be obtained in accordance with 21 CFR 50.25 and 45 CFR 46. Information should be presented both orally and in written form.

Prior to the administration of any study measures, research assistants will obtain consent for screening using an informed consent form (ICF), which describes the study, and reinforces the confidentiality of all survey information. Interested patients who are eligible for the study after an initial pre-screen will sign and date a written informed

consent document. The informed consent process will include discussion of the study purpose; study interventions, study procedures, research visit schedule and reimbursement; risks, benefits, and alternatives to study participation; and confidentiality of research records. The following general principles will be emphasized:

- Participation is voluntary
- Participants can discontinue participation at any time
- Emergency contact information will be provided
- They are required to consent for trial participation
- We will require authorization for study staff to use protected health information, including laboratory test results from OTP and CHC records, and HCV provider
- In the event of psychiatric distress, study staff will require authorization to disclose health information to medical staff
- Treatment related visits will occur through usual systems of delivery of care, and thus may be billed to insurance as any other medical visit.
- There is the possibility that the participant will not receive HCV treatment
- There is also possibility that additional medications (ribavirin) may be recommended/added during treatment, which will not be provided by the study
- There is the potential for direct benefit if the participant receives HCV treatment, as there is a 95% chance that they will be cured based on current clinical trial evidence
- The subject is free to ask questions at any time to allow him or her to understand the purpose of the study and the procedures involved
- Refusal to participate involves no penalty or loss of medical benefits

The aims of the study and all tests to be carried out will be explained. The subject will be given the opportunity to ask about details of the trial, and will then have time to consider whether or not to participate. If they do decide to participate, they will sign and date two copies of the ICF, one for them to take away and keep, and one to be kept by the investigator. These forms will also be signed and dated by the study staff person obtaining the informed consent.

Study staff must inform subjects that the trial involves research, and explain the purpose of the trial, those aspects of the trial that are experimental, any expected benefits, all possible risks (including a statement that if the participant in the study receives HCV

treatment, the particular treatment or procedure may involve risks to the subject or to the embryo or fetus, if the subject is or may become pregnant, that are currently unforeseeable), the expected duration of the subject's participation in the trial, the procedures of the research study, including all invasive procedures, and the probability for random assignment to treatment groups. Subjects will be informed that they will be notified in a timely manner if information becomes available that may be relevant to their willingness to continue participation in the trial. They must also be informed of alternative procedures that may be available, and the important potential benefits and risks of these available alternative procedures. Subjects must receive an explanation as to whether any compensation and any medical treatments are available if injury occurs, and, if so, what they consist of, or where further information may be obtained. Subjects must be informed of the anticipated financial expenses, if any, to the subject for participating in the trial, as well as any anticipated prorated payments, if any, to the subject for participating in the trial. They must be informed of whom to contact (e.g., the investigator) for answers to any questions relating to the research project. Information will also include the foreseeable circumstances and/or reasons under which the subject's participation in the trial may be terminated. The subjects must be informed that participation is voluntary and that they are free to withdraw from the study for any reason at any time without penalty or loss of benefits to which the subject is otherwise entitled.

Neither the investigator, nor the trial staff, should coerce or unduly influence a subject to participate or continue to participate in the trial. The extent of the confidentiality of the subjects' records must be defined, and subjects must be informed that applicable data protection legislation will be followed. Subjects must be informed that the auditors(s), IRB, and regulatory authority(ies) will be granted direct access to the subject's original medical records for verification of clinical trial procedures and/or data without violating the confidentiality of the subject, to the extent permitted by the applicable laws and regulations, and that, by signing a written ICF, the subject is authorizing such access. Subjects must be informed that records identifying the subject will be kept confidential, and, to the extent permitted by the applicable laws and/or regulations, will not be made publicly available and, if the results of the trial are published, the subject's identity will remain confidential.

Informed consent forms must be in a language fully comprehensible to the prospective subjects. Informed consent shall be documented by the use of a written ICF approved by the IRB and signed and dated by the subject and the person who conducted the informed consent discussion. The signature confirms that the consent is based on information that has been provided and all questions have been answered to the prospective subject's satisfaction. Each subject's signed ICF must be kept on file by the

investigator for possible inspection by Regulatory Authorities and/or the sponsor and Regulatory Compliance persons. The subject should receive a copy of the signed and dated written ICF and any other written information provided to the subjects, and should receive copies of any signed and dated ICF updates and any amendments to the written information provided to subjects.

14.4 Subject Confidentiality

Drug abuse and HCV infection require special sensitivity to issues of confidentiality. Patient confidentiality will be carefully protected. Study records will be kept in locked files and/or within limited access, code-protected computer files, available only to the investigators and study personnel. Patient identifiers will be removed and only initials and code numbers will be present on study records and documents.

Protection of subject identity. Subjects will not be identified by name on any written or verbal reports. They will only be identified by a study ID number. Subjects' names and study ID numbers will be kept in a password protected file in the research office of the Principal Investigator. Access will only be allowed to the senior project staff. The link between the subject and the research study will be destroyed 5 years after the end of the study. All research records will be kept in a secure area and locked in a file cabinet in the research office of the PI.

Protection of confidentiality

To ensure that confidentiality is maintained, the following procedures will be instituted:

- Medical staff will not have access to trial survey data, except under specific circumstances. Specifically, report of active suicidal ideation will trigger immediate clinical evaluation by an on-site physician, physician assistant, or psychiatrist, based on the psychiatric distress protocol. Consents will be obtained from participants for disclosure of research information under these circumstances prior to their enrollment in the proposed trial.
- The Research Assistant will complete the Collaborative Institutional Training Initiative (CITI) computer-based training program, which includes a specific module on issues of privacy and confidentiality.
- A system will be used that prevents linking sensitive material to participants' personal identifiers. All documents with participant identifiers, including consent forms, medical records and contact information, will be filed together. All documents that do not include identifying information or signatures will use participants' study IDs rather than names and will be filed

together. All forms will contain either participants' names or their study IDs, but not both. Data collection forms will include no identifiers other than a study ID code. There will only be one electronic document that links participants' names to their study IDs, which will be password protected.

- Study records will be stored on a password protected computer database and/or in locked file cabinets.
- A federal Certificate of Confidentiality will be obtained by each site to protect participants' sensitive information.
- Phone messages left for participants to schedule research visits will not include personal identifying information or mention HCV or OAT
- Publication or presentation of study results will not identify subjects by name.

15 Protocol Conduct

The protocol will be conducted in compliance with federal regulations and the principles of Good Clinical Practice (GCP), including the following processes:

- Protocol registration, activation, and implementation;
- Informed consent, screening, and enrollment;
- Clinical and safety assessments;
- Safety monitoring and reporting;
- Data collection and documentation;
- Study follow-up and close-out;
- Quality management;
- Protocol monitoring and compliance;
- Risk reduction counseling; and
- Specimen collection, processing, and analysis.

15.1 Record Confidentiality

The investigators will maintain appropriate medical and research records for this trial, in compliance with ICH E6 GCP and regulatory and institutional requirements for the protection of confidentiality of subjects. 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 principal investigators from each site will obtain a Certificate of Confidentiality from NIH to further protect subjects' privacy.

15.2 Data Collection, Handling, Source Documents

Clinical research data will be collected as described in detail in Section 12.

Standard GCP will be followed to ensure accurate, reliable, and consistent data collection. Each participating site will maintain appropriate medical and research records for this trial, in compliance with ICH, GCP, regulatory, and institutional requirements for the protection of confidentiality of subjects.

15.3 Protocol Deviations

A protocol deviation is any noncompliance with the clinical trial protocol, Good Clinical Practice (GCP), or Manual of Procedures (MOP) requirements. The noncompliance may be on the part of the subject, 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 Good Clinical Practice:

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 5.20.2d

It is the responsibility of the site to use continuous vigilance to identify and report deviations per site IRB guidelines.

All deviations from the protocol must be addressed in study source documents. A completed copy of the Protocol Deviation (PD) Form must be maintained in the Regulatory File. Protocol deviations must be submitted to the local IRB/IEC per their guidelines. The site PI/study staff is responsible for knowing and adhering to their IRB requirements.

15.4 Recruitment and Retention of Study Subjects

The research staff will recruit potential participants from OTPs and community health centers and by referral from other community-based organizations. Recruitment will be active (medical providers and community outreach workers will inform HCV-infected patients about the study) and passive (clinic counseling staff, word of mouth, and fliers in clinic waiting areas). For active recruitment medical providers and community outreach workers will inform HCV-infected patients about the study and assist with referral, and for passive recruitment subjects will self-refer. Self-referred subjects will meet with their provider to determine whether starting HCV treatment is appropriate.

Potential study participants will demographically and clinically reflect those most impacted by chronic hepatitis C and will be identified in a number of ways: community outreach including posters and written materials at recruitment sites and at other key locations in the community; by self-referral; by referral from local patient stakeholders such needle exchange programs; by referral from staff at OAT treatment centers, participating clinics or other medical or mental health caregivers; and by direct approach from a site Research Assistant / Patient Navigator (RA/PN).

Retention will be enhanced using multiple methods including but not restricted to: 1) conducting interviews with participants at research visits; 2) reminders using text messaging (SMS), written reminders and phone calls; and 3) reimbursement for research assessments.

To assist retention, at enrollment and subsequent visits, the following information will be collected: 1) participants' address, phone number, and social security number (if available and required by local sites); 2) contact information of family or friends; 3) contact information of participants' community-based organizations; 4) contact information of case managers; 5) locations where participants "hang out"; and 6) participants' social media presence and willingness to be contacted by person-to-person messaging on this medium.

15.5 Study Subject Reimbursement

Participants will receive $20 for each of 17 research visits ($20/visit, 17 research visits, $340 total) and an additional $5 for returning one-week electronic blister packs or $10 for two-week (12 weeks, $5/week, $60 total) for a total of $400 per participant. This level of reimbursement is standard for clinical research conducted in our setting, and is not considered undue inducement for research participation.

16 Publication Policy

The project is designed based on the dissemination priorities and needs for the sites, patients and stakeholders involved in its planning and implementation. During the project period, patient partners and other stakeholders will have an active role in developing appropriate material and communicating and disseminating information about the project and its activities and reporting to their various constituencies about progress made towards meeting the goals and objectives of the study. Project staff will work with each to ensure that customized material is produced to ensure that communication is understandable and usable by each constituency. Patient partners will be involved in outreach to the local community through both the participating sites in each city and local media as well as through other community connections to PWID in neighboring cities to make other patients aware of study opportunities to receive treatment for HCV. As progress is made in generating findings, patient and stakeholder partners will be invited to author or co-author articles and opinion pieces describing the study findings for publication in local press and other media outlets. Other advocacy and public health stakeholders will facilitate disseminating study findings based on the communities and organizations they represent. This will be accomplished by sharing study findings to their membership and to their funders through newsletters, website postings, presentations at meetings and conferences, as well as through more formal professional publications. The study has a publication policy and procedure document.

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Appendix One: Patient Navigator Tasks

Patients who are HCV Antibody-positive (Linkage to Care)

1) Navigate patients to on-site viral load testing
2) Follow-up with all patients for post-test counseling
3) Attempt to contact patients lost to follow-up
4) Provide basic HCV-related education: natural history, prevention of transmission, evaluation, and treatment

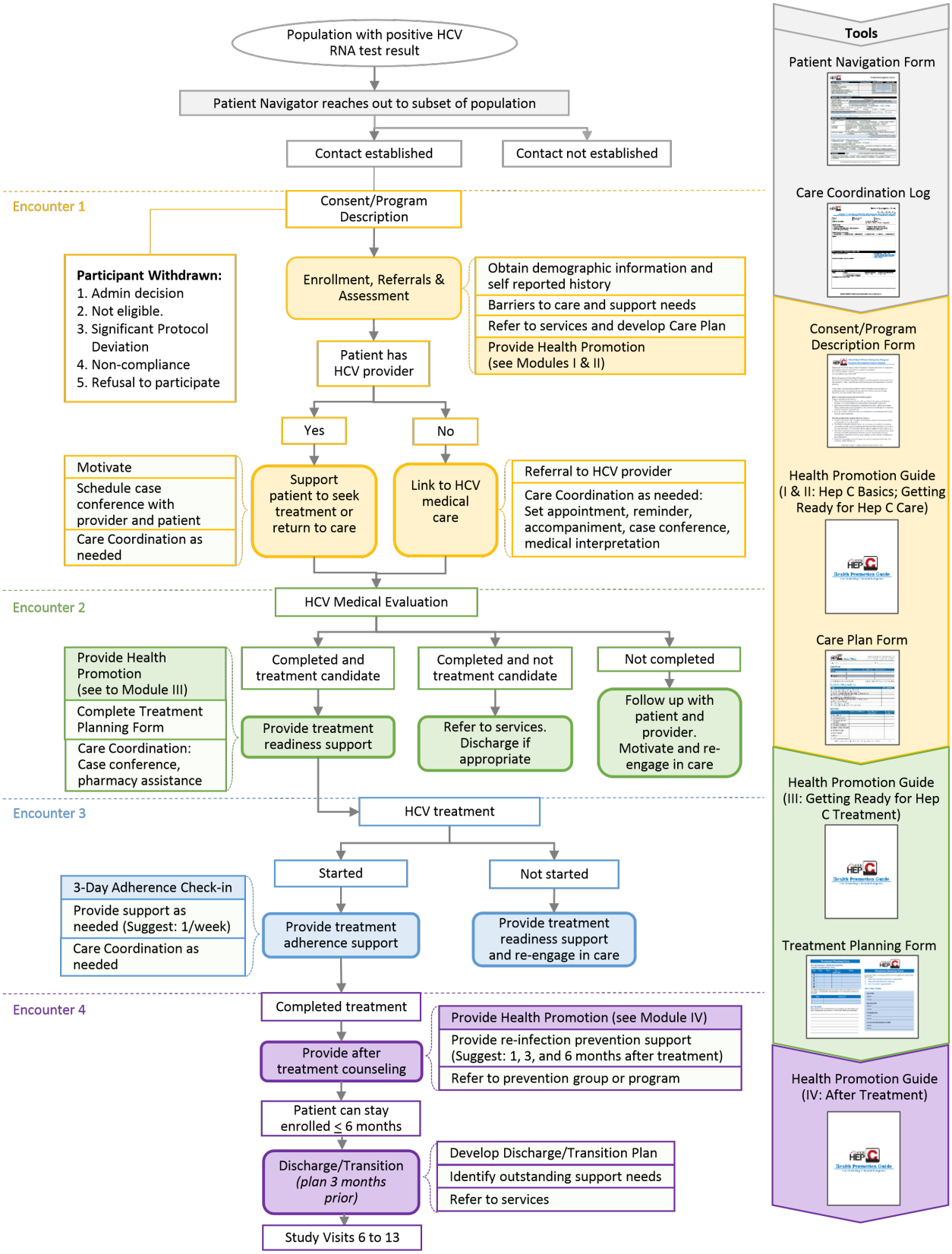
Patients who have chronic hepatitis C (Care Coordination: Case Management, Education, Outreach, Collaboration, Logistical Support, and Other)

1) Schedule patients for first HCV evaluation with HCV specialist (within one week)
2) Schedule patients for follow-up evaluation and treatment meetings
3) Work closely with HCV primary care champion to ensure patients are engaged with HCV care (e.g. weekly HCV clinic and preparation of charts for weekly visits)
4) Promote adherence to all HCV-related appointments
5) Schedule patients for all off-site liver clinic appointments as appropriate (e.g. decompensated cirrhosis; other liver disease; transplant evaluation)
6) Remind patients one day prior to appointment
7) Check to see if patients adhered to appointment
8) Check in with patients after seeing HCV primary care champion:
    a) see how patient is doing (build rapport)
    b) ask patient to clarify next steps
    c) schedule follow-up appointments in real-time (e.g. ultrasound)
    d) elicit fears and concerns
    e) answer questions
9) Identify barriers and facilitators to care and provide motivational interviewing to assist patients in overcoming barriers.
10) Motivate patients to continue to move through the HCV cascade of care
11) Work with any insurance issues and refer to Medicaid office or social worker as appropriate
12) Prior authorizations for all HCV medications, adjuvant medications (e.g. zofran for nausea), and other related-procedures (e.g. MRI for liver imaging)
13) Work with Medicaid managed care plans and mail order pharmacies for ordering and delivering HCV- related medications
14) Work with pharmacist: dispensing medications, checking in regarding patient adherence to medications; counseling with patients; and drug-drug interactions
15) Provide adherence counseling and assist with side effect management for patients on treatment
16) Pre-treatment readiness assessments to identify potential barriers to treatment
17) Make all HCV-related appointments and ensure follow-up:

a) Ultrasound and other imaging
b) Liver biopsy if necessary
c) Other off-site specialists appointments (e.g.dermatology)
d) Upper endoscopy to screen for varices
e) Transplant evaluation

18) Provide HCV education (evaluation, treatment, adherence, and side effect management) including formal brief educational intervention with power-point slides
19) Conduct rapid HCV testing at outreach sites and navigate new HCV antibody + patients to clinic for follow-up viral load testing, primary care, and HCV-related care.
20) Organize and administer any program incentives (e.g. metro cards)
21) Collect all PN-related data and input in timely manner within databases
22) Maintain all PN-related databases
23) Provide weekly updates to HCV team meeting for problem solving and QI
24) Attend local HERO team meetings
25) Report to Project Director
26) Attend national HERO PN team meetings via conference calls
27) Work at multiple clinics in various locations throughout the week
28) Work closely with community to develop and maintain HCV-related networks (e.g. syringe exchange program and CBOs)
29) Work with HCV peers
30) Obtain outside medical records as needed
31) Provide administrate support to the Project Inspire team
32) Send letter and/or telegram as needed for patients lost to follow-up
33) Work with Montefiore/NYDOH teams for exchange of data
34) Other duties as needed

Appendix 2: Check Hep C Patient Navigation Program – Workflow for Project HERO



Appendix Three: Study Visit Table

Table 3: Study Visit Table

		Pre-Treatment			Treatment Visits			Post-Treatment Visits												
Research Visit Activities	**Time (Minutes)**	**Pre-Screening**	**Enrollment**	**Baseline**	**Week 4, ± 1wk**	**Week 8, ± 1 wk**	**Week 12, ± 1 wk**	**Week 24, ± 2 wks**	**Week 36, ± 2 wks**	**Week 48, ± 2 wks**	**Week 60, ± 2 wks**	**Week 72, ± 2 wks**	**Week 84± 2 wks**	**Week 96, ± 2 wks**	**Week 108, ± 2 wks**	**Week 120, ± 2 wks**	**Week 132, ± 2 wks**	**Week 144, ± 2 wks**	**Week 156, ± 2 wks**	**Week 168± 2 wks**
Visit Number			0	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17
TIME (in min)			40	70	37	22	90	70	20	65	15	45	15	25	15	90	15	25	15	90
Release of Information		X	X																	
Informed Consent	30		X																	
Randomization			X																	
Instruments																				
Socio-Demographic Survey	10		X																	
Short Socio-Demographic Survey	5							X				X				X				X
Behavioral Risk Assessment	10			X	X		X	X	X	X	X	X	X	X	X	X	X	X	X	X
Depression (PHQ-9)	5			X			X	X		X						X				X
Anxiety (GAD-7)	4			X			X	X		X						X				X
AUDIT-C	3			X			X	X		X		X		X		X		X		X
Modified ASI – baseline	10			X																
Modified ASI – follow-up	5				X	X	X	X				X				X				X
Substance Use Treatment	3			X	X	X	X	X		X						X				X
EQ-5D	8			X			X	X		X						X				X
Visual Analogue Scale (Adherence)	2				X	X	X													
Medical Outcomes Social Support Scale	5			X			X			X						X				X

		Pre-Treatment			Treatment Visits			Post-Treatment Visits												
Research Visit Activities	**Time (Minutes)**	**Pre-Screening**	**Enrollment**	**Baseline**	**Week 4, ± 1wk**	**Week 8, ± 1 wk**	**Week 12, ± 1 wk**	**Week 24, ± 2 wks**	**Week 36, ± 2 wks**	**Week 48, ± 2 wks**	**Week 60, ± 2 wks**	**Week 72, ± 2 wks**	**Week 84± 2 wks**	**Week 96, ± 2 wks**	**Week 108, ± 2 wks**	**Week 120, ± 2 wks**	**Week 132, ± 2 wks**	**Week 144, ± 2 wks**	**Week 156, ± 2 wks**	**Week 168± 2 wks**
Brief Revised Working Alliance (PN arm only)	5						X													
Stigma Scale	5			X																
Shame Scale	2			X					X							X				X
Health Efficacy Scale	3			X			X													

		Pre-Treatment			Treatment Visits			Post-Treatment Visits												
Research Visit Activities	**Time (Minutes)**	**Pre-Screening**	**Enrollment**	**Baseline**	**Week 4, ± 1wk**	**Week 8, ± 1 wk**	**Week 12, ± 1 wk**	**Week 24, ± 2 wks**	**Week 36, ± 2 wks**	**Week 48, ± 2 wks**	**Week 60, ± 2 wks**	**Week 72, ± 2 wks**	**Week 84± 2 wks**	**Week 96, ± 2 wks**	**Week 108, ± 2 wks**	**Week 120, ± 2 wks**	**Week 132, ± 2 wks**	**Week 144, ± 2 wks**	**Week 156, ± 2 wks**	**Week 168± 2 wks**
Labs																				
HCV Antibody		MC		MC																
HCV viremia		MC		MC	MC	MC	MC	MC	X	X	X	X	X	X	X	X	X	X	X	X
HCV Genotype/subtype				MC	MC															
HIV Test				MC																
HIV Viral Load*				MC	MC	MC	MC													
HIV CD4*				MC	MC	MC	MC													
AST/ALT/Platelets/		MC		MC	MC	MC	MC	MC												
FIB-4 Calculation																				
Total Bilirubin				MC																
Albumin				MC																
Prothrombin time				MC																
FibroSure/Fibroscan/Liver biopsy				MC	MC**	MC**														
Imaging study**		MC		MC																
Child-Pugh Score (exclude B,C)				MC	MC	MC	MC													
Pregnancy test*				MC																
Archiving sample				X				X	X	X	X	X	X	X	X	X	X	X	X	X
HCV GenoSure NS5A/NS5B Assay*								X												
HBV panel				MC																
HAV Status				MC																
Urine toxicology POC assay				X	X	X	X	X		X		X		X		X		X		X

MC = Medical Chart * If applicable **If available

Appendix Four: Implementation Study

Implementation Evaluation--Protocol

We are proposing to add an implementation evaluation to the approved study. We propose to examine 1) implementation 'outcomes'—how well the program was implemented across the eight study sites; and 2) causal factors affecting implementation, i.e. barriers and facilitators.

Implementation outcome data that will be collected in this evaluation include: data on program acceptability, feasibility, dose, and fidelity. Acceptability to patients will be assessed using a single patient satisfaction question administered at the F12 interview, and through a qualitative interview with a convenience sample of approximately 40 (the number of interviews depends on data saturation, and may be as many as 60) patients. Feasibility will be assessed through examination of recruitment and retention records (assessed through study databases); and by an examination of the execution of work plans for each of the 8 study sites. Intervention 'dose' and fidelity will be assessed by examining the degree to which treatment plans are adhered to (collected through administrative data); and by visit logs created by patient navigators indicating the degree to which the patient received the planned elements of navigation.

Barriers and facilitators to implementation will be assessed through interviews and questionnaires collected with key stakeholders in the study, including site leaders, site staff, and patients. We will use the following methods.

1. Site leader interviews. We will conduct between 2 and 5 telephone interviews with site leaders at each site over the next 5 years. Site PIs will assist the team in identifying appropriate clinical leaders. Telephone interviews are expected to last approximately 15-30 minutes and will be recorded and transcribed. Questions will focus on relevant topics such as clinical site research experience, current on site HepC treatment, DOT, PN, local resources, larger societal influences, perceptions of study burden and feasibility, etc. Site leaders will be approached through their local PIs and interviews will be conducted by the Bronx Qualitative Team members. In an initial phone call we will explain the purpose of the study. If participants are willing to participate they will engage in an informed oral consent by telephone. Specifics of these interviews may be found in Table 1.

2. **Grumbach Workplace Environment Questionnaire.** This brief questionnaire addresses the workplace environment in primary care. It was designed to measure staff perceptions of teamwork and adaptability to take on practice improvements and innovations. The questionnaire will also include a few questions about attitudes towards HepC tx for active PWID. The questionnaire will be administered to relevant staff of the clinical sites—including nursing, physicians, support staff, front desk, etc. Participants will be approached at the meeting or in their workplaces and requested to fill out these

forms anonymously. The Project Director will collect the questionnaires during site visits. A waiver of consent is requested for this questionnaire.

3. Working Alliance Questionnaire. This questionnaire will be administered at the F12 follow up research visit to all patients in the PN arm of the study. This questionnaire assesses the quality of the **relationship between the patient and the front line treatment provider.** This questionnaire will be included in the interview packet. No separate consent process will be needed.

4. Staff Interviews. These 10-30 minute qualitative interviews will focus on staff experiences with the HERO project, levels of engagement and enthusiasm, and perceptions of structural/institutional as well as patient level barriers to program implementation. Relevant staff members will be identified through discussions with Site Principal Investigators or local Clinical Site leaders. We will conduct these interviews with identified staff (number is currently unknown, depends on the site, but may be up to 6 staff members per site, or 48 overall). In an initial phone call, we will explain the purpose of the study. If participants are willing to participate they will engage in an informed oral consent by telephone. These interviews will be conducted at various time points with different groups of staff. Specifics may be found in the tables.

5. Patient Satisfaction, Treatment Experiences and Barriers Interviews. These 30 minute qualitative interviews will examine patient experiences, characteristics, and perceptions associated with varied treatment outcomes. They will be administered to patients in various groups chosen for their contrast on key outcomes: patients who successfully adhere to treatment (n<=10) vs. those who do not (n<=10); patients who complete treatment (n<=10) vs. those who do not (n<=10); and patients who remain virus free (n<=10) vs. those who do not (n<=10) for a total of n<=60. The total number depends on data saturation achieved through the analysis: we anticipate that at least 8 patients in each group or approximately 1 per site will be recruited for a total of at least 6 per site. A $15 incentive will be offered to participate in the phone interviews. If participants are willing to participate they will engage in an informed oral consent by telephone.

TABLE I: DATA COLLECTION PLAN FOR BARRIERS/FACILITATORS STUDY			
Pre-Implementation			
Purpose	Data Collection Instrument	Respondent's	Responsible
To understand relevant experiences and characteristics at HERO clinical sites that may impact project roll out	**Site Leader Interviews.** 15-30 minute telephone interviews. Questions will focus on relevant topics such as site research experience, current on site HepC treatment, DOT, PN, local resources, perceptions of study burden and feasibility, etc...	Clinical site medical directors or other stakeholders determined through discussion with PIs	Bronx Implementation Team
To understand characteristics of the work environment that may impact Implementation from the point of view of clinical and admin staff	**Grumbach Workplace Environment Questionnaire.** This brief questionnaire addresses the workplace environment in primary care. It was designed to measure staff perceptions of teamwork and adaptability to take on practice improvements and innovations. The questionnaire will also include a few questions about attitudes towards HepC tx for active PWID.	Relevant clinical and administrative staff of the sites—including nursing, physicians, support staff, front desk, etc. To be administered during staff meeting or in the clinic/health center	Site RAs
Early Implementation Period (3-6 months into project period)			
Purpose	Data Collection Instrument	Respondent's	Responsible
To understand perceptions of HERO among clinic site staff	**Brief staff interviews.** Open ended questions focusing on perceived relevance, burden, feasibility, and complexity of HERO will be conducted with relevant staff identified through discussions with PI or site leaders.	Relevant providers and admin staff	Bronx Project Coordinator @ Site Visit
12 Week Follow Up Patient Interviews			
Purpose	Data Collection Instrument	Respondent's	Responsible
To understand the quality of HERO staff/patient interactions	**Working Alliance Questionnaire (Administered at F12 Interview)**	All Patients in the PN Arm	Site F12 Inter-viewers

Post Implementation –Timeframe TBD			
Purpose	Data Collection Instrument	Respondents	Responsible
To understand site leaders perceptions of the program and barriers/facilitators	**Site Leader Interviews.** A 20 minute telephone interview. Questions will focus on site leader's perceptions of the project—barriers, facilitators, benefits, burden, surprises. The interview will also examine structural/environmental factors such as local politics, insurance regulatory environment, stigma, and similar issues potentially affecting sustainability and replication--	Relevant site leaders as described above	Bronx Implementation Team
To understand frontline worker experiences, characteristics, and perceptions of implementation barriers and facilitators to DOT and PN Interventions	**Frontline Worker Interviews.** This 30 minute qualitative interview will focus on frontline worker experiences with the HERO project, level of engagement and enthusiasm, and perceptions of structural/institutional as well as **patient level barriers** to program implementation.	Frontline workers as many as feasible	Bronx Implementation Team
To understand patient level barriers and facilitators to successful treatment from patient's viewpoint and understand experiences with treatment	**Patient Treatment Experiences and Barriers to treatment interviews.*** This 30 minute qualitative interview will examine patient experiences, characteristics, and perceptions associated with varied treatment outcomes	Purposive sampling from various outcome groups	Bronx Implementation Team

TABLE II: DATA COLLECTION PLAN FOR ASSESSING IMPLEMENTATION OUTCOMES				
Variables	Data Collection & Source	Responsible	Method of Date Analysis	Responsible:
Acceptability of Intervention				
Pt. Satisfaction w TX	1 TX Satisfaction Question @ F12	Site RA	Quantitative	Site RA
Positive/Negative Experiences with TX	Brief Treatment Experiences Interview @ various time points	Site RA	Structured, 'Quantitated' Thematic Analysis w/ Qual Data Analysis Program	Bronx Implementation Team
Feasibility of Intervention				
Recruitment Milestones	Research Database	Site staff	Quantitative	Local/New Mexico
Retention in Intervention	Research Database	Site Staff	Quantitative	Local/New Mexico
Execution of Work Plans	Work Plans for Each Arm with Milestones and Dates Achieved, [i]	Bronx Project Director	Qualitative	Bronx Implementation Team
Intervention Dose				
Directly Observed TX				
# Observed Doses/ #Planned Observed Doses	Nurse calendar/log or patient log--TBD	Frontline Staff	Quantitative	Local/NM
Patient Navigation				
2 in person meetings/ 3 Follow up calls (TBD)	Case Notes or Other Records—TBD with DOH Team	Frontline staff	Qualitative assessment & quant tabulation	Site Staff Supervisor
Fidelity of PN Intervention To Be Discussed with DOH PN Team				
Care Plan Completed	Navigation Care Plan	Frontline staff	Qualitative assessment, tabulation	PN Records
Initial Medical Evaluation Completed	Case Notes	Frontline staff	Qualitative assessment, tabulation	PN Records
Referrals Made	Case Notes	Frontline staff	Qualitative assessment, tabulation	PN Records
Referrals Followed up	Case Notes	Frontline staff	Qualitative assessment, tabulation	PN Records
Education Sessions #1 & 2 Provided	Attendance records/group, Case notes/ind. # minutes	Frontline staff	Tabulation	PN Records

Consent	Data Collection Instrument s
Site leader oral consent	• **Site Leader Interview** • **Site Leader guide post implementation**
Staff Oral Consent	• **Brief Staff interview** • **Frontline Staff Interview Post Implementation**
Patient Oral Consent	• **Brief Patient Experience Interview** • **Patient Treatment Experiences and Barriers/Facilitators to Treatment**
Request waiver of consent—anonymous survey on worksite culture	• **Grumbach Questionnaire**
Regular study consent form—to be embedded in 12-Week Follow up Interview	• **Working Alliance Questionnaire**