Project Title:

Hepatitis C Treatment in PWIDs: MAT or Syringe Exchange Assisted-therapy vs Standard of Care

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Protocol 1. Protocol Title

Hepatitis C Treatment in PWIDs: MAT or Syringe Exchange Assisted-therapy vs Standard of Care

*IRB **16357***

2. Objectives/Hypothesis

Hypothesis: Treatment adherence and hepatitis C (HCV) infection cure rates using a simple 1-pill a day regimen of a direct anti-viral agent (DAA) in two unique care delivery models for marginalized persons with HCV infection, Outside In needle exchange program serving people who inject drugs (PWID) and Old Town Clinic, an integrated multi-disciplinary primary care clinic serving homeless and low income adults, will be similar to HCV patients treated in a traditional Hepatology Clinic at an Academic Health Center

Purpose: Determine if two unique safety net clinics (intervention group) with comprehensive behavioral health, pharmacy and medical services will improve HCV therapy adherence and reduce re-infection rates such that overall cure rates will be maintained and be similar to cure rates seen over the same time period in a traditional hepatology clinic setting (comparison group). The expectation is that these safety net clinics with comprehensive healthcare services should normalize the chaotic lifestyles of the patients that typically utilize safety net clinics.

Goal: If this study can demonstrate that such well-established comprehensive multidisciplinary safety net clinics that see an extremely marginalized population that are typically excluded from access to HCV therapies can achieve similar HCV treatment responses as seen in traditional clinics, the use of such sites as HCV treatment centers can be utilized on a national scale.

AIMS:

1. Identify clients/subjects in each care setting with genotype 1 or 4 HCV infection ≥18 years of age that wish to be treated.
    a. Outside In Injection Drug Users Health Services (n=25)
    b. Old Town Clinic (n=25)
    c. Retrospective cohort of subjects at Oregon Health & Science University Hepatology Clinic (n=50)
2. Prior to treatment each client/subject is administered a questionnaire assessing motivation, readiness for treatment
3. Assess adherence to treatment regimen, laboratory testing, discontinuation rates, cure rates, and reinfection rates 1 year post treatment
4. Compare results across the three care delivery sites and identify any patient-related variables that impact treatment success

3. Background

Since the introduction of the first DAAs to treat HCV about 2 years ago, there are compelling reasons for expanding access to treatment for all HCV patients including their safety and cost-effectiveness.[1] However, certain HCV populations such as the homeless and people who inject drugs (PWID) have a high prevalence of chronic HCV infection. At the same time these populations have significant barriers to accessing care and have low rates of treatment initiation for their HCV infection. The impact of highly potent and well-tolerated interferon-free HCV treatment regimens will remain negligible as long as access to therapy cannot be expanded to the most affected risk groups.

One strategy that addresses several barriers is co-localization or integrated care of HCV screening, evaluation, and treatment with other medical or social services. Co-localization has already been applied to settings with a high prevalence of HCV infection (e.g., correctional facilities and programs providing needle exchange, substance abuse treatment, and methadone maintenance) but is not uniformly available.

One of the major obstacles to HCV care in the homeless and PWID is the lack of treatment settings that are suitably adapted for the needs of this vulnerable population. Nevertheless, HCV treatment has been delivered successfully to PWID through various multidisciplinary models such as community-based clinics, substance abuse treatment clinics, and specialized hospital-based clinics. Models may be integrated in primary care--all under one roof in either addiction care units or general practitioner-based models--or can occur in secondary or tertiary care settings. Additional innovative models include directly observed therapy and peer-based models.[2,3,4]

This current study uses a mixed care model approach where two unique safety net sites, one serving the homeless and the low income and the other, active injection drug users who utilize a needle exchange program, working in concert with a traditional gastroenterology/hepatology clinic to identify and treat HCV patients within their own care environment. A unique feature of this study is maintaining a real world setting for HCV treatment to occur. Allowing therapy to be given in an environment that is familiar and supportive should foster adherence and high rates of treatment success.

The results of this study will give insight into the feasibility of using safety net medical sites such as needle exchange programs and community health centers serving low income or homeless populations to safely and effectively treat this vulnerable population that is disproportionately affected by HCV infection. Furthermore, feedback from clients/patients using validated questionnaires could identify modifiable barriers to treatment success. Findings from this study could help expand the HCV treatment capacity beyond subspecialty practice and even the traditional primary care clinic.

4. Study Design

Study Objectives

Primary Objective: Determine if the clinical effectiveness of Zepatier in treating patients with HCV infection and mild fibrosis in two safety net sites, which offer comprehensives services to normalize the chaotic lifestyles of people who inject drugs and the homeless, is similar to what is expected in a tertiary hepatology clinic that cares for a more traditional patient population.

Secondary Objective: Identify client/patient factors that impact HCV treatment success in this population

Study Endpoints

Primary Endpoint

- Sustained virologic response rates measured at 12 weeks post treatment (SVR12)-Intention to Treat analysis (taking into account treatment discontinuation and failure rates)
- Persistently HCV infection free after 48 weeks of treatment cessation (SVR48)

Secondary Endpoints

- Adherence determined by client/subject self-reported medication adherence measured by percentage of pills taken on a monthly basis, as well as compliance with laboratory testing

- Treatment discontinuation rates including loss to follow up
- Percent of genotype 1a patients with baseline NS5A resistance

Relapse with substance use disorder in Old Town Clinic setting

Exploratory analysis of potential client/subject factors impacting readiness for treatment, non-adherence, or reinfection based on questionnaires administered at baseline and at 48 weeks post treatment

Study Design

This will be a prospective study at the two safety net clinic sites where 25 non-cirrhotic subjects at each site will receive HCV treatment with Zepatier. Patients will be followed by a care team comprised of a medical provider and pharmacist at each care site within their own medical home environment. Subjects will be monitored for treatment and lab adherence. Overall SVR 12 will be assessed for this study group. This SVR12 rate will be compared to the SVR12 rate of a retrospective cohort of 50 consecutive non-cirrhotic HCV patients treated in the Hepatology Clinic at Oregon Health and Science (OHSU) starting in 2015. A prospective cohort will not be necessary at OHSU, since SVR12 rates have been consistently within the range of what has been reported in the literature.

Study Definitions

Treatment failure -

- Primary treatment failure: detectable HCV RNA at week 12 post-treatment.
- Secondary treatment failure: despite achieving SVR12, detectable HCV RNA at 48-week follow-up posttreatment. This would suggest re-infection, if there is evidence of re-exposure to virus. In addition, repeat genotyping will be performed in order to determine if the genotype has changed from baseline. If so, this would also suggest re-infection.

Treatment discontinuation- therapy interrupted by either the subject due to compliance issues/side effects or by medical provider due to safety issues.

Reinfection- achieved SVR12, but at 48 weeks after completing HCV therapy HCV RNA is detected. If there is evidence of re-exposure to HCV infection and/or repeat genotyping demonstrates a different genotype from baseline genotype prior to starting HCV therapy.

Treatment Regimen Compliance -

- Medication Compliance- percentage of pills taken during 12-week therapy. Pill count is assessed at every clinic visit.
- Laboratory Compliance- percentage of completed scheduled lab draws
- Clinic Visit Compliance- percentage of attended scheduled clinic visits

5. Study Population

a. Number of Subjects

A total of 50 *retrospective* subjects will be enrolled at OHSU. Two separate prospective cohorts of 25 patients each will be enrolled at Old Town Clinic and Outside In, prospectively.

b. Inclusion and Exclusion Criteria

Prospective Study Cohort

Consecutive clients/patients with documented chronic hepatitis infection (detectable HCV RNA) seen at one of the study sites that are interested in HCV treatment and fulfill inclusion/exclusion criteria will be enrolled. Each site will determine readiness for treatment. Final approval for treatment initiation and ongoing monitoring during treatment will be under the supervision of the medical provider panel led by Dr. Zaman.

Retrospective Study Cohort

The Electronic Medical Record of the OHSU hepatology clinic will be reviewed and patients treated for hepatitis C with Zepatier selected in a retrospective, sequential fashion, starting at the time of closure of enrollment at the two prospective sites.

Screening Data Disposition

All data collected during screening for patients not meeting inclusion criteria, or meeting exclusion criteria, will be destroyed immediately, EXCEPT for the reason for exclusion, which will be collected and saved in a de-identified manner until study completion for the purposes of establishing external validity.

Inclusion Criteria

1) Genotype 1b and genotype 1a without baseline NS5A resistance or Genotype 4
2) APRI Score <0.7; if >0.7 a Fibrosure/Fibrotest or Fibroscan score of F2 or less, plus no clinical or laboratory evidence of cirrhosis
3) Readiness for treatment based on ability to make >2/3 sequential office visits either prospectively retrospectively.
4) Patients must be assessed to have decision-making capacity, be capable of consenting, and not be displaying evidence of overt intoxication.

Exclusion Criteria

1) Previously treatment for hepatitis C infection
2) Clinical, radiologic, or laboratory evidence of cirrhosis
3) Hepatocellular carcinoma, HIV or hepatitis B virus co-infection, elevated prothrombin time unrelated to anticoagulation, hemoglobin level less 11 g/dL, platelet count $<150 \times 10^9$ cells/L), WBC $<4.0 \times 10^3/mm^3$, aminotransferase levels more than 10 times the upper limit of normal, or albumin level <3.0 g/L, positive office-based pregnancy test.
4) Subjects taking medications that are contra-indicated to administer with Zepatier including phenytoin, carbamazepine, rifampin, St. John's Wort, and cyclosporine. Study pharmacists will assess drug interactions. 5) Persons under the age of 18

c. Vulnerable Populations

All of our subjects enrolled prospectively will suffer from a substance abuse disorder but will only be eligible for consent/enrollment if they are assessed to have decision-making capacity at the time of consent. As such, these subjects do not meet NBAC criteria of a vulnerable population. Neither of the study sites serves subjects who are currently incarcerated, so prisoners will not be asked to consent for the study. In the event that one or our fully consented subjects becomes incarcerated during the course of treatment, arrangements will be made for Zepatier and standard-of-care laboratory monitoring to be continued while incarcerated. However, optional procedures, such as interviews and surveys, will not be continued during a subjects incarceration to avoid potential inducement to participate. Zepatier is contraindicated in pregnancy, therefore pregnant women will not be included in the study. Children are also not eligible to participate.

d. Setting.

This is a multi-site study with both prospective arms of the study operated on OHSU-affiliated but not OHSU-owned properties. Site leaders will be OHSU faculty and all other principle personnel will be OHSU-affiliated and CITI-trained in concordance with OHSU IRB requirements. All sites will be relying upon the OHSU IRB for study oversight.

Outside In Needle Exchange Program

Outside In is a Federally Qualified Health Center and a Healthcare for the Homeless clinic in Portland Oregon. Its mission is to help homeless youth and other marginalized populations move towards health and self-sufficiency. The medical clinic served as a patient centered primary care home for 6000 people in 2015 providing primary and acute care, naturopathic care in both a fixed location and from outreach medical vans throughout the metropolitan region. Roughly 50% of Outside In's primary care patients report homelessness and more than 80% of its patients are at or below the Federal Poverty Line.

Outside In also is home to the United States' first publicly funded needle exchange program. This program began in 1989 and serves over 4,500 unique clients annually. In FY 2015 Outside In's syringe exchange program conducted 144 Rapid HCV antibody tests with 27% of the tests coming back reactive for HCV antibodies. In July 2013 when Oregon liberalized its law regarding secondary prescription of naloxone to reduce opiate overdose, Outside In started Oregon's first and only Naloxone training and distribution program that year. After one year of operation the Multnomah County Health Department reported a 29% reduction in heroin overdose deaths which it credited to that program. Since the start of that program Outside In has conducted over 1400 individual trainings with prescriptions, to active injection drug users and their supports, and has received over 934 self-reports of overdose reversals. Outside In operates two mobile medical vans which it sends with complete provider care teams including medical and behavior health clinicians to remote homeless sites and other health disparity locations such as community mental health facilities. It operates a satellite syringe exchange at one of its most productive homeless outreach sites. Outside In's main clinic facility is located on the southwest end of downtown Portland, (OTC is in the northwest end) where the four main homeless youth serving agencies are located. Outside In has extensive homeless youth transitional services including housing, case management , job training and an alternative school. Outside In operates a tattoo removal program for gang-involved and street-involved people. At its main facility Outside In offers acupuncture, massage and chiropractic care. Outside In is a state certified patient-centered primary care home, providing integrated behavioral health care within its primary care through co-located interdisciplinary teams sharing a panel of patients. We offer same day access which is essential in serving their transient and high-risk patient population.

The overall goal of Outside In's HCV treatment program is to improve the care of its patients suffering from chronic Hepatitis C virus and to standardize the screening, diagnosis, work-up, and treatment of this condition throughout Outside In. Patient-centered design to increase success in the recruitment and treatment of actively using, homeless or high-risk patients is at the core of the creation of this program. Essential parts of Outside In's program include recruitment and referral from Outside In's syringe exchange program as well as referral by the primary care provider (PCP) from within our homeless health services, initial office visit and assessment with an Outside In HCV provider, tailored weekly or bi-weekly medication dispensing, bi-weekly clinical pharmacist visits, monthly lab monitoring, and optional participation in HCV harm-reduction/ re-infection prevention education sessions. All of these services are provided at Outside In, the patients' primary care medical home.

Old Town Clinic

Old Town Clinic (OTC) is part of Central City Concern (CCC), a multi-faceted social service agency whose mission is to provide comprehensive solutions to ending homelessness and achieving self-sufficiency. Old Town Clinic is a Federally Qualified Health Center and a Healthcare for the Homeless clinic located in downtown Portland, Oregon. This is an integrated, multi-disciplinary primary care clinic serving over 4,900 homeless and low-income adults living with a broad range of social, behavioral, and medical conditions. More than 70% of OTC patients are homeless and 99% are at or below 100% of the federal poverty level. The population of Old Town Clinic has a high prevalence of chronic hepatitis C infection. In addition, the patient population has a high prevalence of severe and persistent mental illness, addiction, and chronic medical illness. For these reasons, many of its patients are not currently candidates for chronic hepatitis C treatment, and even if they are candidates, the barriers to receiving treatment are insurmountable. The consequences of which are not insignificant as 24% of its patients are known to suffer from chronic hepatitis C, and among patients with the most advanced illness, the known prevalence is 56%. The morbidity and mortality of chronic hepatitis C infection as well as the costs to the healthcare system have been well described.

OTC is a patient centered medical home and offers many integrated services that help support our patients' health with the goal of increasing their overall wellness. Specifically, we have an onsite and fully integrated clinical pharmacy program. The pharmacy dispenses medications for the majority of our patients, many of whom struggle with medication adherence. To address this our pharmacy offers medical therapy management consultations, bubble packing of medications, medication box management, and daily dispensing of medication as needed. Clinical pharmacy is also integrated with our direct patient care teams and has improved many difficult to manage chronic disease states. For example, we have a diabetes management program that has shown great adherence and improved diabetes control in our patients. As well, our clinical pharmacists help to treat patients suffering from schizophrenia and psychosis by managing and administering long acting injectable anti-psychotic medications. Leveraging our clinical pharmacy services to treat patients suffering from chronic HCV would strengthen patient adherence and their overall treatment experience.

Mental health is also fully integrated into our primary care services. There are psychiatric nurse practitioners and licensed clinical social workers on each care team to offer diagnosis and management recommendations as well as counseling services. For patients suffering from severe and persistent mental illness, OTC coordinates care with a co-located specialty mental health program that offers more intensive behavioral health support including case management. Access to these mental health services will be essential for patients undergoing hepatitis C treatment who are often afflicted with mental illness and trauma.

Another unique offering at OTC is fully integrated Alcohol and Drug treatment services within primary care. We offer level 1 outpatient treatment for individuals suffering from opioid use disorder and others who suffer from comorbid chronic pain and substance use disorders. We have a robust medication assisted treatment program housed within primary care. Specifically, we offer buprenorphine and longacting naltrexone in conjunction with mandatory group and individual counseling sessions. These patients are some of the most adherent of the OTC population because the A&D program requires this (i.e. twice weekly groups, weekly medication dispensing, etc.). This population (i.e. PWIDs or have a history of IVDU) is disproportionately affected by HCV, so having this recovery support will not only improve treatment adherence but will reduce the risk of HCV re-infection.

The overall goal of OTC's HCV treatment program is to improve the care of its patients suffering from chronic Hepatitis C virus and to standardize the screening, diagnosis, work-up, and treatment of this condition throughout OTC. Patient-centered design is at the core of the creation of this program. Patient and provider co-design, utilizing human-centered design principles and tools, has been central to its development.

Essential parts of OTC's program include referral by the primary care provider (PCP), initial office visit and assessment with an OTC HCV provider, weekly medication dispensing, bi-weekly clinical pharmacist visits, monthly lab monitoring, referral to medication assisted treatment or mental health services as indicated, and optional participation in education and peer support sessions. These sessions will be initially modeled after previously validated peer support groups for treatment with interferon-based regimens,[3,5] and further refined through our iterative, human-centered design process. Patients who are recent (previous 12 months) or current injection drug users will be strongly encouraged, but not required, to meet weekly in groups of less than 12 individuals, facilitated by certified drug and alcohol counselors. Patients electing to attend HCV health education sessions will partake in a 1 hour, certified health educator-lead, interactive hepatitis C education session, focusing on medical and social aspects of the disease, adherence, and re-infection prevention. Integrative HCV Treatment Model At Two Study Sites

Outside In HCV Treatment Program

Essential parts of Outside In's program include recruitment and referral from Outside In's syringe exchange program or referral by the primary care provider (PCP) from within our homeless health services, initial office visit and assessment with an Outside In HCV provider, tailored weekly or bi-weekly medication dispensing, bi-weekly clinical pharmacist visits, monthly lab monitoring, and optional participation in HCV harm-reduction/ re-infection prevention education sessions. All of these services are provided at Outside In, the patients' primary care medical home.

- The medical clinic serves as a patient centered primary care home providing primary and acute care, naturopathic care in both a fixed location and from outreach medical vans throughout the metropolitan region.
- Outside In is home to United States' first publicly funded needle exchange program.
- The organization runs two medical vans it sends with complete provider care teams including medical and behavior health clinicians to remote homeless sites and other locations with extensive health disparities such as community mental health facilities.
- Outside In is a state certified patient-centered primary care home, providing integrated behavioral health care within its primary care through co-located interdisciplinary teams sharing a panel of patients.

Old Town Clinic HCV Treatment Program

Old Town Clinic (OTC) is part of Central City Concern (CCC), a multi-faceted social service agency whose mission is to provide comprehensive solutions to ending homelessness and achieving self-sufficiency. Essential parts of OTC's HCV program include referral by the primary care provider (PCP), initial office visit and assessment with an OTC HCV provider, weekly medication dispensing, bi-weekly clinical pharmacist visits, monthly lab monitoring, referral to medication assisted treatment or mental health services as indicated, and optional participation in education and peer support sessions.

Onsite and fully integrated clinical pharmacy program. The pharmacy dispenses medications for the majority of patients, many of whom struggle with medication adherence. To address this the pharmacy offers medical therapy management consultations, bubble packing of medications, medication box management, and daily dispensing of medication as needed.

Mental health is fully integrated into our primary care services. Psychiatric nurse practitioners and licensed clinical social workers on each care team offer diagnosis and management recommendations as well as counseling services. For patients suffering from severe and persistent mental illness, OTC coordinates care with a co-located specialty mental health program that offers more intensive behavioral health support including case management.

OTC has fully integrated Alcohol and Drug treatment services within primary care. They offer level 1 outpatient treatment for individuals suffering from opioid use disorder and others who suffer from comorbid chronic pain and substance use disorders. Because of this, these patients are some of the most adherent of the OTC population because the A&D program requires this (i.e. twice weekly groups, weekly medication dispensing, etc.).

e. Recruitment Methods, by site, estimated to take 2-3 months.

Old Town Clinic. Upon study initiation, the site principle investigator will pull a list of active patients in the Old Town Clinic buprenorphine-based Medication Assisted Program who also carry a diagnosis of chronic hepatitis C. In addition, patients requiring level 2 intensive outpatient substance use treatment receiving methadone or buprenorphine-based Medication Assisted Therapy with co-morbid chronic hepatitis C will be pulled by chart study coordinator chart review. Anyone not meeting the inclusion criteria or with automatic exclusion criteria will be excluded. The study coordinator will then contact the remaining patients in a sequential fashion via telephone with the following script: "Hello I'm _____ a ____ at Old Town Clinic. We are looking for patients in the Suboxone program at Old Town interested in treating their hepatitis C. We cannot guarantee it without a doctors visit, but we may be able to treat your hepatitis C. Would you like to make an appointment to be screened?" We will also post fliers in the meeting rooms stating, "Are you Hepatitis C Positive? Are you interested in treatment? Old Town Clinic is part of a study working to treat people with HCV. For more information and to see if you qualify for this study, please call 971-XXX-XXXX". The first 25 patients that agree to be screened, meet criteria, and sign an informed consent to enroll in the study will be enrolled. Subjects will be reimbursed for each survey or in-depth interview with a $15 Fred Meyer gift card.

Outside In. Upon the study initiation, Outside In's Injection Drug Users Health Services Program will begin handing out fliers to all clients of the syringe exchange program as well as posting fliers on the bulletin board in the waiting room. These fliers will read, "Are you Hepatitis C Positive? Are you interested in treatment? Outside In is part of a study working to treat people with HCV. For more information and to see if you qualify for this study, please call 503-535-XXXX". This outreach process will be augmented with a respondent-driven sampling method called "snowball sampling," which uses social networks to find more clients in hard to reach populations. Representative seed subjects will be given

three coupons (fliers) to be given to other syringe exchange clients who also might be treatment candidates. Subjects may also be referred to study by their Outside In primary care provider. The phone line will be answered by the site coordinator and will have a voicemail that says "Thank you for your interest in our study. For this study, you need to be a current injection drug user. You must be over the age of 18. Please leave a name and a phone number you can be reached at. All calls will be returned the morning of the next business day. Thank you for your interest." The site study coordinator will return the client's call (two attempts will be made). This staff will confirm the initial screening conditions, inquire about insurance status, and make a medical appointment if appropriate. If the client is uninsured, he/she will be directed to OHP (Oregon Medicaid) enrollment and asked to re-engage with the study when insurance is active. If the client is insured by OHP, an appointment will be made for the client to meet with a treating medical provider. The provider appointment will serve as a medical screening visit to include missing baseline lab testing necessary to determine eligibility, the results of which will be helpful in determining inclusion. The first 25 patients that agree to be screened, meet criteria, and sign an informed consent to enroll in the study will be enrolled. Subjects will be reimbursed for each survey or in-depth interview with a $15 Fred Meyer gift card.

OHSU (Retrospective). The OHSU principle investigator, or IRB approved surrogate, will review the hepatology clinic Electronic Medical Record for patients treated for hepatitis C with Zepatier and select subjects in a retrospective, sequential fashion, starting at the time of closure of enrollment at the two prospective sites.

f. Consent Process

The consent coordinator will obtain consent during the intake appointment, after the initial screening process as detailed below. The consent coordinator will be an IRB-approved, OHSU affiliated employee of the study site, with 50% of their FTE covered by grant funding. This will occur in person, in a confidential clinic exam room, with ample time for questions and clarifications. The consent form will also be provided prior to the appointment so subjects have time to read over it and highlight any questions or concerns they may have. Subjects with low self-reported reading literacy will have the consent form read to them with a teach-back to confirm understanding. While all study coordinators will be employees of their parent organizations and will have access to the medical record, they will not be medical providers with a long standing relationships with the subjects to minimize potential for coercion and conflicts of interest.

For the purposes of this pilot study, only subjects who identify as proficient in the English language will be enrolled. The scientific rationale for this is based on a lack of validated non-English language questionnaires suiting our study question. In addition, the Medication Assisted Therapy population at the Old Town Clinic site of Central City Concern has only English speaking drug and alcohol counseling groups (present in East-Side Clinic, not participating in our study), potentially creating bias if non-English speaking patients were enrolled at the Outside In site.

Consent will follow a clinic visit with a study provider, who will use a basic capacity assessment to determine eligibility to consent. This will include the following general principles of being able to understand, express a choice, appreciation, and reasoning.[9]

6. Procedures Involved

- The primary therapeutic intervention will be one tablet of Zepatier (elbasvir 50mg/grazoprevir 100mg) daily with or without food for 12 weeks. This dosage is consistent with current FDA approval for the treatment of hepatitis C.

- Screening, treatment interventions, and follow up are outlined below. All of the following represent standard of care interventions, with the exception of survey data collection and in-depth qualitative interviews. These interviews serve the purpose of better understanding potential barriers to successful treatment and to identify potential mitigating innovations in the care of this complicated and neglected population.

Treatment Scheme

Baseline Testing (already performed as a part of standard of care for a patient with HCV infection)

- CBC with differential, Complete Metabolic Profile, GFR, INR, HCV genotyping with NS5A resistance testing for genotype 1a, HCV RNA, HIV, pregnancy test in female of childbearing age
- APRI score or Fibrosure or Fibroscan to determine fibrosis stage. APRI score is defined as AST level in IU/L over 40 IU/L (upper limit of normal value) divided by platelet count in $10^9/L$ multiplied by 100 or.

Screening Visit

- Consent process including discussion of the consent form
- History and physical to exclude signs and symptoms of cirrhosis
- Inclusion and exclusion criteria assessed
- NS5A resistance testing for genotype 1a subjects (subjects excluded if baseline resistance present)
- Assess subject's readiness for treatment: Subjects must have established care as a primary care patient at Outside In or Old Town Clinic. They must express a desire to be treated and to adhere to all laboratory monitoring and visit requirements.
- Screen failure subjects will be linked to appropriate care within the study site or at OHSU hepatology for further management

Visit 1

- Clinic Visit
- Once enrolled, completion of validated questionnaires (see Appendix that includes additional references) that assess the subject's understanding of health, current health status, addiction and severity of addiction, social support, and degree of stigma. These assessments have been described in hepatitis C infected population.[6,7,8]

Visit 2

- Clinic visit
- Verify the following studies/assessments are complete including CBC; INR, complete metabolic profile; GFR; genotype 1a, 1b, or 4 HCV RNA; no baseline RAVs for genotype 1a subjects
- Verify Readiness for treatment

- Verify questionnaires completed
- Pregnancy counseling

Visit 3 (Initiation of HCV treatment)

- Clinic visit
- Check in post-survey on subject well-being
- Pharmacy dispenses 2 weeks, or less if indicated* of HCV medication

*Given the complexity of this population, the study pharmacist and clinicians will determine the most appropriate dispense frequency and method depending on the subjects' needs.

Visit 4 (week 2 of HCV treatment)

- Clinic Visit
- Compliance assessment
- Pharmacy dispenses another 2 weeks, or less if indicated, of HCV medication

Visit 5 (week 4 of HCV treatment)

- Clinic Visit
- Compliance assessment
- HCV RNA (if detectable, repeat HCV RNA in 6 weeks)
- Pharmacy dispenses 2 weeks, or less, if indicated, of HCV medication

Visit 6 (week 6 of HCV treatment)

- Clinic Visit
- Compliance assessment
- Recheck HCV RNA in those subjects who had detectable HCV RNA at week 4. If on repeat testing at week 6, viral load has increased by 10 fold >1 log10 IU/mL discontinue therapy. **Visit 7 (week 8 of HCV treatment)**
- Clinic Visit
- Compliance assessment
- Check CMP. If liver enzymes >10 fold discontinue therapy

VISIT 8 (week 12 of HCV therapy) - End of Treatment

- Clinic Visit
- Compliance assessment

VISIT 9 (week 24) - 12 weeks after treatment completed

- Clinic visit
- HCV RNA to assess for SVR12, repeat genotype to clarify re-infection vs failure if +

VISIT 10 (week 60) - 48 weeks after treatment completed

- Clinic visit
- HCV RNA to assess for SVR48, repeat genotype to clarify re-infection vs failure if +
- Re-administer questionnaires

TOTAL DURATION - about 18 months

Quantitative Survey Data.

The following surveys will be performed and have been submitted for IRB approval:

- Chronic Illness Anticipated Stigma Scale (CIASS)
- MOS Social Support Survey
- SF-36 "Health and Well-Being" Survey

In addition, in-depth qualitative interviews will be performed Interviews will cover salient issues in participants' lives at the community, organizational, household levels, as well as relationships (friends, family and sexual partners) perceived to influence study participation, treatment acceptability and adherence; risk taking behavior; and treatment preferences. By emphasizing the social and physical context of participant's lives and their understandings of health, interviews are intended to provide insight into the ways in which these contexts shape treatment adherence and possible reinfection. The following constructs are constructs and sample themes that will guide in-depth interviews.

Level	Factors	Topics/Theme
Individual	Self-worth	Please tell me about experiences when you've been denied HCV treatment in the past? Do you feel that you deserve to be treated for HCV? What does having access to HCV treatment mean to you? Do you think that people who use drugs deserve treatment?

	Perceived treatment selfefficacy	Do you think you will be able to take the treatment as prescribed? What factors do you think will make it challenging for you?
	Risk Behaviors	What is your understanding of safer injection practices? What risk behaviors do you think put you at risk for Hep C (ex. Needle sharing, sharing cocaine straws, etc)? How often did you/do you use safer practices (eg. Needle exchange).
Household	Sexual Partner	How has your sexual partner shown to be supportive of your health? How has your sexual partner made it more difficult for you to be healthy? How does your sexual partner feel about your participation in this study?
	Family	How has your family shown to be supportive of your health? How has your sexual partner made it more difficult for you to be healthy? How does your family feel about your participation in this study?
	Household resources	Income/financial resources/housing stability/work and migration/household size/access to health care
	Life Events	Birth, deaths/funerals, employment changes/changes in relationships
Organizational	Clinical sites	Perception of hospitals; perception of CBOs; comparing perception of context of study sites
	Group	Participation in support groups
	membership	
	Social services	Access to other services in relation to HCV treatment (e.g., housing, recovery, ORT, needle exchange)
Community	HCV perceptions	HCV acceptances/stigma; experiences of discrimination; What do people in your community think about HCV?
	Community resources	Access to health and other social services, public transportation; CBOs
	Cultural Norms	Practices around pill/medication taking, cultural beliefs about doctors and medical providers (e.g., trust, conspiracy theories)
	Information flow and beliefs	Rumors/beliefs about clinical studies, HCV transmission, HCV treatment
		Influence of institutional belief systems (e.g., churches, recovery fellowship)
		Informal and formal social and community networks (e.g., drug use networks)

7. Data and Specimens a. Handling of Data and Specimens

All data will be collected by the primary provider, site principle investigators, or site coordinators. This data will be disassociated with personal identifiers, re-associated with a nondescript study ID, and uploaded into OHSU-sanctioned confidential data management service such as RED Cap, on a daily basis.

We will collect basic demographical information, including age, gender, ethnicity, substance abuse disorder/drug of choice and current use status, and housing status. The primary outcome measured will be SVR at 24 weeks (12 weeks post-treatment). Secondary outcomes include adherence (% pills missed, per fill and total), relapse or ongoing injection drug use at 48 weeks, and re-infection or treatment failure at 48 weeks.

Data storage will be for a period of 5 years or less, unless formal permission requested of the OHSU IRB for extension. Subjects will be consented for indefinite data storage.

Please see uploaded data collection and consent forms.

b. Sharing of Results with Subjects

All personal, clinical information will be shared with subjects in accordance of the standard of care. This includes lab values (done at CLIA certified laboratories Quest and Labcorps), imaging results, and other aspects of routine hepatitis C treatment. Results of secondary measures, including survey data and indepth interviews, will not be shared directly with subjects. Subjects will be able to access the final publication(s) upon request.

c. Data and Specimen Banking

Subjects will be assigned a study ID on paper and data will be entered into an encrypted/password protected excel spreadsheet by the site principle investigator or study coordinator. The study ID will not contain any of the 18 HIPPA identifiers and will be available only to the PIs and IRB approved study collaborators. This document will be maintained, password protected, in the RED Cap repository. At each visit, a subject's study ID will be accessed from the Master List and a de-identified, study ID-linked opaque envelope with data sheets for all 10 visits will be pulled from a secure location. All non-clinical care data will be initially collected on paper by the data collector, provider, or study coordinator and then entered into de-identified data sets in the RED Cap repository by the study coordinator on a weekly basis. The paper copy will be replaced into the opaque envelope and then confirmed by a separate, IRB approved study volunteer. Standard of care clinical data will be entered in the electronic medical record and endpoints pre-specified in this protocol will be transferred to the RED Cap repository by the study coordinator on a weekly basis. When the study is fully enrolled and all participants complete the 48week visit, or are lost to follow up, the paper datasets will be destroyed in medical recycling facilities at each site.

In the retrospective OHSU cohort, all data will be entered immediately into RED Cap and then confirmed by a separate investigator at the OHSU site.

As part of the primary consent document, all participants will legally consent by written signature to storage of non-biological study data in a secure repository for future investigations. No biological specimens of any type will be stored beyond what is needed to complete laboratory tests at the point of care. For instance, blood will be drawn and sent to the clinical laboratory (LabCorp, Quest Diagnostics)

and stored ONLY for the purposes of performing the lab, in concordance with standard practices. In most cases this will not exceed a week and never more than two weeks. No genetic testing will be performed as a part of this study and thus none will be shared. All electronic data will be maintained encrypted in the RED Cap repository. Only the primary investigator, Atif Zaman, and two coinvestigators, Ryan Hutchison and Andrew Seaman, will have access to these data following study termination. These data will be maintained separate from personal identifiers, and only the PI and coinvestigators will have access to the master spreadsheet linking study ID and personal identifiers. These personal identifiers will not be made available to external researchers at any time, and so no personally identifiable information will be shared with external researchers. Andrew Seaman, co-investigator and primary study contact, will be listed as the repository guardian. If contacted for use of study data for any purpose, he will be responsible for ensuring data are released according to OHSU policy and the IRB approved repository protocol, executing a repository sharing agreement in case data are released for future research, ensuring the security and confidentiality of all stored data, ensuring the security and confidentiality of data during transfer, and tracking acquisitions and releases of data. He will also maintain access to the master spreadsheet linking study ID to personal identifiers, in order to identify data sets for which consent has been withdrawn and ensuring no future use.

After study completion, any future release of data collected will be contingent upon the repository guardian verifying a separate full IRB approval for each specific human subject research activity that uses identifiable repository data. The repository guardian will be personally responsible for verifying that future releases of data are done in concordance with pre-proposed limits and the original consent. Data transport at the time of any potential future IRB approved data sharing will be clarified and approved at the time of data by submission of an updated Repository Sharing Agreement and separate IRB approval. Any updated data requests and Repository Sharing Agreements will be stored alongside study data in the Red Cap repository in a separate file entitled “Repository Sharing Agreements and External Data Requests.” This will be maintained and tracked by Andrew Seaman. External researchers will be required to use the Red Cap repository for all data storage, therefore data transfer will not be necessary and data security ensured.

No data submittal from outside sources is expected.

8. Data Analysis

1) For primary endpoint: descriptive analysis and chi-squared test for comparative analysis

2) For secondary endpoints:

- Descriptive analysis

- Explore bivariate and multivariate associations between psychosocial factors computed through scales (e.g., stigma, social support, quality of life) and (a) treatment readiness at baseline, (b) treatment outcomes [SRV, biological outcomes, etc.] at 12 months, (c) re-infection (or SRV) at 48 months. Demographic controls will include age, education, work status, and relationship status.

- Conduct constant comparative qualitative analysis of focus group and individual discussions using Atlas.ti software. The domains of analysis will include lived experiences with stigma, discrimination, positive and negative social support systems, and risk management. Emergent themes and domains identified through qualitative analysis will result in a richer understanding of factors that contribute to implementing successful treatment for people who currently use drugs.

In addition to the above, mixed methods data will comprise biological data, psychosocial data collected via questionnaires, and qualitative narrative data from transcribed in-depth interviews.

Using Dedoose software, the research team will work together to systematically analyze the data in the following steps: 1) exploratory within-case analysis; 2) descriptive across-case analysis; 3) analytic within-case analysis; and 4) analytic across-case analysis—each "case" being an individual included in the study.

The overall goal is to draw connections among the domains laid out in the socio-ecological conceptual framework, exploring patterns that indicate how social and institutional experiences may shape vulnerability to HCV and success in treatment outcomes. This type of reflexive analysis is crucial when performing real-world clinical research that takes into account psychosocial factors and social context.

Exploratory within-case analysis involves reading interviews and marking sections with compelling and/or representative stories, quotes, or instructive idioms. Noteworthy aspects of each case are summarized, contributing to the development of a preliminary set of codes. Rather than deciding a priori the taxonomies for sorting individuals, themes and codes emerge from the data itself.

Descriptive Across-Case Analysis involves generating descriptions of key domains articulated in the socio-ecological conceptual framework. This across-case analysis will describe the range within each domain, articulating—for example—the range of participants' experiences interacting with medical institutions, trust in medication, experiences of stigma related to HCV or drug use, subject social network's views of medical treatment, as well as institutional elements of receiving care at community clinic settings with multiple social services.

For the analytic within-case analysis, the team will develop and test explanations of how the institutional and social contexts of people's lives shape their treatment outcomes. This includes adherence to treatment, SVR, and vulnerability to HCV reinfection. This involves pooling interview, biological and psychosocial data to describe frequencies and relationships between key domains and outcomes. This analytic within-case analysis will correct for any theoretical oversights in the conceptual framework and may generate new analytic codes.

Analytic across-case analysis entails comparative analysis, distinguishing between groups of people who exhibit different behavioral patterns. This allows the investigators to go beyond simple assertions about majority and minority patterns and to make analytic—as opposed to descriptive—statements about how certain values or behaviors relate to broader psychosocial and institutional factors.

Power/Sample Size:

Based upon a sample size of n=50 subjects in the combined safety net/needle exchange clinics and 50 subjects in the retrospective comparator group, this study has 80% power to detect a 20% difference between groups; this calculation is based on the assumption that the retrospective comparator group will have and SVR12 rate of 95% (taking into account treatment discontinuation and relapse rates, i.e. intention to treat analysis) compared to SVR12 rate of 70% in the safety net clinic patients.

In the intervention group (safety net clinics) a total of 50 subjects will be enrolled to allow for a 10% attrition and loss to follow up.

9. Privacy, Confidentiality, and Data Security

All data will be collected and entered in a private, clinical care environment, behind closed doors. All study collaborators with access to personal data, de-identified or not, will be required to undergo full OHSU IRB training.

At Old Town Clinic, subjects will be recruited as described in Section 5e. There will be limited risk of a privacy violation with this method. The consent process will be performed during the course of a clinical visit, in an exam room, one-on-one with the site coordinator.

At Outside In, subjectss will be recruited as described in Section 5e. There will be limited risk of a privacy violation with this method. The consent process will be performed after a clinical visit in a private office in the syringe exchange, one-on-one with the site coordinator.

At all sites, laboratory and/or imaging tests, clinical visits, dispensation of medications, and communication of test results will be performed in concordance with HIPPA appropriate clinical care. All surveys and qualitative data will be collected in a private space, such as an exam room or meeting room behind closed door.

For more details, please see section 7c above.

10. Provisions to Monitor the Data to Ensure the Safety of Subjects

See DSMP document, attached.

9. Risks and Benefits a. Risks to Subjects

- Surveys and Questionnaires. Some of the questions in the questionnaires or interviews have the potential to be re-traumatizing. All study personnel have training in trauma informed care and know how to minimize this risk. Subjects have the right to refuse to answer any questions.

- Lab Tests and Images. There is minimal risk of discomfort associated with lab draws.

- Treatment. About 1/100 people experience a temporary increase in their serum transaminase, ALT, to about 5 times the upper limit of normal. This typically resolves after completion of treatment. In previous studies, about 1/10 patients experienced headaches and fatigue during treatment. However, this is about equivalent to, or only slightly higher than, placebo in most studies. In one study, patients on Zepatier™ were slightly more likely to have nausea than patients on the placebo. Zepatier™ can interact with some other medications, these will be screened for by study pharmacists and clinicians prior to drug initiation.[10]

b. Potential Benefits to Subjects

Zepatier™, and other direct acting antiviral agents targeting hepatitis C, are extraordinarily effective at eradicating the disease, between 92 and 97%[10]. The morbidity of hepatitis C is described well above. Patients with lower fibrosis scores are being denied access to treatment by insurance companies in this and other states due to cost concerns, despite this being contrary

to national guidelines. Patients are also frequently denied for having a substance abuse disorder, even though the majority of new infections in the United States occur in this population. As such, we know very little about the treatment of hepatitis C in active or recent PWIJs.

Subjects who participate in this study will have free access to a highly effective, FDA approved treatment for hepatitis that will likely cure their disease. They will also have access to intensive, wrap around services they would not likely enjoy at a referral center where they would typically get treated. The ancillary data collected in surveys and interviews may help individualize therapy options, including prescribing frequency, etc., and will contribute to the body of knowledge to help better care for their community.

10. Drugs or Devices (delete if not applicable)

Open label drug supplies will be required by Merck.

Our institution's pharmacy will require packed and labeled medication containers in English.

At conclusion of the study or upon drug expiration, the Merck GRS will be responsible for issuing a Drug Disposition Letter to the investigator for US based studies.

The investigator will be responsible for the destruction of the supplies at the study center pursuant to the ICH/GCP Guidelines, local regulations and the investigator's institutional policies. Clinical supplies must be received by a designated person at the study site, handled and stored safely and properly, and kept in a secured location to which only the investigator and designated assistants have access. Clinical supplies are dispensed in accordance with the protocol. The investigator is responsible for keeping accurate records of the clinical supplies, the amount dispensed to and returned by the subjects, and the disposition at the end of the study.

Zepatier is FDA approved and well tolerated. The prescriber information is included in study documents.

11. References

1) Bruggmann P, Litwin AH. Models of care for the management of hepatitis C virus among people who inject drugs: one size does not fit all. Clin Infect Dis. 2013;57 Suppl 2:S56-S61.

2) Islam MM, Topp L, Conigrave KM, et al. Linkage into specialist hepatitis C treatment services of injecting drug users attending a needle syringe program-based primary healthcare centre. J Subst Abuse Treat. 2012;43(4):440-445.

3) Aspinall EJ, Corson S, Doyle JS, et al. Treatment of hepatitis C virus infection among people who are actively injecting drugs: a systematic review and meta-analysis. Clin Infect Dis. 2013;57(Suppl 2):S80-S89.

Education and peer support sessions references modeled after previously validated peer support groups for treatment with interferon-based regimens

4) Sylvestre DL, Litwin AH, Clements BJ, Gourevitch MN. The impact of barriers to hepatitis C virus treatment in recovering heroin users maintained on methadone. J Subst Abuse Treat 2005; 29:159–165.

5) Grebely et al. Optimizing assessment and treatment for hepatitis C virus infection in illicit drug users: a novel model incorporating multidisciplinary care and peer support. European Journal of Gastroenterology & Hepatology 2010, 22:270–277.

Questionnaire instruments based on the following references where the scales were used, validated with HCV treatment clients.

Addiction Scale:

6) AI Newman, S Beckstead, D Beking, et al. Treatment of chronic hepatitis C infection among current and former injection drug users within a multidisciplinary treatment model at a community health centre. Can J Gastroenterol 2013;27(4):217-223.

Both MOS Social Support and Addiction Scale:

7) Mason, K et al. (2015) Beyond viral response: A prospective evaluation of a community-based, multidisciplinary, peer-driven model of HCV treatment and support, International Journal of Drug Policy 26:1007–1013

Constant Comparison Analysis Method:

8) Glaser, Barney G. "The constant comparative method of qualitative analysis." *Social problems* 12.4 (1965): 436-445.

Capacity:

9) Grisso T, Appelbaum PS. Abilities related to competence. In: Assessing competence to consent to treatment A guide for physicians and other health professionals, Oxford University Press, New York 1998. p.31

Zepatier Complications:

10) 1) Zepatier™ Prescriber Information, Merck & Co. https://www.merck.com/product/usa/pi_circulars/z/zepatier/zepatier_pi.pdf. Accessed 8/20/2016.