Protocol Title: Oregon HIV/Hepatitis and Opioid Prevention and Engagement (OR-HOPE) Study: Tele-HCV Treatment Trial

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ClinicalTrials.gov ID: NCT04798521

Protocol Revision Date: October 13, 2022

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Objective

The main goal of this study is to test the efficacy of a peer-facilitated telemedicine HCV treatment implementation strategy for people who use drugs versus local HCV treatment referral for achieving HCV sustained viral response at 12 weeks post-treatment (SVR12).

Background

Untreated drug use is associated with increased hepatitis C (HCV) risk. People living in rural areas – with limited access to prevention and treatment resources – may be particularly susceptible to unchecked HCV transmission. A recent analysis identified six rural county characteristics associated with acute HCV infection rates - mainly due to injection drug use - including drug-overdose deaths, prescription opioid sales, per capita income, white non-Hispanic race/ethnicity, unemployment, and limited buprenorphine prescribing capacity.

HCV transmission is primarily driven by injection drug use. As a result, HCV is endemic among people who used drugs (PWUD). Guidelines state that HCV treatment should be prioritized among patients with substance use disorders, yet only a small percentage (<10%) of PWUD access treatment. The advent of newer highly effective, direct-acting anti-HCV treatments provides an opportunity to limit or even eradicate HCV. However, realizing treatment benefits depends on whether PWUD can be identified, tested, and linked to care, and many PWUD in rural communities struggle to engage with traditional health settings and testing mechanisms. In particular, venipuncture based diagnostics can be traumatizing and challenging for people with current or past injection drug use. Several studies held outside of the United States have suggested improved test acceptance with dried blood spot (DBS) versus traditional venipuncture by as much as four fold and test operating characteristics where acceptable. These tests have not yet been validated for use in the United States with commercial laboratories. For this purpose, we will implement the study in two phases. Phase 1; validating the DBS testing measures, Phase 2; implementing telemedicine hepatitis C treatment after DBS diagnosis. Continuing to phase 2 will not be contingent on phase 1.

New systems of care delivery that integrate HCV treatment in rural areas are urgently needed. Telehealth interventions, which directly connect patients to remote treatment providers, are a potential solution which may support HCV treatment uptake in rural areas. Peer support specialists are people with lived experience in recovery who reach, engage, and retain hard-to-reach populations. They utilize their past shared experiences drug use and recovery to develop rapport and link patients to care. Peer support specialists can facilitate HCV testing and linkage to telehealth HCV treatment for people who use drugs.

Study Design Non-blinded, randomized controlled trial. In-depth qualitative interviews assess attitudes and barriers to treatment.

The study will be implemented in two phases; Phase 2 is not contingent on Phase 1.

[redacted]Study Population

a) Number of Subjects

In Phase 1, potential participants will be pulled from a convenience sample at a Portland clinic providing care for the urban area. An initial target sample of 100 Hepatitis C positive participants will be enrolled for DBS validation. Power will be reassessed based on feedback from receiver operating curve model and additional participants enrolled up to a total of 100 Hepatitis C Positive participants, if necessary. A total of 500 potential participants can be screened expecting 1 in every 4 participants will be positive HCV.

In Phase 2, rural peer care coordinators (PCCs) and research assistants recruit up to 200 PWUD participants from high-needs rural Oregon counties. Study staff specifically target untreated populations recruited from local syringe exchange programs and direct community outreach (e.g. community barbeques, parks, homeless shelters, food pantries, etc.). Participants are encouraged to refer others for study screening.

A subset of up to 40 study participants will complete in-depth qualitative interviews regarding their experiences of hepatitis C treatment.

Inclusion and Exclusion Criteria

Phase 1: Initial DBS Validation Aim
Participants are eligible for inclusion if they:

1) present in person to Central City Concern (CCC) health services for other critical needs
2) elect to screen for hepatitis C, HIV, and hepatitis B while waiting for other health service completion
3) are age 18 years or greater

Participants are excluded if they:

1) inability to perform consent, DBS testing, or incentive distribution without increasing participant social exposure or personal protective equipment utilization

actively receiving HCV treatment

Phase 2: TeleHepC Aim
Participants are eligible for inclusion if they:

1) live in the study area
2) have injected drugs or report recreational opioid use without injection in the last 90 days
3) are age 18 or greater
4) have chronic active, untreated hepatitis C (defined as positive HCV RNA)
5) are seeking treatment for hepatitis C infection.
6) are able to communicate in English (this is due to the fact that less than 5% of the population in which we are targeting will be non-English speaking; see “Non-English Speaking Subjects” for additional information).
7) are enrolled in health insurance

Participants are excluded if they:

1) Have decompensated cirrhosis, defined as Child-Turcotte-Pugh (CTP) score of 7 or greater, or CTP B cirrhosis. CTP scoring is a composite of laboratory metrics (bilirubin, albumin, PT/INR) and clinical findings, including:
    a. increased abdominal or lower extremity swelling
    b. confusion consistent with hepatic encephalopathy
2) Are pregnant or breastfeeding

b) Vulnerable Populations

Children: Children will not be included in the study; subjects age 18 and greater are eligible for inclusion.

Prisoners: This study is likely to enroll persons involved in the criminal justice system related to substance use. The study will not recruit persons incarcerated/detained in a correctional facility or currently considered "prisoners" by local or state laws, but will not exclude parolees or probationers. Those participants who become incarcerated during the course of their involvement with this study will continue to be followed to ensure safety and data integrity. If necessary, specific documents for incarcerated participants will be developed and approved by the OHSU IRB. Appropriate progress notes will be written to ensure complete documentation of any interaction with an incarcerated participant, specifically mentioning confidentiality procedures.

The project has been granted a federal Certificate of Confidentiality. An OHRP Prisoner Research Certification Letter will be filed through the OHSU IRB and distributed to the sites. Local sites will be covered by both OHSU's Certificate of Confidentiality and the OHRP Prisoner Certification to enable study follow up visits for participant who may become incarcerated.

c) Non-English Speaking Subjects

Oregon opioid use disorder demographics suggest the Oregon Hispanic/Latino population has been relatively spared from this epidemic. Hispanic/Latino patients accounted for 3.7% of opioid use disorder treatment admissions in the North Coast and Southwest Oregon grant target regions in 2015, and nearly all speak English. We consequently anticipate a very small fraction of study participants will be mono-lingual Spanish speaking. The very small numbers provide insufficient statistical power to assess differences by language group. We thus believe that collecting Spanish language data is not justified on scientific grounds for this study.

Setting

Participating Sites:

1 Oregon Health & Science University (OHSU) leads the project, under the direction of Dr. Korthuis. OHSU will participate in data quality assurance during study implementation analysis, train PCCs and research assistants (RAs) in study procedures, conduct analyses, and disseminate qualitative and quantitative results. HIV Alliance and Comagine are deferring to OHSU's IRB; the Oregon Health Authority will be using its own IRB for project review.

2 HIV Alliance is a community based service organization providing support for HIV and HCV treatment and prevention and syringe exchange services in rural Oregon counties. HIV Alliance outreach workers will serve as intervention PCCs. HIV Alliance PCCs will recruit and provide linkage to care for PWUD, and an HIV Alliance research assistant staff will support HIV Alliance syringe exchange staff in collecting survey and laboratory data.

3. Bay Area First Step (BAFS) is a community based service organization that provides housing, and peer-delivered services designed to support individuals and families. BAFS peer mentors will serve as intervention PSSs. BAFS PSSs will recruit and provide linkage to care for PWUD and collect survey data. BAFS plays an active role in the community and has strong relationships with potential participants.

4. Comagine conducts qualitative focus groups and interviews and lead the qualitative analysis.

5. Oregon Health Authority investigators will assist in administrative support of tele-HCV treatment and advise the study team on implementation, interpretation, and dissemination of study findings.

6. Implementation Locations: The study catchment area includes Douglas, rural Lane, Josephine, Coos, Curry, Tillamook, Umatilla, and Clatsop counties.

7. Central City Concern: CCC is a community-based homelessness services organization located in Portland, Oregon. They will participate as the Phase 1 site for DBS validation. CCC hepatitis C team staff will perform usual HCV screening and linkage-to-care interventions, consent individuals for DBS validation study inclusion, perform DBS testing, and deliver and track incentives.

8. Oregon Washington Health Network (OWHN) is a community-based network that addresses mental and physical health, and houses peer support specialists. Peer support specialists will recruit participants and facilitate telemedicine appointments. The OWHN research assistant will consent participants and conduct study assessments.

d) Recruitment Methods

Participant Recruitment:
Phase 1: Central City Concern continues to screen for and treat hepatitis C during the COVID-19 pandemic providing clients are presenting in-person for other critical health services. Individuals are offered HCV screening by clinic intake and HCV team staff. CCC clients on campus who opt-in to screen for hepatitis C will be offered venipuncture screening and confirmation labs as per usual clinical practice. After assent to testing, individuals will offer optional participation in DBS validation study.

Participants will receive $30 upon completion of DBS test.

Phase 2: HIV Alliance already supports syringe exchange and rapid HIV/HCV screening in Douglas, Lane, Josephine and Coos Counties. Community-based syringe exchange programs will serve as initial recruitment sites and supplemented with community settings (e.g. parks, homeless shelters, community barbeques, etc.). Research staff will also approach participants of the Oregon HOPE study who have previously consented to be contacted for future research and offer them study participation. Our preliminary data suggest that HCV treatment is highly sought-after by PWUD in intervention counties.

This project will use **snowball** sampling to recruit participants. Research staff will encourage participants to use their personal networks to invite individuals who may be interested in partaking in the intervention. There will not be incentives provided for referrals or a specific set number of participants encouraged to recruit.

Compensation: Participants will receive compensation in the form of cash if they are located in Douglas, Josephine, Coos, Curry or Josephine County. OWHN participants will receive compensation in the form of Visa gift cards.

In the event a participant becomes incarcerated, with their permission, the study team may give their study compensation to a friend or family member to pass along to them so they may have access to it while incarcerated. If the participant does not give permission, compensation will be given to participant when they are able to receive it.

Activity	Cash or gift card Incentive Amount
Prescreen/ Rapid Test/ Blood Draw/ Dried Blood Spot Testing, Full Consent	$20
Screening blood draw	$20
If necessary second blood draw for missed blood draws	$20
Return for Results and Baseline Survey	$15
4 - Week survey	$20
End of treatment survey	$30
*12-weeks after end of treatment survey	$20
*12-weeks after end of treatment blood draw	$40
36 weeks after end of treatment survey, reinfection labs	$30
Total	$215

Cash Incentives:
Tracking systems will be handling cash compensation. The RA will document the serial number of each bill upon obtaining the cash and again when distributing cash to the participant. Research staff will internally audit and count cash incentive records each week. The Quality Assurance staff member will audit monthly. When carrying cash in the field, only small, pre-counted amounts of cash will be carrier. These will be kept in a locked box in a discrete location of the vehicle.

Study participants may choose to seek substance use treatment at residential treatment facilities. Some residential facilities discourage or prohibit patients from having cash at the facility while in treatment. When a study participant is a patient of such a facility and continues to engage in study visits and activities, field staff will hold their study incentives in a locked box at the study office, and distribute funds to the participant when they leave residential treatment.

Gift Card Incentives:
Tracking systems will be handling electronic gift cards. The RA will document the gift card number upon distribution. Research staff will internally audit the gift card count. The electronic gift card tracking sheet will be kept in a secure folder on Box

e) Consent Process

Phase 1:
Potential participants will be consented by IRB-approved CCC HCV team staff at the time of usual care. Extreme efforts will be made to ensure potential participants are able to maintain social distancing precautions before, during, and after the engagement with the HCV team. Consent will be offered at the time of testing in a private room one on one with HCV team staff using existing COVID-19 protocol screening practices, consisting of N95 mask and face shield for staff and surgical mask for participants. All surfaces, pens used for consent, and high touch surfaces will be sterilized as per CCC practices. Staff will remind consenting participants that participation is voluntary and that they may withdraw their consent at any time. Participants will be assessed for understanding of study procedures.

Phase 2:

People who use drugs will be consented by IRB-approved research assistants, Peer Care Coordinators or syringe exchange outreach staff employed by HIV Alliance who have completed human subjects training. The consent process will take place in a private area with only the participant and the Peer Care Coordinator or syringe exchange outreach staff present. In cases where PWUD are consented in

community-based settings (e.g. parks, etc.), research staff and peers will make sure they are out of hearing distance of others for consent and data collection. Peer care coordinators or syringe exchange outreach staff will remind consenting participants that participation is voluntary and that they may withdraw their consent at any time. Participants will be assessed for understanding of study procedures.

Procedures

Phase 1 Procedures:
Prescreening Procedures:
Participants presenting for standard of care HCV, HIV, and HBV screening will consent to Phase 1 of the study using a full consent form. This includes consent for:

- Blood draw for hepatitis C RNA and hepatitis B core Antibody
- Dried Blood Spot card testing procedure (RA or self-administered)
- Blood samples to be shipped to an external lab

All labs will be reviewed by the study clinicians except for the DBS card and serum lab specimens collected for DBS validation, which will not be used for clinical decision making. The serum lab specimens collected for DBS validation will only be sent to Molecular Testing Laboratories for the purpose of DBS card validation and results will not be relayed to the participant.

Chart abstraction will be performed in order to collect basic demographic information. Past lab test results will also be abstracted in order for comparisons to be performed.

Phase 2 Procedures:

Pre-Screening Procedures:

The HCV rapid test will be optional. If participants self report a positive HCV test previously, they can enroll in the study by self-disclosure of +HCV. If their HCV status is unknown, a rapid test will be performed. If a positive rapid test in the past is reported, an optional rapid test can be completed as part of the study. People who test negative have the option to retest at 6 months. It is anticipated that a significant number of potential participants will screen negative for HCV. If a participant opts to have the HCV rapid test done, a positive result is an eligibility requirement for the study. Participants will be asked to sign a full consent form to indicate consent for rapid HCV testing, Inclusion/Exclusion check-list, and Locator Form completion—as well as the screening phase, randomization, and treatment arm interventions. Upon consent, establishment of baseline known positivity and treatment experience, peers or RAs will perform point of care HCV rapid antibody testing (OraQuick® HCV Rapid Antibody Test). (See figure 1: Telemedicine Study Flow Diagram). The HCV Rapid Antibody Test is a finger prick that can either be administered by study staff or self-administered, depending on participant and/or staff preference If it is decided that a self-administered test will be performed, participant will be given an instruction sheet on how to administer the test. Study staff will be present to answer questions and ensure the procedures are correctly followed. Study staff will assist participant in registering for Medicaid Accountable Care Organization (ACO), if needed and applicable.

Upon positive rapid HepC test, participants will be moved to the screening phase. Those with a negative rapid HepC test are not eligible for the study.

Peers and/or RAs will assist participants with reactive tests to go to a community laboratory for completion of one of four screening algorithms based on past treatment experience (see figures 2, 3)

Screening Procedures:

Participants with a positive HCV RNA will be accompanied to the lab for a serum lab draw and confirmatory lab draw ordered by the study clinician. Due to the health conditions that many participants are experiencing (dehydration, collapsed veins, etc.), it is likely that participants will need to return for a second confirmatory lab draw. Additional compensation will be provided if a second blood draw is needed. Research staff review screening survey and lab tests are entered into Child-Turcot-Pugh (CTP) calculator. Only participants with a CTP score of 6 or platelets < 150,000mm^3 will be referred for study clinician evaluation to confirm treatment eligibility; who will be blinded to treatment allocation until eligibility determined. All others will be fully screened by research assistant in the community. Once enrollment is confirmed, all participants will complete baseline surveys and randomization and then continue with treatment arm interventions as per Figure 1.

Central City Concern ONLY:
Participants with reactive antibody tests will also be offered participation in the hepatitis C and hepatitis B core antibody dried blood spot validation study, which would include performing a point of care dried blood spot test and completing confirmation serum HCV PCR and hepatitis B surface antibody testing. DBS specimens will be collected by peers and/or RAs and serum for confirmation by community partner laboratories. The DBS card will be shipped to Molecular Testing Laboratories for testing.

Allocation:

Participants are randomized using a centralized random number assignment for treatment allocation developed at OHSU and assigned through RedCap.

Intervention Design:
Central City Concern ONLY: Phase 1: Once in-house potential participants are identified they will be offered participation in the DBS study by IRB-trained CCC HCV team staff. Participants will provide a phlebotomy-derived blood sample and finger stick capillary blood sample for DBS card. These will be sent to MTL for DBS validation using standard human biohazard sample laboratory storage and shipping techniques consistent with MTL procedures. Incentives will be dispensed at the time of DBS sample collection or along with critical medications or services already provided, whichever method entails less on campus time for participants.

Phase 2:
Participants are randomized to peer-facilitated telehealth-HCV treatment intervention versus referral to local HCV treatment providers to initiate HCV treatment. After labs confirm preliminary eligibility, randomization will be generated by REDCap after baseline and consent. Participants with a CTP of 6 will connect with a study clinician over WebX to confirm eligibility. The participant is withdrawn if the study clinician deems ineligible. Local HCV treatment referral providers have treated at least one patient with HCV previously. They are encouraged to participate in the OHSU HCV ECHO tele-mentoring sessions, but are not study participants.

Study Arm 1: Tele-HCV Treatment Arm Procedures:

Participants allocated to telemedicine intervention arm are scheduled for treatment assessment by a study clinician. For a majority of participants, this will also be the treatment initiation visit. If additional studies are necessary for routine treatment decision making, peers will assist participants in navigating health system barriers and arrangement of second telemedicine visit. The telemedicine study clinician will perform a standard of care hepatitis C treatment initiation history and submit a prescription for DAAs. Prior authorizations will be completed by study clinician pharmacist.

All patients initiating treatment will be prescribed HCV medication treatment for 4 weeks at a time. The majority of patients will require two separate dispensations at week 0 and week 4 for a total of 8 weeks of medications, with a small subset requiring third, 4-week dispensation for a total of 12 weeks of therapy. The study clinical pharmacist will check in with the participant by telephone or telemedicine visit at week 0, week 4, and end of treatment to 1) determine general medication tolerance, 2) assess quality of adherence and 3) dispense medications by mail or ensure medications received, depending on participant's insurance. Peers will assist participants in keeping telehealth appointments and navigating medication pick up or storage, if not mailed directly to the home. Participants who report new onset of jaundice or other signs of hepatic decompensation during participation will be scheduled for a follow up telemedicine visit with a physician by the research assistant, receive repeat laboratory studies if needed, and if necessary, be referred to local providers for ongoing medical care. If problems or side effects arise during treatment, participants will call the research assistant, who will connect them to a study clinician.

HCV labs will be repeated at 12 weeks post end of treatment and results will be relayed to the participant in the SVR12 follow up visit with the research assistant, along with follow up surveys. Those successfully achieving SVR12 will be counseled on ongoing harm reduction methods. Those showing persistent HCV viremia at 12 weeks post treatment will be referred to community-based HCV treatment providers for treatment re-initiation. All will be scheduled for 36 week post end of treatment survey visit.

SVR12 labs will be collected 12 weeks post-treatment in community partner labs. Dried Blood Spot specimens will be once again collected at this point by research assistants at the point of SVR12 survey data collection.

Telehealth visits will be performed via the chosen web platform of the participant. This includes but is not limited to: Facebook, Facetime, Skype, Zoom, Webex, WeChat, etc. The treatment initiation visit, pharmacist adherence assessments, and SVR12 lab communication will all be documented in the electronic medical record using PHI and no study identifiers.

Study Arm 2: Community Linkage-To Care Arm (Control Condition) Procedures:

Participants allocated to the community linkage-to-care arm will complete screening, be offered enrollment, and undergo informed consent as in the telemedicine arm. Following study inclusion and enrollment, research staff will refer the participant to a local community health clinic to engage in hepatitis C care and seek treatment. Peers will assist patients to engage with local primary care and health plan resources and will receive an information sheet on optional clinics to attend and questions to ask their provider. TAU participants will be encouraged to take this to their visit. Research assistants will outreach to participants regularly to determine if they have engaged in local health resources and schedule assessment visits. A bidirectional release of information will be requested. The study clinical pharmacist or research assistant will assess adherence medication adherence at week 4 and end of treatment via telephone. SVR12 laboratory testing will be performed by the community provider with at least one telephone reminder prior to lab due date. 12 weeks post end of treatment study assessments will coincide with SVR12 lab results visit and 36 week post end of treatment assessments performed as in the telemedicine arm.

Chart abstraction for participants in both arms will be performed in order to assess the number of and types of interactions the peers have with participants.

In either arm, participants who do not initiate treatment by 12 weeks after randomization will begin their assessment timeline, mirroring treatment timeline for an 8-week direct acting antiviral regimen. For these participants, the study research assistant will collect study assessments at week 16 (corresponding to 4-week post-treatment initiation), week 20-22 (corresponding to end of treatment visit), week 32 (corresponding to 12 weeks post-treatment visit), and week 56 (corresponding to 36

weeks post-treatment visit) after randomization; the primary study outcome will be assessed at 32 weeks after randomization.

Participant Assessments:

Phase 1:

- Blood draw and DBS specimen collection for HCV RNA and Hepatitis B core antibody

Phase 2:

Assessment/Activity	**Pre-Screen**	**Screen**	**Baseline (Week 0)**	**4-Week after treatment initiation**	**End of Treatment**	**12-week Post-Treatment**	***36-Week Post Treatment Completion**	**As Needed**
Pre-Screening Survey	X							
Demographics		X						
Inclusion/Exclusion		X						
Rapid HCV Test	X							
CPT Assessment		X						
Participant Survey								
Medical Care History			X		X	X	***X	
Barriers to treatment			X		X	x	***x	
Engagement with Harm Reduction & Substance Use Treatment			X	X	X	X	***X	
Substance Use			X	X	X	X	***X	
Perceived Stigma of Drug Use			X	X	X	X	***X	
HCV Treatment History			X		X			
HCV Treatment Completion					X			
HCV Treatment Adherence				X	X			
Treatment Satisfaction					X			
Experience with Telemedicine					**X			
Experience with Peer Support Specialist					**X			
Blood Draw/ Medical Procedures								
HCV RNA		X				X		
Hepatitis B Sag		X						
Hepatitis B SAg		X						
Hepatitis B cAb		X						
Hepatitis A Ab		X						
CMP		X				X		

CBC		X				X		
INR/prothrombin		X						
HCV genotype		X						
B-HCG (women<50)		X						
SC Reviews Labs		X				X		
Ultrasound								**X
Telemedicine Visit			**X					
Medication Counseling			**X	**X	X*			
HCV Genotype and Resistance Testing								**X
Chart Abstraction					X	X		
Peer interaction log					X			
HCV treatment provider visits					X			
Administrative								
Written informed consent		X						
Locator Form	x		X	X	X	X		X
Master Enrollment Log			X					
Progress Note Check List	X	X	X	X	X	X	X	
Reportable Events Log								X
Adverse Event								X
Inventory Form								X
Visit Compensation Log	X		X	X	X	X	X	

***X: 36 Week Survey only if participant qualifies
**X: Only Telemedicine Pt.
*X: Number of weeks of treatment depends on ppt.

Participants complete brief REDCap surveys regarding symptoms, substance use, and harm reduction engagement at baseline, 4 weeks, end of treatment, 12 post end of treatment, and 36 weeks post end of treatment. These surveys will be conducted over the phone or in person.

Participants undergo phlebotomy at screening and 12 post end of treatment.

Study Measures:
The primary outcome is sustained viral response at 12 weeks post treatment (SVR12). Secondary outcomes include a) HCV treatment initiation, b) HCV Treatment completion (filled final prescription and self-reported > 90% HCV treatment pills taken), c) engagement with harm reduction resources, d) substance use, e) perceived stigma, and f) engagement in addiction treatment resources. Exploratory endpoints include a) treatment satisfaction with hepatitis C treatment, adapted from the single-item Medication Satisfaction Questionnaire, and b) reinfection vs. virologic relapse/failure.

Adherence to Phone Visits: Adherence to these phone visits is defined as +/- 5 days

Prescreen, baseline and follow-up surveys collected in the field or via phone will first be documented on paper forms. These will then be entered into REDCap by the RA. The source documents will be kept in a locked file cabinet in a secure location.

Qualitative interviews will be recorded on an encrypted recorder and stored on a secure, encrypted computer.

Survey data will be used to determine HCV status of participants with a detectable plasma HCV RNA, which were collected on or after SVR12 timepoint (either 12 weeks after end of treatment for those who initiated treatment or 32 weeks after randomization for those who did not initiate treatment). The primary SVR12 outcome will be sustained viral response 12 weeks after treatment for participants who initiated treatment within 6 months. Participants who did not start treatment within 6 months will be considered treatment failure. Measuring detectable plasma HCV RNA for both participants who initiated and did not initiated within 6 months of randomization will provide a framework to assess for potential biasing impact of spontaneous clearance on assumption of treatment failure for participants who did not initiate treatment within 6 months.

Probable Relapse/Failure: Probable virologic relapse or failure is defined as a detectable plasma HCV RNA 12 weeks or more after the end of treatment if a) participant denies any injection drug use, or b) participant injecting drugs but notes 100% adherence to recommendations on Safe injection practices, including use of clean works (cooker, cotton, rinse) with every injection.

Probable Reinfection: Probable reinfection is defined as a detectable plasma HCV RNA 12 weeks or more after the end of treatment if a) participant completes full course of DAA regimen, and b) participant notes injection behavior of substantial risk, including i) Receptive use of injection equipment (needles, cotton, cooker) from someone of either unknown HCV serostatus or known positive serostatus on one or more occasion and ii) use happened between end of treatment and HCV RNA test

Indeterminant Relapse vs Reinfection: Indeterminant virologic relapse vs reinfection is defined as a participant with a detectable plasma HCV RNA 12 weeks or more after the end of treatment in participants a) not completing DAA regimen, and b) with injection behavior of substantial risk, as noted above.

<u>Qualitative Interview Procedures:</u>
We will conduct qualitative interviews by telephone with a sample of purposively selected study participants. An interview guide will be used, and interviews will last approximately 45 minutes. Up to 35 interviews will be conducted by trained researchers. Participants will be reimbursed $50 for their participation. The participant qualitative interview guide will assess tele-HCV acceptability, satisfaction, perceived quality of care, advantages and disadvantages relative to face-to-face appointments, and barriers and facilitators to treatment initiation and adherence. Questions will also examine the role of peers in facilitating telemedicine, medication access, and adherence.

We will also conduct virtual focus groups with peer support specialists and tele-HCV clinicians. The peer support specialist focus group guide will assess tele-HCV and HCV treatment barriers and facilitators; peer specialist activities and adaptations; and advantages and disadvantages of tele-HCV. The clinician focus group guide will assess peer-assisted tele-HCV procedures; barriers and facilitators; experiences engaging with specialty pharmacies, payers, and peers; and clinical considerations related to tele-HCV.

Data and Specimens

a) Handling of Data and Specimens

Survey Data: Participants complete brief surveys regarding symptoms and substance use at baseline, 4, end of treatment, 12 weeks post-end of treatment, and 36 weeks post end of treatment**.** Survey data will be collected from PWUD by Research staff or PCCs, via 2-in-1 laptops or local office PCs or hand-held devices using REDCap data collection, detailed below (Privacy, Confidentiality, and Data Security).

Biologic Specimen Data: Biological specimen data will be stored at Peace Health, Mercy Medical, and Molecular Testing Labs. Serum samples drawn for DBS validation will be completed at Peace Health and Mercy Medical and shipped to Molecular Testing Labs.

Participant Locator Form Data: We will collect identifying information (name, social security number, date of birth, address, phone numbers, employer information, e-mail address, and other contact information) to use for follow-up of patient for future studies. The locator form also asks what forms of social media are commonly used and where the individual commonly spends most of their time. Participants will be contacted on social media using a highly-private account specific to the study. Index after the study is completed. Data will be collected on paper and the original will stored in a locked file cabinet at HIV Alliance for the duration of the study. Data will be abstracted into a spreadsheet in Box, maintained behind the OHSU firewall, for future use. Only HIV Alliance and OHSU will have access to this information.

b) Sharing of Results with Subjects

Results of HCV tests will be shared with the participant.

c) Data and Specimen Banking

De-identified specimens may be shared with other researchers, including the National Rural Opioids Initiative data coordinating center at University of Washington, Molecular Testing Labs, and other National Rural Opioids Initiative collaborators. This study does not include genetic research. Participant contact information (including name, date of birth, address, and Social Security Number) will be entered by study staff into a spreadsheet in OHSU BOX and stored behind the OHSU firewall. Participants who indicate willingness to be contacted for future studies in the consent form may be contacted and offered participation in future studies. Dr. Korthuis will serve as the guardian of this repository. Dr. Korthuis will ensure that data is received and released according to OHSU policy and the IRB approved repository protocol. A repository sharing agreement will be executed each time data is released for research purposes. Dr. Korthuis will track all releases of data. Should a participant withdraw their consent, Dr. Korthuis will indicate this in an additional spreadsheet that will be kept in OHSU BOX, and will ensure that the participant's data is destroyed. Participants from OR-HOPE indicate in the informed consent form whether or not they agree to future contact regarding participation in additional studies.

To certify documentation of local IRB approval to the OHSU IRB, a copy of the approval letter from the contributing site will be included in the submission to the repository. Consent to contact for future studies and to store data will be obtained from the participant when the participant signs the optional section of the informed consent form. To document whether the person from whom the data was obtained signed a legally effective consent and authorization, study staff will review the signatures and date from the original consent form and indicate the date that it was signed in the data collection spreadsheet.

To ensure security and confidentiality during the collection of data, only study staff will be entering data into the data collection spreadsheet in OHSU BOX. Only OHSU's PI and Research Assistant and HIV Alliance study staff will have access to the data in OHSU BOX. Only Dr. Korthuis will be able to grant access to the BOX files. A Certificate of Confidentiality will be obtained to further protect the sensitive information obtained from participants.

[redacted]Data Analysis:

Pre-specified analyses for this study will be intention-to-treat (ITT) comparisons between telemedicine and treatment as usual (local treatment referral) on primary and secondary outcomes. Prior to conducting these analyses, we will compare baseline covariate distributions (demographics, etc.) between randomized groups using standardized mean differences (SMDs) and bivariate statistical tests (e.g. t-tests, Chi-square tests). If a significant imbalance in any variable is noted, i.e., a SMD > 0.25 and $p < .2$, we will include that variable as a covariate in future analyses. All primary and secondary analyses will utilize generalized linear (mixed) models (GLMMs) with distributions and link functions appropriate for the distribution of the outcome variable. Fixed effects of interest in the models will be timepoint (baseline, 4 weeks, end of treatment, 12 weeks post-treatment, 36 weeks post-treatment), randomized group (telemedicine vs. TAU), and their interaction. If more than one timepoint is included in the analysis, GLMMs will include person-level random intercepts to account for repeated measurements on subjects. Hypotheses will be tested using between-group comparisons at each timepoint of interest, or within-group comparisons across timepoints.

Hypothesis 1: Participants randomized to receive tele-HCV treatment will have superior SVR-12 rates compared to those randomized to TAU (referral for local treatment).

Analytic strategy: We assess the effect of telemedicine versus TAU on SVR at 12 weeks post-treatment completion using logistic regression. Missing HCV viral load data will be considered non-suppressed in the main ITT analysis. Sensitivity analyses will include a per-protocol analysis and a repeat of the main analysis using multiple imputation of missing data.

Hypothesis 2: Participants randomized to receive tele-HCV treatment will have superior rates of HCV treatment initiation (filled first prescription) compared to those randomized to TAU.

Analytic strategy: We assess the effect of telemedicine versus TAU on treatment initiation by 4 weeks post-baseline using logistic regression. Missing treatment initiation data will be considered non-initiated in the main ITT analysis. Sensitivity analyses will include a per-protocol analysis and a repeat of the main analysis using multiple imputation of missing data.

Hypothesis 3: Participants randomized to receive tele-HCV treatment will have superior rates of HCV treatment completion (filled final prescription and self-reported > 90% HCV treatment pills taken) compared to those randomized to TAU.

Analytic strategy: We assess the effect of telemedicine versus TAU on treatment completion by 12 weeks post-baseline using logistic regression. Missing treatment completion data will be considered incomplete in the main ITT analysis. Sensitivity analyses will include a per-protocol analysis and a repeat of the main analysis using multiple imputation of missing data.

Hypothesis 4: Participants randomized to receive tele-HCV treatment will have a higher likelihood of engagement with harm reduction resources, lower rates of substance use, lower stigma, and higher engagement in addiction treatment resources compared to those randomized to TAU (referral for local treatment).

Analytic strategy: We assess the effect of telemedicine versus TAU on these outcomes at all post-baseline timepoints using mixed effects regression models. Missing outcome data will be handled using full information maximum likelihood. We will conduct per-protocol analyses as sensitivity analyses.

Qualitative Evaluation. Audio-recorded interviews will be professionally transcribed; transcripts will be uploaded into qualitative analysis software (NVivo™). Comagine research staff create a coding scheme, conduct coding, and revise in an iterative process that has been successfully implemented by the study team in other mixed-methods projects. The qualitative data provides complementary information to illuminate and expand quantitative findings, including survey results and measures of treatment initiation and completion.

Privacy, Confidentiality and Data Security

Our study procedures reflect high levels of protection for subjects.

Training will include time for direct communication of specific roles. HIV Alliance oversees PCC hiring, support, and intervention implementation at in participating counties. Study site visits will be a critical aspect of study success. OHSU research staff will visit PCC field sites at least quarterly support implementation and review data collection.

Data will be stored in a manner intended to preserve patient confidentiality. Consent forms and all PHI will be stored in locked cabinets and on password protected, secure computers. Only study team members will have access to data on secured computers. Participant hard-copy survey data will be stored only at study sites in a locked cabinet until study conclusion. Survey data will be identified only with a unique randomly generated identifier. The identifier will be used instead of subject names or medical record numbers and will not contain any part of the 18 HIPAA identifiers. The file linking the unique identifier with the patient's name will be stored in a separate password-protected file on a secure computer at study sites. Only the study site and overall Study Coordinator, and OHSU PI (Todd Korthuis) will have access to the linked file. Survey data will be entered in the secure OHSU REDCap system by study staff, and study team members. Site and OHSU study staff will have access to the de-identified data in REDCap. No identifiable information will be emailed between investigators. Data are coded before any transfer. De-identified data may be shared following data lock with the national rural opioids initiative data coordinating center at University of Washington.

Survey data will be collected using OHSU's instance of REDCap. Access to the database will be limited to OHSU IRB-approved study staff that are approved to contact or interact with participants. REDCap is a secure, customizable, web-based application for building and managing databases (see https://octri.ohsu.edu/redcap/index.php). REDCap resides on a server housed in ITG's Advanced Computing Center (ACC) and is maintained by developers in the Oregon Clinical and Translational Research Institute (OCTRI) in accordance with all relevant OHSU policies and guidelines. Additionally, ACC employs a second firewall within the OHSU network to attain a high level of security and access control. In situations when a secure WiFi connection is not available for REDCap data collection, REDCap Mobile App will be used as an offline data collection means until a WiFi connection is available to securely transmit data to the main REDCap database. REDCap Mobile App database is encrypted on the mobile device's hard drive using SQLCipher to prevent someone from breaking into the file in the event of a stolen device. The REDCap Mobile App will be used on an encrypted laptop/tablet purchased through ITG. REDCap Mobile App with reviewed and approved by ITG Security Engineering group prior to implementation. As a back-up, we may need to collect data using paper surveys and then entering data into REDCap when an internet connection becomes available. If paper surveys are used, those files will be held in a locked case, and stored in locked cabinet in a locked office to securely handle these data.

Qualitative Data. Interviews will be digitally audio-recorded and professionally transcribed and transcripts will be uploaded into qualitative analysis software (NVivo) by Comagine study team members. Recordings will be destroyed following analysis. Qualitative interview data will be stored at Comagine on secure servers in password-protected files, accessible only to researchers and subject to Comagine's policy on safeguarding electronic data. Study documents and audio recordings will not contain any identifiable information, but instead will be assigned a unique study identifier. The list linking participants to their unique identifier will be password-protected and maintained within the study's secure REDCap database.

All study personnel will complete on-line training in appropriate conduct of research through the OHSU IRB, or equivalent training. The Institutional Review Board of Oregon Health & Science University has policies in place that meet the requirements of 45 CFR 46, Subpart C. The Board

reviews all protocols that involve prisoners; does not permit waivers of consent for subjects who are prisoners; requires OHRP certification once IRB approval is granted; and includes a prisoner representative on the Board during consideration of prison-related proposals, continuing reviews, and amendments. The research protocol will also adhere to the federal policies for protection for children involved as subjects in research (45 CFR 46, Subpart D). The proposed research complies with the Additional Protocol Requirements of 45 CFR 46, Subpart A. The research will be on a condition (substance use disorder) that particularly affects children age 13-21.

[redacted]Risks and Benefits

a) Risks to Subjects

Risk of Underlying Conditions: As the study population will have significant ongoing health and substance use issues, events related to complications of HCV and substance use may occur, including admission for substance use detoxification and treatment, hospitalizations for medical and psychological complications, and death. These events will be captured on study specific forms.

Risks to Confidentiality: There are also risks to confidentiality, particularly because we collect information about substance use. There is also a risk to confidentiality when using telehealth due to the internet and Wi-Fi use.

Phlebotomy Risks: Blood drawing for confirmatory testing may cause pain or bruising at the site and carries a small risk of infection.

Telemedicine Risks: Telemedicine participants may be less likely to engage in other primary care services than peer-assisted primary care intervention arm.

b) Potential Benefits to Subjects

Subjects may benefit from participation in the proposed study by being diagnosed with HCV and offered assistance in enrolling with health insurance, and harm reduction services during screening. Subjects who are diagnosed with hepatitis C may also benefit by gaining access to treatment and cure in a region with little current treatment access.