University of Cincinnati
Institutional Review Board-Social and Behavioral Sciences (IRBS-S) Protocol

TITLE: Southern Ohio Prevents Hepatitis (StOPHeP) Study Protocol

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Sponsor: Centers for Disease Control and Prevention

I. PURPOSE/GENERAL STUDY INFORMATION

a. Background:

Approximately 2.7 million U.S. residents in the population sampled by the National Health and Nutrition Examination Survey (NHANES) have chronic hepatitis C (HCV) infection (Denniston et al. 2014), with national estimates ranging from 3.5 to 5.3 million. HCV is associated with increased morbidity and mortality. Persons with HCV are at risk for developing cirrhosis and hepatocellular carcinoma (HCC), both of which can lead to end-stage liver disease (ESLD) and liver failure. HCV is the primary reason for liver transplantation in the U.S. and HCV is the fastest growing cause of cancer-related deaths (El-Serag 2012). A study of mortality records from 1999 to 2007 found that hepatitis mortality exceeded HIV-related mortality (Lyn et al. 2012) by 2007. In the CDC's Chronic HCV Cohort Study (n=1,590), the mean age of death was 59 years old, which is 15 years younger than the average age at death in the general population, and the mortality rate among HCV-infected persons was 12 times higher than the age-adjusted rate for all-cause mortality. Not only does HCV have a considerable human cost, it also represents a considerable drain on the U.S. healthcare system, with 5-fold higher annual healthcare costs than those for other patients (El-Serag 2012).

Injection drug use (IDU) is the leading transmission mode of HCV in the U.S. (CDC 2011), with young persons who inject drugs (PWID) representing the fastest growing group at risk (OHAIDP & HHS 2014). There is now a new national epidemic of opioid IDU, and the growing rate of PWID is intimately tied to the abuse of prescription opioids and the epidemic of drug overdose deaths. Many individuals—particularly those in suburban and rural areas-- initiated IDU through misuse of prescription opioids (Havens et al. 2007), while others who are no longer able to find or afford prescription opioids are transitioning to heroin. The factors that drive the transition from oral to intravenous use and from prescription opioids to heroin are not well understood and are certainly influenced by the availability of heroin which can be less expensive than illicitly obtained prescription opioids. Among addiction treatment-seeking patients with opioid dependence, approximately 41.7%-81.1% have chronic viral hepatitis (Jimenez-Trevino et al. 2011; Hser et al. 2006). Among PWID who recently were diagnosed with HCV, excluding those remaining seronegative, a linear 10% decrease in heroin and cocaine IDU was seen in each additional 3-month follow-up period over several years (Bruneau et al. 2014); this demonstrated that knowledge of hepatitis serostatus can result in reduction in IDU and changes in drug use behaviors. However, HCV reinfection and superinfection were seen in 39% of active IDUs in Amsterdam (van de Larr et al. 2009), illustrating the infectious consequences of continued IDU. Without access to diagnosis and treatment of chronic HCV and without measures to prevent acute HCV among susceptible PWID, their morbidity and mortality rates will only continue to increase.

In terms of the "HCV continuum of care" for testing and treatment, the following grim data from surveys and observational cohort studies in the U.S. reveal that only 50% of the 3.5-5.3 million estimated to be chronically-infected have been tested (OHAIDP & HHS 2014); only 32%-38% have been referred for care; only 7%-11% have actually been treated; and only 5%-6% have been cured (although it should be noted that these data come from the interferon-based treatment era) (Holmberg et al. 2013). The primary reason patients do not seek HCV treatment is because of lack of knowledge of their serostatus; secondary reasons include concerns about treatment side effects and having no symptoms (Edlin et al. 2005). In the new era of all-oral, specific antiviral treatment for HCV, many studies have shown that patients with genotype I, the predominant

strain in the U.S. and the hardest to treat, have achieved cure rates in excess of 90% (Ahal 2014, Kowdley 2014). This success rate emphasizes the urgent need to increase the currently low numbers of HCV-infected individuals who are diagnosed and then successfully linked to care, treated, and cured.

Insufficient Routine Screening & Medical Education. Underdiagnosis of HCV, despite the CDC and U.S. Preventive Services Task Force recommendations to test all the "baby boomers" born between 1945-1965 and at-risk populations such as PWID, is a significant problem because of low awareness among both patient and provider populations about the risk factors for HCV. Many organizations that provide services to PWID, like addiction treatment programs, may not routinely test for HCV or actively try to link patients with appropriate HCV treatment providers. Moreover, healthcare providers may not be aware of how to distinguish between cleared infection that occurs spontaneously in ~15-20% of those infected, and chronic infection, which requires a 6 month interval from the first positive HCV antibody test to a confirmatory test and evidence of active viral replication as detected by the quantitative RNA polymerase chain reaction (PCR). So failure to diagnose is one significant obstacle.

Financial Barriers. While we have seen amazing advances in pharmacotherapies to treat HCV, access to these new, costly medications may thwart efforts to reduce population-level consequences of HCV. Persons that are known to be at risk for HCV may not have health insurance and may not know how to access free testing available at local health departments, which is likely to be true in the southern Ohio counties targeted in this epidemiologic study. The availability of services such as testing for HCV, HBV and HIV and provision of HBV vaccine through public health departments varies from county to county in Ohio, adding another layer of complexity for referral and linkage to care. Access to treatment-- which remains very expensive-- has been limited by lack of insurance coverage that only now may be rectified by access provided by the Affordable Care Act (ACA) and the expansion of Medicaid in Ohio. While the Centers for Medicare and Medicaid Services (CMS) will now pay for a HCV screening test for adults at high risk for infection, with "high risk" defined as persons with a current or past history of IDU, a history of receiving a blood transfusion prior to 1992, and those who were born from 1945 through 1965. Retesting is covered annually only for persons who have had continued IDU since the prior negative screening test (CMS 2014). Moreover, it remains to be seen whether insurance obtained through the ACA will pay for the expensive medications to treat HCV which are estimated to be ~$150,000 for a 12 week course of 2 DAAs plus monitoring that will lead to cure, such as sofosbuvir plus simeprevir (Lawitz 2014, Sulkowski 2014).

Accessibility of HCV Prevention and Treatment Services. Even among those who are correctly diagnosed, a minority are referred to HCV care and an even smaller proportion are begun on combination antiviral therapy. There are fewer than 300 hepatologists in the U.S. and few gastroenterologists showed great interest in managing HCV in the era of interferon/ribavirin-based treatment. Some providers may be reluctant to treat PWID because of concerns regarding reinfection and medication adherence (Aspinall et al. 2013). However a recent meta-analysis found that PWID can be effectively treated for HCV (Aspinall et al. 2013), and another meta-analysis found that 83.4% of drug users successfully completed HCV treatment (Dimova et al. 2013). Increasingly, the treatment of HCV does not require liver biopsy, and the risk-benefit ratio for interferon-sparing therapies favors early treatment, rather than waiting for disease progression to justify these expensive regimens. As treatment is rapidly evolving toward all-oral regimens that are well-tolerated, more infectious disease physicians and generalists are beginning to manage HCV, although that is a fairly recent development. The management of HCV now increasingly depends on the physician's experience and comfort with genotyping, the potential need for viral resistance testing, and monitoring outcomes based on HCV RNA PCR (viral load) measurements, parallel to the current management of HIV. However, access to medical specialists, particularly those with experience in treating hepatitis, is limited in rural areas and may seriously impede public health initiatives in these areas. It is particularly important to provide linkage to care in rural areas, as nearly all of our partner organizations have reported challenges in linking PWID with HCV treatment. This proposal addresses this barrier by providing PNs to not only assist with scheduling referrals, but also to actively link participants with HCV care; this will be accomplished by partnering with existing case

management services and by employing social media to support and educate participants and help them problem-solve around perceived obstacles.

Stigma. Obtaining the appropriate referrals and navigating the intricacies of the complex healthcare system-- especially for marginalized populations such as the uninsured, individuals of low socioeconomic status, members of populations with health disparities (including those residing in Appalachia), and PWID—present additional hurdles to access and linkage to care, contributing to the "treatment gap" for HCV. PWID may be discriminated against or treated poorly in the health care system by providers (Crawford & Bath 2013) that perceive addiction as a moral failing, rather than a chronic medical disease. Patients may be blamed for their risky behaviors that made them vulnerable to hepatitis or HIV, and this, combined with low self-efficacy and/or self-worth, further exacerbates limited access to medical care. Peer navigators are thought to improve linkage to care because they have the lived experienced of drug addiction and are more likely to treat patients with respect, dignity and empathy.

Fragmented Care. PWID frequently need services from a variety of organizations including addiction treatment programs, harm reduction programs (syringe exchange, naloxone for overdoses), medical care, mental health care, and social services. These services are infrequently co-located or even coherently presented to patients as a comprehensive set of services. Providers, particularly in rural areas, may refer PWID to programs providing hepatitis prevention services and treatment but do not actively link patients with these services that are vital to decreasing HCV transmission among PWID. Many PWID lack adequate linkage with medical care providers in general, and research has demonstrated that integrated addiction and medical care improves outcomes (Weisner et al. 2001). Changes due to the ACA are increasing opportunities to address the medical consequences associated with IDU by expanding reimbursement for addiction services into general medical practice that lie outside of the addiction specialty treatment system (Buck 2011). Timing is critical, given the recent start of the ACA and the escalating opioid epidemic across the U.S., to improve identification of PWID who need to be tested for HCV and referred to prevention and treatment services. In addition, it is crucial that interventions improve linkage to care that is not only focused on access to addiction treatment, but to the full spectrum of preventive services and treatment such as: 1) testing and treatment for HIV and viral hepatitis, 2) overdose prevention education and access to nasal naloxone to prevent fatalities, 3) syringe exchange programs to limit acquisition of HIV and hepatitis B and C, 4) mental health services, and 5) primary and specialty (infectious diseases, hepatology) medical care (Bruggmann & Litwin 2013). Our study incorporates a comprehensive and integrated strategy to detect, test and link PWID with prevention and treatment services.

Significance: As the opioid epidemic continues to ravage non-urban areas in this region, young adults are at very high risk of HCV. There is an urgent need to better define this population in terms of demographic characteristics, risk behaviors, and social networks; to prevent infection; and to link infected individuals to appropriate medical care. In southern Ohio, HCV has become a significant public health problem. Recently released data from the Ohio Department Health found that the overall HCV rate in 2012 was 87.5 cases per 100,000 population, which is significantly higher than the 2011 national HCV rate of 0.4 cases per 100,000. However, suburban and rural counties in southern Ohio have significantly higher rates of HCV compared to urban counties and to Ohio as a whole. Even more striking is the fact that the HCV rates are highest in southern Ohio's Appalachian counties. In fact, the rate of HCV in Scioto County (classified as both Appalachian and rural) is 376% higher than in Hamilton County (where Cincinnati is located), and 653% higher than in Cuyahoga County (where Cleveland is located). The high HCV rates In southern Ohio are believed to be associated with the opioid epidemic and injection drug use.

Counties across southern Ohio, Scioto County in particular, also have some of the highest rates of overdose deaths (and prescription opioid trafficking) in the entire country (Winstanley et al. 2012). The Ohio Department of Health has estimated that the annual state-level cost of fatal and non-fatal drug poisoning is $3.7 billion, which was almost half of Ohio's 2011 state budget deficit (Winstanley et al. 2012). Not only does southern Ohio have high rates of opioid misuse, dependence and IDU, it is now one of the few states with SEPs that primarily serve suburban and rural PWID with one located in Portsmouth (Scioto County) since 2011, and

one located in Hamilton County since 2014. Most of the existing research on comprehensive HCV prevention and treatment for PWID (Bruggmann & Litwin 2013) are based on methadone treatment programs. Methadone treatment programs are ideal locations to address HCV because they have frequent, often daily contact with clients; however, they are infrequently found in suburban or rural areas. While southern Ohio has seen drastically increasing rates of opioid addiction over the past decade, it has been very challenging to open a methadone program in these areas, in part because of the significant federal regulations that must be met to obtain "Opioid Treatment Program (OTP)" designation in order to dispense methadone. While southeast Ohio has recently seen two addiction treatment programs be designated as federally-recognized OTPs (Health Recovery Services, a recruitment site in this study, is one), neither program has received sufficient community support to start dispensing methadone. The targeted counties for this study in southern Ohio have also been recognized has having the poorest health in the entire state. Among Ohio's 88 counties, 18 of our target 21 counties rank in the bottom half of Ohio's "County Health Factors Rank" and 7 rank among the lowest 9 (#80-88).

Purpose : The overall goal of this study is to gain a clearer epidemiologic picture of young PWID with or at risk for HCV, and to develop an integrated comprehensive approach for detection, prevention and linkage to care for PWID with HCV among young PWIDs who reside in suburban and rural areas in southern Ohio, as well as is the adjacent areas of Kentucky and West Virginia, which have very similar social and economic characteristics. We will accomplish this by collaborating with addiction treatment providers, public health agencies, and syringe exchange programs in the target areas to identify, test, refer and link PWID to a range of prevention and treatment services. The goal of this study is consistent with the recently released National Action Report on Viral Hepatitis that recommends improving awareness of HCV serostatus among infected individuals from 45% to 65%(OHAIDP & HHS 2014).

a. **Specific Aims.** The specific aims are consistent with the CDC funding requirements and are listed below.
   i. **Aim 1**: Identify and describe the demographic characteristics and risk behaviors of young (18-30 years old) non-urban PWID in the target area, and test participants for HCV, hepatitis B (HBV) and HIV.
   ii. **Aim 2**: Improve linkage rates to addiction treatment, primary care, mental health and specialty treatment (infectious diseases, hepatology) for young non-urban PWID through the use of Peer Navigators.
   iii. **Aim 3**: Provide education on safe injection practices and referrals to syringe exchange programs to young non-urban persons who are actively injecting to prevent the spread of viral hepatitis and HIV.
   iv. **Aim 4**: Use a closed social networking site (SNS) to provide peer-facilitated support for the uninfected prevention group ("Prevention Room") and for the linkage-to-care group for PWID with HBV, HCV and/or HIV infection ("Treatment Room"), available both online and via smartphone.
   v. **Aim 5**: Perform follow-up assessment and re-testing of study participants for HCV within 12 months of enrollment to determine rates of new and chronic HCV infection and HCV reinfection among PWID who are treated and cured.

b. **STUDY DURATION**

Target Recruitment: A total of 400 people will take part in this study at study sites across southern Ohio.
Study Duration. Each subject will be in the study for one year. There will be a total of 5 study visits: consent/enrollment/baseline, and every 3 months thereafter (months 3, 6, 9, 12).

II. FUNDING

a. Sponsor:
This study is funded as a cooperative agreement by the Centers for Disease Control and Prevention (CDC). The CDC has funded a second research site, at the University of New Mexico, and we will be closely with both the CDC and the University of New Mexico (UNM).

b. Role of the Sponsor: As a cooperative agreement, the CDC will be taking an active role in the development, execution, data analysis and dissemination of the study findings. This funding mechanism requires that we have uniform data collection with the University of New Mexico site. The CDC requires that our data be shared with UNM investigators and CDC staff, with the intent of combining data from both sites for the primary analyses.

III. FACILITIES

The majority of study team members will be located at the University of Cincinnati in either the College of Medicine (Holmes, Infectious Diseases) or the College of Pharmacy (Health Professions Building).

a. This study will recruit participants from the following sites:
   i. The Cincinnati Exchange Project (mobile van with various locations)
   ii. City of Portsmouth Health Department syringe exchange program (Portsmouth, OH)
   iii. Northland Treatment Center (Milford, OH)
   iv. Health Recovery Services (Athens & Jackson, OH)

IV. RESEARCH TEAM

The UC-based study team consists of the Principal Investigator (Dr. Judith Feinberg), Co-Investigator (Dr. Erin Winstanley), Project Coordinator (Amanda Stover), Peer Navigator Coordinator (Elizabeth Harrison) and a Peer Navigator to be located in Portsmouth. The non-UC based study team includes representatives of each of the recruitment sites (Joe Gay PhD from Health Recovery Services, Lisa Roberts RN from Portsmouth Health Department. and Shawn Ryan MD at Northland Treatment Center). A third Peer Navigator will be hired under the Health Services Recovery subcontract. All study team members will be required to complete CITI training.

Peer Navigators: This project will utilize Peer Navigators (PNs) to screen participants, obtain written informed consent and collect baseline epidemiological data and blood samples for hepatitis and HIV serologies. The PNs will ideally be young to middle-aged adults with lived experience of IDU or drug use, have at least two years in recovery, and who come from the same rural or suburban population, depending on the recruitment site. These characteristics reflect our preferences and we realize that we may not be able to successfully recruitment persons that meet all of these requirements, hence we will emphasize hiring persons who have the lived experience of addiction and experience working with stigmatized patient populations such as HIV or serious mental illness. All the PNs, except the one hired by Health Recovery Services, will be UC employees and therefore they will be subject to university hiring policies, training, and employee conduct standards. We anticipate working with UC Human Resources to determine our ability to randomly drug-test PNs as permitted by UC policies. PNs will be trained in research methods by Drs. Feinberg and Winstanley, and will complete all UC-required CITI and Biohazard training. The PNs will also receive specific training about HCV so they can educate their study subjects on prevention of disease acquisition and prevention of transmission and reinfection. The PNs will make available a list of local area referrals (for medical and mental health care, drug treatment programs, social services, etc) to participants as requested. They will be responsible for the following study activities: 1) identification and enrollment of the target population; 2) provision of hepatitis and HIV prevention education including safe injection and safe sex practices; 3) facilitation of linkage to needed services, including primary care and specialty treatment (infectious diseases, hepatology), behavioral health treatment, syringe exchange programs, and ancillary social services; 4) provision of peer-facilitated support to HCV-uninfected and -infected study participants via a closed social networking site (SNS), and; 5) performance of follow-up assessment and re-testing to determine rates of HCV reinfection if cured or spontaneously cleared and chronic HCV infection. The PNs will be supervised by Elizabeth Harrison, who currently works for the Cincinnati Exchange Project, and has significant experience both working this population and knowledge of federally-funded research study requirements.

PNs will work with subjects to ensure linkage with comprehensive services (addiction treatment, syringe exchange, safe injection practices education, hepatitis and HIV prevention education and treatment)

in collaboration with local agencies. PNs will help subjects with potential barriers to services, including assistance with enrollment in the Affordable Care Act and expanded Medicaid as appropriate, and will assist subjects in navigating the complex maze of potential services: addiction treatment, mental health care, general medical care, hepatitis B vaccination, and chronic HCV treatment. Obstacles to care will be recorded. All referrals to medical care, mental health care and social services will be offered using a patient-centered model. The proposed PN intervention is novel because it 1) adapts the data on peer/patient navigators from cancer care for application to the significant and growing IDU epidemic, 2) is patient-centered, 3) uses true peers (similar age and past history of IDU) to provide education, referrals and linkage to care assistance, and 4) permits ongoing interaction with participants using a closed SNS, texting and email to create a virtual support group for young PWID in isolated rural environments, which should also help retention for follow-up. The closed SNS will include access to online hepatitis prevention and treatment resources, and discussions moderated by the PNs and clinical experts; importantly, it will provide subjects with sustained connection to their PN, to one another, and to the study. In addition to delineating the epidemiology of IDU in southern Ohio, the primary outcome goal is to increase the proportion of young non-urban PWID who are aware of their hepatitis C serostatus by an absolute margin of 20%, the goal set by the 2014 National Action Report on Viral Hepatitis. Other outcomes include: 1) identification of risk factors for young PWID, by collecting demographic data and tracking injection networks; 2) rates of referral and linkage to addiction treatment and treatment for chronic viral infections; 3) prevention of new HCV infections; 4) the impact of peer support through social media on rates of retention both in the study and in care; and 5) the rate of new HCV infection and HCV reinfection after cure or spontaneous clearance These are important results that are relevant to patients, clinicians, and society.

V. PARTICIPANTS

a. Eligibility:

Persons eligible for the study must meet the following criteria:

1) 18-30 years old
2) injection drug use within the last 12 months
3) resident of a suburban or urban county in Ohio, Kentucky or West Virginia as defined per CDC funding requirements using the National Center for Health Statistics Urban-Rural Classification Scheme for Counties
4) able to give written informed consent
5) willing to provide blood samples for virological testing
6) English-speaking
7) unlikely to be sentenced to jail or prison within 90 days of study entry.

b. Recruitment

Subjects will be recruited from 1) Health Recovery Services (addiction treatment) in Athens and Jackson; 2) Portsmouth Health Department's syringe exchange program; 3) Cincinnati Exchange Project (syringe exchange program) and 4) Northland Treatment Center (addiction treatment) in Milford. Potential participants may be identified by staff at the recruitment sites, may be referred from other treatment programs and public health agencies, or may be self-referred. Young PWID who reside in adjacent Kentucky or West Virginia counties may participate if they are willing to travel to one of the Ohio recruitment sites. Information about the study will be posted at the recruitment sites, drug treatment programs, public health agencies, community support programs, naloxone distribution programs and associated websites and social media outlets. To characterize the social networks of PWID, we will conduct 2 'waves' of respondent driven sampling. Initial participants ("seeds") will each be given 3 study recruitment cards and asked to give the cards to 3 persons ("wave 1") in their social networks with whom they either inject drugs and/or have had a sexual relationship

with in the past 12 months. Subjects recruited as part of "wave 1" will also asked to recruit 3 of their social network members (meeting the same requirements as wave 1) and this would comprise "wave 2."

c. **Consent Process**

Study staff or the PNs will explain the study to potential participants in detail and will review the consent form page by page.

VI. Participant Contact/Monitoring.

Contact Information. The PN will ask each subject what is their preferred way to communicate regarding: 1) accessing prevention and treatment services, and 2) to schedule follow-up study visits. **The study team may use phones, email, text messaging, reminder letters, and social media to communicate with subjects**. Sensitive information, such as drug use and infectious diseases testing results, will not be communicated via text message or using social media. The study team will only communicate sensitive information either in-person, over the phone or by using encrypted email. The study team members and the subjects will receive training on secured forms of communication and how to protect their information online. Subjects will also be asked to provide contact information for 2 people who will know how to get in touch with them.

Social Networking Site (SNS). NING will be used as a platform for a closed social networking site. NING is similar to Facebook and has many of the same features such as a "wall" on which users posts are viewed, instant private messaging, user profile page, groups, and events. NING can be used to create a closed (requiring a username & password) or open (publically accessible) SNS. The StOPHeP SNS will be set up as a closed social network and access will controlled by the study coordinator. Google is not allowed to "crawl" any of NING pages for content nor does it appear in a standard web-based search. Dr. Winstanley has experience using NING for a closed SNS that is being used to enhance engagement and retention in an addiction treatment program site in North Dakota, funded by the Substance Abuse and Mental Health Services Administration. As part of study enrollment, subjects will be provided with information regarding the StOPHeP SNS and given instructions on how to access the site, as well as how to protect their information online. For example, subjects will be required to set-up their username using an alias or only their first name and that they do **not** use pictures that would identify themselves. The StOPHeP SNS will be facilitated by the study team and it will include content generated by study team members and study subjects. Study team members may use the closed SNS to disseminate HCV prevention and treatment education, as well as other information relevant to subjects. Similar to Facebook, subjects can "choose" to friend other members on the StOPHeP SNS and friends' activity appears as a newsfeed on the wall. Participants will be assigned to the "prevention room" if they are not HCV-infected, or to the "treatment room" if they already have HCV at study entry or acquire it during the course of the study, as the emphasis on HCV education will vary by subjects' serostatus. Study staff, including the PI, Co-I and project manager will also participate in the StOPHEP closed social network in order to monitor the accuracy of information transmitted (QA) and to answer questions outside the PNs' knowledge base and training. Referrals to drug treatment programs, general medical care, HCV-specific care and other services will also be available from the PN in consultation with the study staff and staff at the recruitment sites. Additionally, a Facebook community page (Stophep which is not yet "live") and Twitter account (@STOPHEP) will be used to disseminate general information regarding hepatitis, HIV and information on StOPHeP. The Facebook and Twitter accounts may be used to maintain contact with study participations, however only non-sensitive information will be communicated in this manner; only private messaging will be used to remind subjects to call to schedule a study visit.

Information Tracking. The study Research Assistants and Peer Navigators will track participants using a REDCap database. Additionally, call logs may be used to track follow-up assessments. Call logs will be stored on an encryptedUSB drive; which will be kept in a locked file cabinet in a locked office at UC. Paper copies of tracking information will be also kept in a locked file cabinet in a locked office.

a. **Payment**

Participants will receive a $10 gift card for each study visit they complete, as well as a $10 gift card for each member of their social network that enrolls in the study. The maximum amount of payment per subject for the seeds and wave 1 is $80 [(5 study visits at $10 each=$50) + (3 social network members enrolled at $10 each =$30)]. Subjects recruited as part of wave 2 will only be eligible to receive a maximum of $50.

VII. RESEARCH RELATED ACTIVITIES

Data Collection. The survey instruments will be collected in a face-to-face interview conducted by the PN or another study team member and will enter the subjects' responses directly into REDCap. If for any reason there are Internet problems in accessing the REDCap database, the responses will be recorded onto a paper copy of the instrument and transported in a locked box to UC for data entry and secure storage. The data we will collect includes sociodemographic information; behavioral and medical risk factors associated with injection drug use (for both the subject and their social network members); history of testing and/or treatment for HCV, hepatitis B, and HIV; history and treatment for mental health and substance abuse problems; drug use and injection histories; general and sexual health; knowledge of HCV prevention and treatment services; and barriers to accessing behavioral and medical services. The follow-up assessments will be conducted in person, every three months, and cover the same domains as in the baseline instrument.

Study Procedures. After obtaining written informed consent, subjects will complete the study survey by interview (approximately one hour) and asked to provide a blood sample. All subsequent study visits will take place at the recruitment site unless other arrangements are made to meet at another location. At each of the 5 study visits, two tubes of venous blood (15 ml each) will be obtained over the course of the one-year study period. Virologic laboratory testing will be done on one of the two tubes of blood taken at study visits and the second tube will be stored at the UC Retrovirology Reference Laboratory (Director, Dr. Feinberg) for future analysis.

Laboratory Testing/Analysis. Subjects will be tested for HIV, hepatitis c and hepatitis b at baseline and every subsequent follow-up visit. Some of the testing will be conducted through this research project and/or via other means. For example, Northland Treatment Center routinely conducts HIV, hepatitis c and hepatitis b testing as part of their routine clinical practice for new patients. Rather than re-testing subjects, we will extract the test results from the subject's medical record at Northland Treatment Center – provided that they have signed the informed consent document and the release of information form. Similarly, some subjects may be able to receive free testing from their local health departments and we will request those testing results. For subjects who have not undergone a recent test as part of their standard clinical care, we will conduct those tests as part of their study participation. Routine serologic testing will be conducted by Quest, a national commercial laboratory. Laboratory reports will be sent directly to Dr. Feinberg and the PN Coordinator, Ms. Elizabeth Harrison, in the Infectious Diseases research offices in Holmes Hospital. Results will be communicated to the PNs by encrypted email and they will share results with the study participant as described above.

VIII. STATISTICAL ANALYSIS

a. Power Analysis.

The power analysis used the baseline awareness of HCV status of 31.2%, which is based on the Havens and colleagues (2012) study conducted in rural Kentucky and assumes a 20% absolute increase in knowledge. With 0.80 power and alpha=0.05, a sample size of 204 will be adequately powered to detect that difference. We then doubled the sample size in order to ensure that we would be adequately powered to separately measure a 20% absolute increase in HCV awareness in both the suburban and rural participants. Therefore we determined that a sample size of 400 will ensure that there is both adequate power to address the primary outcome with a potential 20% loss to follow-up, as well as to facilitate sub-group analyses (e.g., determining differences in risk factors for injecting prescription opioids versus heroin).

b. Data Analysis.

The data analysis will be conducted using StataSE ver. 13 (Stata Corporation, College Station, TX). Descriptive statistics will be used to compare study participants based on recruitment site and whether they reside in a suburban or rural county, or within a micropolitan area (defined as a population of at least 10,000) of a rural county. Multivariable logistic regression will be used to identify risk factors associated comorbid diseases related to IDU. The results will be presented as odds ratios and will control for known risk factors. It is anticipated that the risk factors may vary by recruitment site (addiction treatment program versus syringe exchange program), whether the participant was currently injecting or was abstinent at baseline, and geographic area (suburban, micropolitan, rural); hence we will determine whether separate regression equations need to be generated. Per the cooperative agreement requirements, the data will be securely transported to the CDC for additional analysis.