Community-based, client-centered prevention homes to address the rural opioid epidemic

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Study Protocol

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ABBREVIATIONS

ACASI	Audio computer-assisted self-interview
ARCW	Aids Resource Center of Wisconsin
DCC	Data coordinating center
DSMP/B	Data safety monitoring plan/board
HCV	Hepatitis C virus
HIV	Human immunodeficiency virus
MAT	Medication-assisted treatment
OBBT	Office-based buprenorphine treatment
PN	Prevention Navigator
PS	Prevention Specialist
PWID	People who inject drugs
RDS	Respondent driven sampling
ROI	Rural Opioid Initiative
SSP	Syringe service programs
STI	Sexually transmitted infection
UW	University of Wisconsin
WEDSS	Wisconsin Electronic Disease Surveillance System
WI DHS	Wisconsin Department of Health Services
WSLH	Wisconsin State Laboratory of Hygiene

STUDY SUMMARY

In response to RFA-DA-17-014, HIV, HCV and Related Comorbidities in Rural Communities Affected by Opioid Injection Drug Epidemics in the United States: Building Systems for Prevention, Treatment and Control (UG3/UH3), our research team has proposed a multi-phase, mixed-methods study that aims to implement and evaluate a novel community response model, which we have named the Community-Based, Client-Centered Prevention Home.

Using the organizational infrastructure of a large, multi-site syringe service program serving a geographically disperse population of people who inject drugs in rural communities across Northern Wisconsin, we will build locally responsive systems to facilitate uptake of evidence-based prevention services for high-risk clients. The Client-Centered Prevention Home model incorporates prevention case management and mobile health information technology into traditional harm-reduction services delivered at syringe service programs, which we hypothesize will increase use prevention services. During the first 2 years the project (UG3 phase), we will perform needs assessments in 6 rural Wisconsin counties in partnership with local stakeholders, and use respondent driven sampling to conduct a cross-sectional epidemiologic evaluation to estimate the prevalence of HIV, viral hepatitis and sexually transmitted infections. Contingent upon meeting recruitment and data collection goals, during years 3-5 (UH3 phase) of the project we will deploy and evaluate the Client-Centered Prevention Home model in the 3 counties demonstrating highest vulnerability to worsening epidemics of opioid injection. The 3 remaining counties not selected for implementation will serve as comparison sites in a quantitative evaluation of program effectiveness during year 5.

The growing problem of opioid injection in rural Wisconsin is highly significant because it exemplifies trends observed nationally indicating severe vulnerability to worsening epidemics of HIV, HCV, and opioid overdose deaths in rural communities that are substantially underserved by evidence-based prevention interventions. This proposal is highly innovative because it will be the first study to use an evidence-based mHealth strategy and a formal implementation science approach to enhance coordination of prevention services in syringe service programs. It has potential for high impact because of our team's state-wide reach, broad access to at-risk individuals, and robust infrastructure for conducting a rigorous, multi-site evaluation of our proposed model.

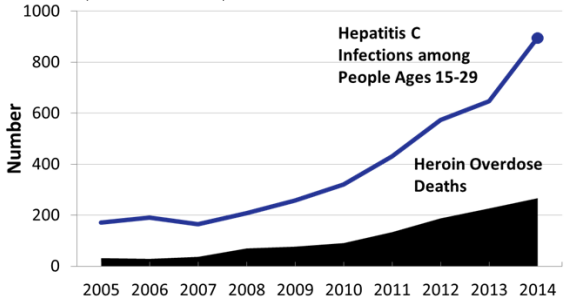
1.0 BACKGROUND & SIGNIFICANCE

HIV, hepatitis C virus (HCV) infection, and opioid injection represent interdependent epidemics of enormous and increasing public health significance. In the past decade, HCV surpassed HIV/AIDS as the leading cause of infectious death among U.S. adults,[1] while opioid overdose overtook motor vehicle accidents as the number one injury-related cause of death.[2,3] Evidence-based strategies to effectively prevent[4-7] and manage[8-11] these conditions exist, yet recent outbreaks of HCV and HIV among young people who inject opioids in rural areas of the U.S. demonstrate the failure to implement these tools in communities where they are needed.[12-15] The ***scientific premise*** of the proposed research is that multiple social, structural, and behavioral factors prevent opioid-injecting rural residents from receiving evidence-based strategies for prevention of HIV, viral hepatitis, and overdose. Through an innovative, dual-phase, mixed methods study design, we propose to test whether a novel community response model, the Client-Centered Prevention Home, can improve uptake of essential prevention services when implemented in syringe service programs serving rural communities.

1.1 Opioid injection has devastating consequences on patients, family members, and communities. In the U.S. in 2012, an estimated 2.1 million people had opioid use disorder related to prescription painkillers and 467,000 to heroin.[16] Healthcare costs related to prescription opioid abuse were estimated at $25 billion in 2007, and total societal costs at $55.7 billion.[17] Opioid use has risen steeply in recent years. From 1991 to 2013, opioid prescriptions rose from 76 million to 207 million.[18] Emergency department visits related to the nonmedical use of opioids rose from 144,600 in 2004 to 305,900 in 2007.[19] From 2000 to 2013, unintentional prescription opioid overdose deaths tripled and heroin overdoses more than quadrupled.[20]

In Wisconsin (WI), increases in opioid use disorder have also risen, and are accompanied by substantial increases in the incidence of HCV among young adults and adolescents (**Figure 1**). The proportion of drug and alcohol treatment admissions in WI for heroin and other opioids tripled between 2005 and 2014.[21] In late 2010, WI detected a cluster of new HCV infections in six contiguous rural counties, driven primarily by injection of heroin and other opioids by adults under 30.[22] In 2014, 53% of HCV infections in young people and 42% of opioid overdoses or deaths occurred among residents of rural counties.

Figure 1. Increases in HCV cases reported among people ages 15-29 and heroin overdose deaths, Wisconsin, 2005-14



1.2. Increases in opioid injection consequences represent a failure to translate evidence into practice. Although the global epidemic of injection opioid abuse is heterogeneous and dynamic,[23] there is scientific consensus about a package of evidence-based interventions that are efficacious for preventing the spread of HIV. The World Health Organization (WHO), The United Nations office on Drugs and Crime (UNODC), and the Joint United Nations Programme on HIV/AIDS (UNAIDS) have endorsed universal access to 9 interventions for people who inject drugs, and have issued technical guidance for evaluation monitoring of this goal.[24] This "Comprehensive Package," listed in **Table 1**, includes biomedical interventions (e.g. HIV antiretroviral therapy, viral hepatitis immunizations) that tend to be delivered in health care settings, and lower-cost, "harm reduction" strategies such as needle and syringe programs that are in most cases delivered in community-based, non-clinical settings.

Medication-assisted treatment (MAT) for opioid use disorder, referred to as opioid substitution therapy (OST) in the WHO document, has demonstrated significant clinical, societal, and financial impact through increased abstinence rates,[25,26] reduced relapse rates,[27] and reduced criminal costs.[28] Yet, MAT has experienced low adoption rates and, in many areas, is not a standard part of addiction treatment.[29,30] Despite strong evidence of effectiveness, it is estimated that fewer than one-quarter of opioid-dependent persons are enrolled in methadone maintenance. This is largely due to a limited distribution to a relatively small number of highly-regulated clinics, restrictive dosing schedules, and its high stigmatization. Buprenorphine, approved by the FDA in 2002, provides an effective alternative to methadone and can be implemented in treatment settings outside the traditional methadone maintenance framework.[10] Recent investigations show that among addiction treatment organizations that offer buprenorphine therapy, many patients are turned away due to limited physician prescribing capacity.[31,32]

Table 1. Comprehensive package of prevention services for people who inject drugs

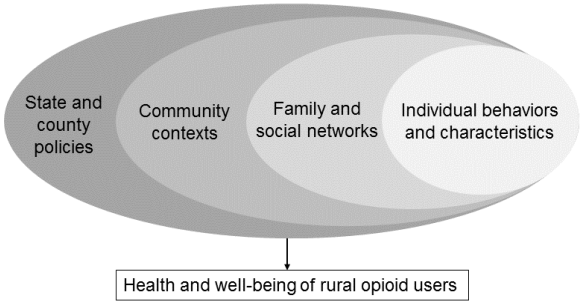
1. Needle and syringe programs (NSP)
2. Opioid substitution therapy (OST) and other evidence-based drug dependence treatment
3. HIV testing and counseling (HTC)
4. Antiretroviral therapy (ART)
5. Prevention and treatment of sexually transmitted infections (STIs)
6. Condom programs for people who inject drugs and their sexual partners.
7. Targeted information, education and communication for people who inject drugs and their sexual partners.
8. Prevention, vaccination and treatment for viral hepatitis
9. Prevention, diagnosis and treatment of tuberculosis.

1.3. Rural opioid injectors are particularly underserved by health systems. Formative research by our group found that, while comparable numbers of rural and urban syringe service program (SSP) clients reported they had never been tested for HCV, geographic inaccessibility appeared to play a particularly important role among rural clients.[33,34] We found that for every 10 miles a rural client lived from the location of a SSP, the odds of ever being tested for HCV decreased by 20%,[33] whereas no such association was observed for urban clients. Comparable research in numerous North American settings confirm that non-urban residents have inferior access to not only sterile injection equipment, but also ancillary services facilitated by SSPs such as clothing, food, referrals, and social support.[15,35] Shortages of providers with specialty training in HIV,[36] viral hepatitis,[37] and addiction treatment[38,39] are also commonplace in rural areas.

1.4. Theoretical frameworks

Framework for UG3 Phase: A social ecologic model of prevention services delivery. The social-ecological framework, drawn from ecological systems theory[40] (**Figure 2**), guides many public health prevention efforts. This framework posits that targeted outcomes are influenced by factors in four distinct spheres: (1) individual, (2) interpersonal, (3) community, and (4) societal. Our community response model serving opioid drug users incorporates aspects of care at all four levels. Societally, the legality of SSPs, laws governing opioid and naloxone access and drug paraphernalia possession, and safe access to treatment services, including methadone or buprenorphine, can impact safe injection drug use and/or treatment. On a community level, stigmas associated with opioid use, HIV/HCV testing, and drug treatment can impede willingness to access available services. Interpersonally, social support for safe injection use within drug using networks can influence injection practices or help people access support services. Individually, people who inject opioids often face many barriers to safety, such as lack of health insurance, employment, and low education.

Figure 2. The social-ecological framework



Framework for UH3 Phase: Applying the Chronic Care Model to comprehensive prevention services. Recognition of opioid use disorder as a chronic, relapsing condition in need of management over the life-course is a fundamental component of effective prevention strategies for people who inject opioids. The U.S. health system currently has critical deficiencies in its capacity to meet the prevention needs of rural opioid users. There have, however, been important lessons learned over the past decade about how systems of care can be improved overall to better deliver treatment for complex, chronic health problems. The current opioid crisis demands that we find alternative service delivery models to "fill the gaps" left by the mainstream health system. To have optimal impact, these new models should incorporate evidence-based strategies known to effectively meet the needs of people with chronic conditions.

The Chronic Care Model--developed in the early 2000s as part of initiatives to reduce costs and improve outcomes for treatment of diabetes, heart failure, and other conditions--emphasizes a team-based, longitudinal care approach.[41,42] The model's 6 elements emphasize patient empowerment, community engagement, and efficient use of information resources to enhance quality of services (**Table 2**). While the Chronic Care Model was designed to improve medical care for complex chronic illnesses, its central features are clearly applicable to prevention services.[43] In the following sections, we describe how this framework is applied to the proposed model of Client-Centered Prevention Homes within SSPs.

Table 2. Six Elements of the Chronic Care Model applicable to opioid epidemics

1. **Health Systems**: Create an organization that provides safe, high-quality services
2. **The Community**: Mobilize community resources to meet the needs of clients
3. **Self-Management**: Empower and prepare clients to manage their health needs
4. **Delivery System Design:** Assure effective, efficient service and self-management support
5. **Decision support:** Promote services consistent with scientific data and client services
6. **Health information systems**: Organize data to facilitate efficient and effective services

1.5. The Community-Based, Client-Centered Prevention Home incorporates elements of the Chronic Care Model into the delivery and coordination of community-based services to prevent HIV, viral hepatitis, and opioid overdose. It leverages unique strengths of community-based organizations, and SSPs in particular, to engage marginalized and stigmatized communities that are underserved by the health care system. It also seeks to enhance the quality, efficiency, and reach of community-based services by incorporating evidence-based strategies shown to improve chronic illness management in primary care clinical settings.

Client-centeredness refers to services that are "culturally competent," "linguistically specific," and tailored to the client's stage of behavior change.[44] In many communities, SSPs exemplify these characteristics. By providing non-judgmental and compassionate services, occasionally in unauthorized or clandestine settings, SSPs have engendered the trust of drug-injecting clients who live in communities where drug use is criminalized, and provide a venue where clients feel welcomed and supported. Unfortunately, SSPs typically lack resources and infrastructure to monitor and improve quality using tools which have been embraced in primary care settings, indicating that a health systems approach to enhancing service delivery to prevent HCV and HIV within SSPs could have a major impact.

Prevention Case Management is a client-centered intervention combining intensive risk reduction counseling and case management to people at high risk for HIV infection.[45] Evidence from demonstration projects, including data published by the Wisconsin AIDS/HIV program,[46] support its effectiveness for reducing needle-sharing[46,47] and overall drug use.[48,49] Prevention case management interventions have also shown benefit by reducing homelessness[50] and other unmet service needs,[51] and by improving psychological and emotional symptoms.[50] Care coordination strategies

incorporating case management approaches have been shown to be effective for linking patients receiving methadone maintenance to hepatitis prevention and care services.[52]

Health homes seek to integrate and coordinate services using a person-centered philosophy. Introduced in 1967 by the American Academy of Pediatrics, the concept has since expanded to describe care that can be operationally characterized as *accessible*, *comprehensive*, *family-centered*, *coordinated*, *compassionate* and *culturally effective*.[53] Developed and endorsed by the four major primary care physician associations in the U.S. in 2007, the Patient-Centered Medical Home approach is now actively promoted by the Agency for Healthcare Research and Quality (AHRQ) as a standard of excellence in primary care.[54] In WI, the State AIDS/HIV Program and Vivent Health collaborated with the state legislature to gain approval for the Wisconsin Health Home State Plan Amendment (SPA), taking advantage of the opportunity provided under the Affordable Care Act of 2010 for states to receive funding for "coordinated care through a health home for individuals with chronic conditions."[55]

The Wisconsin SPA, one of only 26 Medicaid Health Homes approved to date in the U.S., focuses exclusively on comprehensive care coordination for people diagnosed with HIV/AIDS and at least one other chronic condition.[56] Vivent Health, as the lone agency administering *Medicaid Health Home* services for people living with HIV/AIDS in Wisconsin, is ideally positioned to translate its service coordination expertise into *prevention home services* to people who inject opioids in rural communities. The proposed prevention home model is inspired by and based on the same principles as the patient- centered medical home, but its scope is limited to coordination of essential services needed to prevent HIV, hepatitis, and other consequences of opioid injection (see **Table 3**). It is not an alternative to comprehensive medical care; rather, the prevention home model is an adjunct to clinic-based care for a *specific population* with *extraordinary prevention needs*, in the context of a *public health crisis*. Next, we describe enhancements to traditional SSP services which form the foundation of the Client-Centered Prevention Home model.

Table 3. Emphasized features of medical and prevention health homes

AHRQ Definitions	**Patient-centered medical home** (health care settings)	**Client-centered prevention home** (community-based settings)
Comprehensiveness	Addresses all of patient's medical and prevention needs	Comprehensive, evidence-based services for *specific* conditions
Person-centeredness	Relationship-based, oriented to the whole person	Relationship-based, non-judgmental, tailored to stage of change
Care-coordination	Provider-led, team based clinical care over the life course	Community-based prevention case mgt. during periods of risk
Accessibility	Ensuring access to clinical care, e.g., after-hours availability	Reducing geographic barriers, e.g., through mobile services
Quality & Safety	Decision support tools, QI activities, population health mgt.	Strategic use of available health IT resources, mHealth tools

1.6 COVID-19 Outbreak and Amended Intervention (Aim 3)

In February 2020 the Minnesota Department of Health announced an outbreak of HIV among people who inject drugs in Hennepin and Ramsey Counties. Many of the cases were co-infected with HCV and struggled with homelessness. Due to its close proximity to Wisconsin and the transient nature of the population, local SSP in Wisconsin have increased efforts in testing for HIV and tracking new HCV infections. Concurrently, an increase in new cases of the novel Coronavirus, or COVID-19, began to appear throughout the state. On March 13, 2020, Wisconsin reported 18 confirmed cases

and the Governor declared a Public Health Emergency, mandating closures of all K-12 schools in the state. Many organizations began changing operations to ensure that their staff began working from home. By March 23, 2020 the Governor issued a Safer at Home order to decrease the spread of COVID-19.

At Vivent Health, where the Wisconsin Rural Opioid Initiative is housed, operations decreased to two days a week and staff have minimized face-to-face time with clients. PWID are expected to call ahead of time to pick up a prepackaged syringe kit along with naloxone. However, little is known on the long-term effects of limited operations on people who inject drugs. The prospect of sheltering in place and measures put in place by the SSP and other organizations poses a disruption to syringe services, access to essential preventative services, and other face-to-face support needed by PWID. By offering a crisis-response based virtual navigation program, we are fulfilling our ethical duty to prevent HIV, HCV, and overdose in a novel way with PWID in rural WI.

1.7 Measuring the impact of the COVID-19 Pandemic on people who inject drugs

We are now approaching the third year of the COVID-19 pandemic, which collided with a worsening, ongoing overdose epidemic that killed 9,260 people in Wisconsin from 2000-2019 from opioid overdose alone. Consistent with national and state-level trends indicating increases in fatal and nonfatal overdoses,[65,66] overdose mortality in Wisconsin increased by 28% during 2020 relative to 2019[67] Unfortunately, provisional 2021 data suggest it will be the deadliest year for drug overdose deaths in Wisconsin and the US.[67] Beyond exacerbations to overdose mortality, prior studies also suggest that COVID-19 itself has disproportionately impacted people who use drugs, and that low vaccine confidence may continue to drive poor outcomes. Studies have shown that people who use drugs are at increased risk for COVID-19 infection, hospitalization, and death.[68] Regarding vaccination, a survey of people who inject drugs in Wisconsin conducted by our team in March-May 2021 indicated that 50% of respondents were hesitant to be vaccinated for COVID-19, consistent with prior studies.[69] Actual COVID-19 vaccination rates and predictors of vaccine uptake have not yet been examined. However, prior studies suggest the potential for considerable under-vaccination for COVID-19 and other infectious diseases that disproportionately impact people who inject drugs (e.g., hepatitis A and B[70]). The extent to which people who inject drugs have accessed other recommended vaccines (i.e., hepatitis A and B) is also unknown, yet has important implications for understanding access to preventive care during the COVID-19 pandemic and potential long-term impacts on liver-related morbidity and mortality.

2.0 STUDY OBJECTIVES

The overall objective of this project is to leverage our team's successful track record of research, surveillance, and service delivery in Wisconsin to implement an innovative yet widely replicable service delivery model for rural opioid users, which we have named the Community-Based, Client-Centered Prevention Home. The key features of this approach are its implementation in *community-based organizations* rather than traditional clinical settings, its focus on *client-centered service coordination*, and the incorporation of a *mobile health (mHealth) information system* to optimize *quality* and *comprehensiveness*. Building on our prior success engaging "hidden" populations of rural opioid injectors in research, our specific aims are:

Aim1: To estimate the prevalence of HIV, viral hepatitis, and sexually transmitted infections among people who inject drugs to get high, and the availability of essential prevention services, in 6 rural Wisconsin counties.

Aim 1a: To quantify the impact of the COVID-19 pandemic on participants by summarizing COVID-19, overdose, and vaccination rates and risk and protective factors for these outcomes. We will achieve this aim via linkage of identifiable information from Aim 1 participants with several registries from the Wisconsin Department of Health Services (vital records, hospitalization data, Wisconsin Electronic Disease Surveillance System, Wisconsin Immunization Registry).

Aim 2: To comprehensively assess unmet needs and available resources for the provision of essential prevention services for people who inject drugs to get high in rural communities:

Aim 2a – We will analyze diverse sources of public health surveillance and administrative data to characterize areas at greatest community-level vulnerability to worsening epidemics of injection drug use.

Aim 2b – We will engage key stakeholders from affected communities to identify provider-level characteristics that facilitate person-centered (e.g. relationship-based, culturally sensitive) service delivery.

Aim 2c – We will use ethnographic methods and validated questionnaires to describe individual-level barriers to optimal engagement in prevention and treatment services.

Aim 3: To evaluate the impact of the Client-Centered Prevention Home model, deployed within syringe service programs in counties with high burden of injection drug use, on the proportion of clients who receive the package of 9 essential services endorsed by the World Health Organization to prevent HIV/HCV in people who inject drugs. We will use input from local stakeholders and a proven implementation science framework (NIATx) to translate lessons learned through Aims 1 and 2 into a service model that is responsive to the unique needs of rural residents and adaptable to communities with varying degrees of resource limitation.

This project will be conducted by an experienced, interdisciplinary team working across academic, public health, and non-governmental sectors. The main community partner Vivent Health, formerly known as the AIDS Resource Center of Wisconsin (ARCW), is a unique, state-wide organization that provides harm reduction services, including syringe services and confidential HIV and HCV testing, to clients at 10 fixed sites and numerous mobile units reaching all 72 Wisconsin Counties. Based on our preliminary studies and prior collaborations, we have selected 6 rural counties as the focus of the epidemiologic evaluation and community needs assessment during the UG3 phase. Contingent upon meeting recruitment and data collection goals, in the UH3 phase of the project we will select the 3 counties demonstrating the highest need, then deploy and evaluate the Client-Centered Prevention Home model at Vivent Health field offices located within these service areas. Service areas not selected for implementation will serve as comparison sites in the assessment of program effectiveness during Year 5.

Study Coordination

The Division of Infectious Diseases at the University of Wisconsin School of Medicine and Public Health is the coordinating center for this study.

Investigators from numerous academic departments at UW-Madison and Tulane University will collaborate to refine study methodologies and adapt data collection and laboratory infrastructure during the fall of 2017, with a goal of commencing recruitment of subjects in January 2018.

Investigators will also participate in national working groups as part of a multi-site collaborative agreement including researchers in other states and Scientific Staff from the National Institute on Drug Abuse.

Study Phases

Phase 1 (UG3) September 2017 – August 2019 Study activities • Creation of working groups • Building stakeholder support in 6 target communities • Client survey and seroprevalence study in syringe service programs • Community needs assessment	**Phase 2 (UH3)** September 2019 – August 2023 Study activities • Development of Prevention Case Management Protocol • Enrollment of syringe service program clients in Prevention Case Management Program at 3 Vivent Health offices • Adaption of A-CHESS mobile health application (2021 Pilot). • Virtual Prevention Navigation Implementation Cohort Study (during COVID-19 Pandemic)
Additional Phase 1 Activities (UG3) February 2022 – December 2023 Study Activities • Link UG3 data with several registries from the WI Department of Health Services to ascertain longitudinal outcomes of interest during the COVID-19 pandemic • Quantify rates of COVID-19 infection, testing, vaccination, and mortality from DHS data • Quantify fatal overdose rates and nonfatal overdose hospitalization rates • Quantify hepatitis A and B vaccination prevalence	

Phase 2 (UH3) Objectives

Participants in the intervention will undergo a 12-week intensive multilevel harm reduction case-management intervention geared towards coordinating referrals to reduce substance use disorder and increase engagement in the substance use disorder care cascades, and reduce vulnerability to HIV, STIs, and HCV and increase in engagement in the HIV, STI, and HCV care cascades. As shown in Figure 3, participants in the intervention arm will work with Prevention Navigators to undergo a risk assessment and identify problems that they will create goals to achieve. Each session after that will

be used to review the needs assessment and goals. During their last meeting, participants and prevention navigators will develop a discharge plan that will enable the participant to work on their goals on their own.

COVID-19 Response and Amended Intervention. Wisconsin's Shelter in Place mandate has statewide closure effects, including the limiting of services delivered by Vivent Health, our main community partner. To best respond to this crisis and help PWID in rural WI, we will adjust our prevention navigation model to a virtual, COVID-19 risk related navigation for a short period of time (through Sep 2020).

Participants enrolled in the COVID-19 virtual navigation study will work with a navigator 4 times over the course of one month (1x/week) to reduce the risk of HIV, HCV, and overdose during this especially difficult time. Navigation will be focused on crisis response, safe drug seeking and sharing behaviors, at home HIV and HCV testing, overdose risk reduction, safe housing, stable food sources, and other relevant topics for PWID during the pandemic. After a trial of this model (ending Sep 2020), we will resume the original UH3 model (3 month intervention, and baseline, 3-month, and 6-month assessments) in a virtual format.

Figure 3. Phase 2 (UH3) Study Flow

✶ Intervention participants enrolled between February 1, 2023 and March 31, 2023 are excluded from the 6 months post baseline assessments. The final study assessments for these participants is 3 months post baseline.

3.0 SELECTION OF SUBJECTS

In preparation for this study, our team analyzed WI county-level data reflecting various aspects of the opioid epidemic to (1) understand geographic heterogeneity of opioid injection and its consequences in order to prioritize communities in greatest need of prevention services; (2) build capacity to monitor changes in opioid-related disease burden over time on a state-wide level; and (3) establish a framework to assess the impact of the community response model in counties served by the new model in comparison to those not served. In Table 4, we list the 6 counties we have selected as high-priority candidates for implementation of the Client-Centered Prevention Home model. They were

chosen because county-level data indicate a high burden of opioid injection and HCV infection, and because they are located in close proximity to a Vivent Health prevention office that could feasibly deliver services to the majority of residents.

Table 4. County-level data describing opioid epidemic in Vivent Health syringe service program.

Variable	Douglas County†	Eau Claire County†	Marathon County†	La Crosse County	Outagamie County	Brown County
HCV cases in ages 15-29 (per 100,000	156.1	92.7	92.7	72.0	68.5	60.0
Opioid-related hospital visits (per 100,000 pop.)	205	79.9	48.7	83.8	67.4	70.8
Opioid prescriptions filled (per 1,000 pop.)‡	968.3	745.2	801.4	753	649.1	760.9
Percent of opioid prescriptions >90 MME daily‡	6.2	4.3	5.6	6.3	7.4	4.7
Syringes distributed by Vivent SSP in 2016 Q3	64,426	53,867	49,261	53,567	48,807	46,317

† Expected UH3 implementation site based on preliminary data (subject to change); ‡ Data obtained from WI Prescription Drug Monitoring Program

In the first phase of the study, we identified sufficient resources to ensure the feasibility of our proposed intervention in 5 of the 6 counties we have studied, and have selected 3 service regions for which the intervention will be ideally suited. The 3 study sites include La Crosse County, Marathon County, and Brown County.

In addition to confirming there are sufficient resources in the study areas, our research showed that the 3 selected communities differ from each other in notable ways, which will provide opportunities to study how implementation strategies may differ in varying contexts. For example, Brown County was unique in that the RDS survey engaged a much higher than expected number of Native American respondents. Respondents in Brown County also more commonly listed heroin as their “drug of choice,” while respondents in all other sites indicated methamphetamine was their preferred drug.

COVID-19 Response and Amended Intervention. In response to the national crisis, and to best serve PWID in rural WI, we will recruit subjects in our 3 intervention sites (Brown, Marathon, and La Crosse Counties). Additionally, we will be resampling participants who were enrolled in the UG3 phase of the study and who have given permission to be contacted about future research opportunities. Each navigator will have a case load of no more than 15 participants at one time throughout the course of this pilot. Once we have concluded the pilot in Sept 2020, we will resume aim 3 procedures.

4.0 REGISTRATION PROCEDURES

Participant recruitment for Aim 1 (UG3 Phase).

Using a cross-sectional study design, we will enroll 1,200 people who inject drugs to get high and live in rural communities. Based on the volume of syringes distributed in 2016 at the six rural Vivent Health offices listed above, we anticipate enrolling 200 individuals at each site.

Eligibility screening and enrollment of seeds. Individuals will be eligible for enrollment if they are 15 years of age or older, have injected any drug to get high in the past 1 month, and reside in a rural community. Rural residence will be determined by ZIP code, which will be programmed in the screening instrument on REDCap. The system will classify the ZIP code as rural if the ZIP Code RUCA Approximation is >4 or the participant lives in a catchment ZIP code for the SSP.

A research assistant will screen clients for eligibility, either on site at Vivent Health or by phone. Vivent Health staff will notify clients of the opportunity to speak with research staff by phone if they

report living in a rural community, are 15 or older, and are actively injecting drugs. To minimize the involvement of Vivent Health staff in the screening process at sites where having Vivent Health staff engaged in research would interfere with routine prevention activities, we have developed a flexible screening process that can be done without the involvement of Vivent Health staff. At certain sites, Vivent Health staff may become engaged in research and fulfill the research assistant role for the purpose of screening, if the agency determines this is the best strategy for managing the flow of clients and study participants. Specifically:

1. As a matter of routine (i.e. independently of the study), syringe program staff collect the following information from clients: Age, zip code of residence, whether the client is actively injecting drugs, whether they are interested in referrals to drug treatment. Staff members also participate in several outreach testing events that are outside of the SSP centers, while testing for HCV and HIV at these events, staff collect information on age, zip code of residence, and whether the client is actively injecting drugs. During the study enrollment period, staff will notify clients of the opportunity to participate in the study if they report that they inject drugs, are 15 years of age or older, and reside in one of the targeted rural zip codes. Among those in testing events, SSP staff will pass along information telling the participant that they may be eligible to participate in the study. We have hired research staff to be on site who will help in screening and enrollment into the study.

2. Questionnaire by telephone. The screening questionnaire has been uploaded as part of the application.

3. If clients are determined to be eligible, then the research staff will collect their name and date of birth, and assign them a study ID number. They will then provide detailed information about the study procedures by reading the consent document. Copies of the consent document will be available in the private room at the Vivent Health prevention office, so that the client can read along and ask questions. Among participants recruited from outreach events, UW research staff will provide them the consent document and go over the study procedures in detail.

4. If the client agrees to participate, they will write down their assigned study ID and end the phone call. They will then notify the SSP staff that they have agreed to participate. SSP staff will direct them to the study computer, where they will complete the study questionnaire using the ACASI interface. The first step of the computerized questionnaire will be to review the full text of the consent document and to submit their electronic signature and study ID number, which will be stored with the study data. In alternative settings such as outreach events where internet connectivity is not reliable, a paper version of the consent form will be signed and securely stored by a research assistant before proceeding with any study procedures.

5. Rapid testing for HIV, hepatitis C and syphilis will be conducted by SSP staff, using standard procedures used by the agency that are independent of the research protocol. The data collection forms used by the SSP staff will be shared with the research team. Rather, specific data elements needed for the study will be securely transmitted to researchers at the time of data analysis.

Recruitment via respondent-driven sampling (RDS). Upon study completion, participants will be asked to refer up to 4 eligible peers to participate in the study. As part of the ACASI questionnaire interface, they will view a brief training video that introduces the concept of RDS and emphasizes the goals of the study, which is to identify people in their rural social network who also inject drugs to get high.

Seeds will receive $20 remuneration for survey participation on the day of enrollment, and will receive $10 for each eligible peer recruit who enrolls in the study. With customization of existing RDS coupon software,57 computerized tracking of study coupons allows monitoring recruitment chains, allocation

of incentives, and collection of data necessary to generate weighted sample statistics. By adjusting the number of coupons provided to recent recruits, we will be able to limit or accelerate the rate of referrals, which assists in maintaining appropriate workload of SSP and research staff and achieving recruitment goals.

Participant recruitment for Aim 2 (UG3 Phase).

The research team will conduct individual elicitation interviews with SSP clients, SSP staff, and local professionals involved in providing prevention and treatment services to people who use drugs in each of the 6 selected communities. A more rigorous approach to quantitatively assess barriers for medical providers, we will conduct a mail-based and email survey among 1,500 family medicine providers.

SSP staff, comprised of prevention specialists in the Vivent Health participating field offices, will be the points of first contact in each community. We have developed a semi-structured interview guide that will elicit staff perceptions about the target population, and the availability of prevention resources and health services. We will use these interviews as a starting point to collect names of providers and local agencies that provide services to people who inject drugs. This will allow us to build a referral network for provider interviews (Aim 2b), and to complete the local needs assessment.

A quantitative assessment of provider-level barriers will be conducted via a mail and email based survey among family medicine providers in WI in order to characterize barriers to optimal care and investigate opportunities to reduce health disparities among people who inject drugs (PWID). We will survey approximately 1,500 physicians specializing in family medicine who have a practice location in Wisconsin, as identified through an electronic database purchased from SK&A. To make specific comparisons among providers who have adopted office-based buprenorphine treatment (OBBT) in their primary care practice to those who have not, we will use a case-control study design, matching providers who have received a DEA waiver to prescribe buprenorphine to up to 2 non-waivered providers who practice in the same county. Cases have been identified through the Substance Abuse and Mental Health Services Administration's (SAMHSA) website. SAMHSA's database will be crosschecked by internet searches and phone confirmation to ensure that each provider is still practicing at reported location. We theorize that providers who have adopted office-based buprenorphine treatment have general awareness of the epidemic, and understanding barriers they face may be imperative. Controls (non DEA-waivered providers) will be drawn from the SK&A database. To achieve the target sample size of 1,500 providers, additional family medicine physicians will be sampled from the database, with priority given to providers practicing in the rural counties targeted in the parent study.

SSP clients will be recruited for individual-level interviews (Aim 2c) among participants who consent to participate in the client survey and seroprevalence study, described in Aim 1. Clients who participate in the cross-sectional study described above will be systematically invited (e.g., every nth person) to also participate in a qualitative interview. We anticipate conducting qualitative interviews with 5% of the cross-sectional sample (n=60) divided among the 6 counties. Additional interviews will be conducted if warranted by the data but a sample size of 30-50 is usually sufficient to achieve saturation and redundancy, a marker of sufficient sample size.58

Participant recruitment for Aim 3 (UH3 Phase, 2019-2021).
Based on preliminary data, burden of opioid-related illness, and familiarity with supportive local stakeholders, we selected La Crosse County, Marathon County, and Brown County as the implementation sites for this study. Eau Claire, Douglas, and Outagamie Counties will serve as the

nonintervention sites, where participants will receive services as usual. In the fall of 2019, 3 full-time Prevention Navigators were hired and trained to conduct the intervention. Participants in this phase of the study will be recruited into one of two groups, Prevention Navigation, or usual services. Beginning in year 3, SSP clients at the 6 selected Vivent Health sites will be notified about the study by prevention specialists or SSP staff if the client 1) tests for HCV or HIV at the SSP, 2) inquires about services that may be in the prevention home through casual conversation, 3) the client engages in naloxone training, 4) through posted materials of the availability of new resources for improving prevention services and linkages to treatment in the SSP and community offices, 5) recruit through flyers and posted materials in the SSP and local community resource offices, and public areas, 6) through Vivent Health Facebook advertisements, 7) through our study website listed on our flyers, and/or 8) through respondent-driven sampling (RDS). Upon the completion of the first two attended Prevention Navigation sessions, participants will be given a referral coupon and asked to refer one eligible peers per coupon to participate in the study. Vivent Health will dispense coupons that have been prepared by UW research staff. SSP clients at the nonintervention sites will be recruited at the time the Vivent Health staff member assists them with regular exchange services. Nonintervention sites will aim to enroll about one participant every-other week.

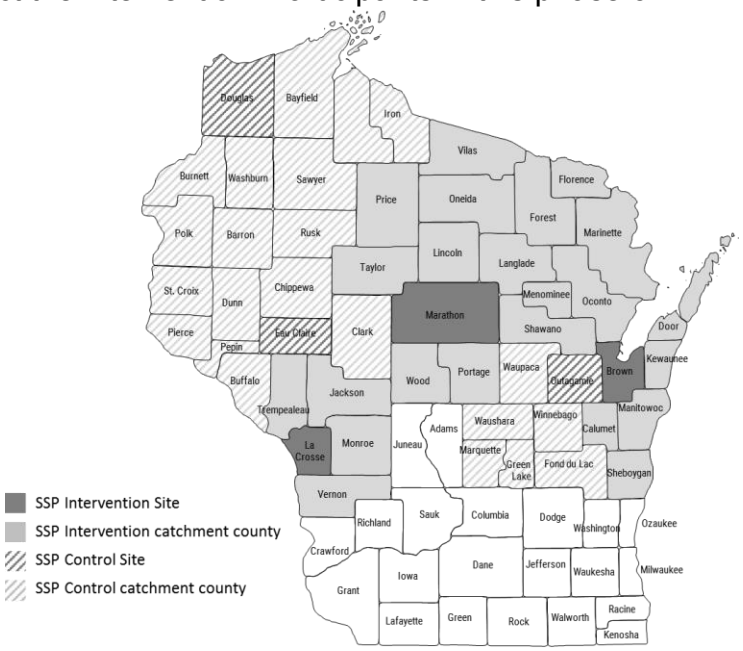
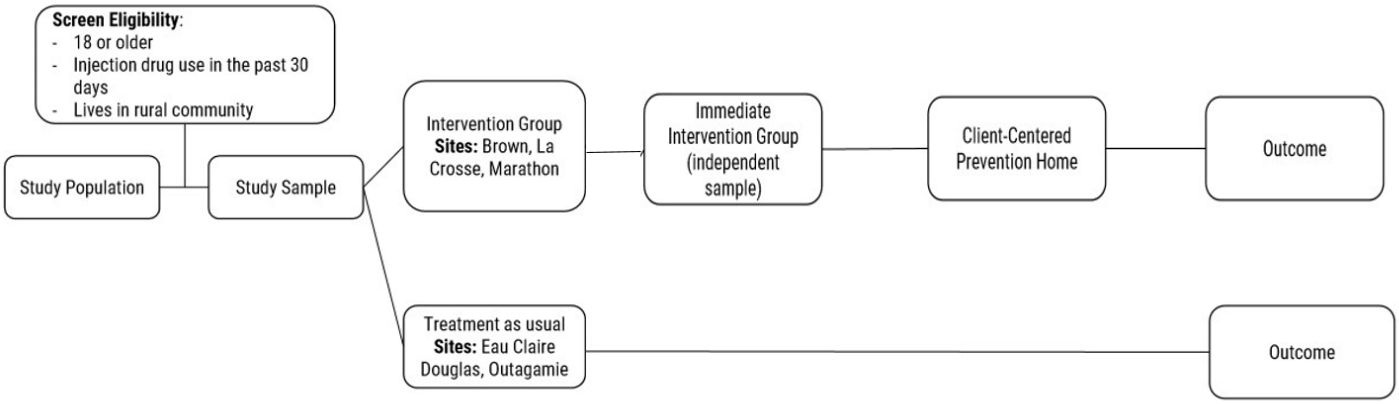


Figure 5. Parallel crossover (wait-list control) and cross-site study design



Eligibility screening and enrollment at baseline. Individuals will be eligible for enrollment if they are 18 years of age or older, have injected any drug to get high in the past 1 month, and reside in a rural community. All persons who access services at the northern Wisconsin SSPs will be considered rural community members, so long as they reside in the state of Wisconsin. County of residence and zipcode will be collected, stored in the participant file, and recorded in REDCap.

Among nonintervention sites, eligibility criteria will be the same as intervention sites, with the exception of allowing Minnesota residents to participate in the Douglas County office.

At intervention sites the PN will administer the screening questionnaire in person or over the phone with the client. If the PN is not available, the client may answer the screening questionnaire on their own and immediately validate their answers with the PN before eligibility is determined (not applicable if virtual). Eligibility requirements will not be listed or shared with the clients. The screening questionnaire has been uploaded as part of the application. If the PN is unavailable, Vivent Health SSP staff will also be research trained and able to administer the screening questionnaire in person or over the phone.

If clients are determined to be eligible, then the research staff will collect their name and date of birth, and assign them a study ID number. They will then provide detailed information about the intervention, study procedures, and the consent document.

If the client agrees to participate, they will be read a verbal consent script over the phone, by video conference, or in-person by the prevention navigator, SSP staff, or UW staff. They will be required to answer T/F questions regarding the consent before giving verbal consent. Participants will fill out a locator form at this time to help SSP staff contact the participant for follow up visits.

Rapid testing for HIV and hepatitis C will be conducted by Vivent Health SSP staff, using standard procedures determined by the agency that are independent of the research protocol. The data collection forms used by the SSP staff will be shared with the research team in order to retrieve specific data elements needed for the study. Study forms will be securely transmitted to researchers after each research assessment.

Clients at the nonintervention sites who are determined to be eligible after SSP staff administer the screening questionnaire will have their name and date of birth collected and assigned a study ID number. The SSP or UW staff member will go through the study procedures and read a verbal consent script over the phone, by video conference, or in-person. They will be required to answer T/F questions regarding the consent before giving verbal consent. A locator form will be filled out at this time. Rapid testing for HIV and hepatitis C will be conducted by the SSP staff member using the same standard procedures as above. The data collection forms will again be shared with the research team securely after each research assessment.

All clients who are determined to be eligible will have a SSP or UW staff member go through the ACHESS specific activities (surveys and option activities) and read a verbal consent script over the phone, by video conference, or in-person. The participant will be required to provide verbal consent.

COVID-19 Pilot Intervention. Participants will be recruited to the virtual prevention navigation implementation pilot program through three avenues.

1) Participants who participated in phase 1 and consented to future contact will be recruited for the study
2) Clients who access current SSP services will receive a flyer in their safe injection supply bags with contact information to call if interested in the study
3) SSP staff may engage clients about the study if a client calls into the SSP asking for services

Participants will be eligible for enrollment if they are 18 years of age or older, have injected drugs in the past month, reside in a rural WI community, and can speak and understand the English language. Clients will speak with the Prevention Navigator to determine eligibility, consent to the study, and schedule their first navigation session. If the client agrees to participate, their name, DOB, county and zip code of residence, and phone number will be collected. Navigators will have a case load of no more than 15 participants at one time to ensure workload is manageable, with a final recruitment

number of n=108 intervention participants and n=108 control participants. Navigators may take down a client's phone number, per Vivent Health policy, in order to contact the individual when spots open.

We will pause recruitment for our originally proposed UH3 protocol until at least Sep 2020 when the pilot has ended.

5.0 DATA COLLECTION

5.1 Data collection for Aim 1.

Epidemiologic survey and needs assessment for rural WI. During years 1 and 2 of this project, we will conduct a cross-sectional prevalence study among residents of rural communities in the catchment areas surrounding 6 Vivent Health Prevention Offices (Figure 3). Four of these offices are located in counties (Eau Claire, La Crosse, Marathon, Outagamie) classified by the National Center for Health Statistics (NCHS) as rural. Douglas and Brown Counties are not classified as rural by virtue of their proximity to the larger cities of Duluth, MN and Green Bay, WI, respectively. Both counties have total populations of fewer than 250,000 residents, however, and our analysis of residential ZIP codes provided by SSP clients showed that the Vivent Health offices in these counties served clients from a large geographic area across rural Northern Wisconsin, where the prevalence of HCV among young people who inject drugs is highest.

Rapid testing for infectious diseases. Upon enrollment, participants will provide 3 fingerstick whole blood samples for rapid testing of HIV, HCV and syphilis. Vivent Health prevention staff are trained to perform point-of-care tests for these infections using the Alere Determine™ HIV-1/2 Ag/AB Combo (Alere Inc., Waltham, MA); the OraQuick® HCV Rapid Antibody Test (OraSure Technologies, Bethlehem, PA); and the Syphilis Health Check™ (Trinity Biotech, Bray, Co Wicklow, Ireland), respectively. During the 20 minutes while awaiting test results, participants will complete an interviewer-administered survey (described below). If all 3 rapid tests are non-reactive, then the study visit will end after he or she has completed the questionnaire and received recruitment training and referral coupons. If any of the 3 rapid tests are reactive, then SSP staff will perform venipuncture to collect a blood specimen to be sent to the Wisconsin State Laboratory of Hygiene (WSLH) for confirmatory testing, record multiple methods of re-contacting the client, and arrange a follow-up visit to review confirmatory test results and provide linkage to care, if needed. In the event that a participant cannot provide a blood specimen for confirmatory testing due to poor venous access, they will be invited to return at a later date for another blood draw attempt. Those confirmed to have active HIV, HCV, or syphilis infection will be linked to a local provider with the assistance of a Vivent Health case manager.

Laboratory-based confirmatory testing and specimen handling. Specimens received by WSLH will be processed for confirmatory testing per standard protocols (see Facilities and Resources for details). After completing the required testing and reporting test results to the testing agency and the WI Surveillance System, WSLH staff will store plasma specimens in preparation for shipping to the CDC and/or GHOST laboratories, as described in Section 5.2

Collection of baseline demographic and risk behavior data. We worked closely with the Vivent Health Director of Prevention and syringe program staff to develop strategies to ensure that research activities are minimally-disruptive to the daily, core prevention activities of ARCW staff. Our pilot studies within SSPs have shown that this is essential for ensuring study protocol fidelity, maintaining high-quality data collection, and maximizing client willingness to participate. We will take advantage of existing data collection forms that are used during HIV and HCV testing encounters to capture necessary individual-level data elements. All publicly-funded HIV testing sites in WI are required to use a uniform data collection and reporting system called Evaluation Web (Luther Consulting, LLC, Carmel, IN). Rapid HCV testing supported by WI DHS requires that agencies report client-level data

using the Wisconsin Electronic Disease Surveillance System (WEDSS). With participant consent, the paper data collection forms used to capture the required demographic and risk behavior information will be transmitted to the UW-Madison based study coordinator via secure fax-to-PDF system, and will be stored on an encrypted server in a directory separate from other study data.

Additionally, the laboratory infrastructure upon which the Wisconsin UG3 study was developed allows an opportunity to undertake a broader epidemiologic investigation that will more fully characterize the HCV epidemic in rural Wisconsin. All blood samples collected for HCV RNA confirmatory testing in the state of Wisconsin undergo testing at the Wisconsin State Laboratory of Hygiene (WSLH). The WSLH retains serum specimens from positive and negative confirmatory HCV RNA tests for up to 5 years. Using stored serum specimens collected during 2016-2017, we will conduct a baseline investigation of transmission clusters involving residents of rural Wisconsin communities.

Baseline Survey. Data elements not captured through existing workflows of SSP staff but necessary to achieve the research aims will be collected using a research team administered phone survey. At least two staff member will be available at all times during business hours. We will have 3 researchers available most days and develop an “on call” system to facilitate 2 phone-based study assessments by phone at a time. The survey will consist of short answer and multiple choice questions designed to efficiently assess drug use history, access and utilization of prevention services, and injection related risk behaviors (see **Appendix 2** for proposed measures).

To maximize willingness of clients to participate within the context of a routine Vivent Health prevention encounter, we will pilot-test the survey to ensure it can be completed within 20-25 minutes.

To facilitate recruitment of participants who have difficulty traveling to Vivent Health offices, we will begin recruiting and enrolling participants at outreach events that are organized by Vivent Health. We described the steps for recruitment and enrollment above. The survey will be administered during the outreach event via computer if there is an adequate internet connection. To increase flexibility in these settings, the survey may also be conducted via telephone with a UW-Madison researcher, who will administer the questionnaire verbally and enter responses directly into the Qualtrics survey. If internet or phone communication is not feasible, then a research assistant may administer the questionnaire in person using a pen-and-paper version. In this situation, the research assistant will subsequently perform data entry.

A data use agreement has been set forth between the University of Wisconsin-Madison and University of Washington, where a limited dataset from the University of Wisconsin is required to be submitted to the University of Washington as part of the NIH-funded Rural Opioid Initiative data harmonization project. The University of Washington Data Harmonization Coordinating Center (DCC) will be harmonizing data across eight sites in order to create new, combined datasets to be used for analyses across the consortium. Only data from this study (#2017-0866) will be sent to the DCC from UW-Madison.

Harmonization means the DCC will be combining similar data domains and questions across all sites in order to build large data sets that will be useful in answering questions that individual sites are not able to answer alone, either due to the nature of the question or sample size limitations. The University of Washington and other grantees will perform data analyses on these data for peer-reviewed publication. The harmonized datasets will be provided to other investigators funded under this study as required for analysis and will be considered under the umbrella of mandated DCC activities.

Upon execution of the agreement, the team’s data manager will upload study datasets to the Rural Opioid Initiative (ROI) Upload Server through a web interface. Access to the interface is controlled by usernames and passwords. Access is assigned to individual, designated ROI staff by the University

of Washington Data Coordinating Center (DCC). The web page uses the HTTPS protocol to transfer ROI data files securely to the Upload Server. HTTPS transfers are encrypted using Transport Layer Security (TLS, the successor to SSL), protecting the data en route to the server. The Upload Server is managed in accordance with the DCC's information security policies (https://uwcirg.github.io/hipaa-policies), and authorization for specific DCC staff is based on their project-related needs and responsibilities.

Data documentation will also be uploaded in the form of a data dictionary specifying all data elements within the dataset, including their description, valid values, and data type. Upon receipt of the dataset and documentation, the DCC data manager will work with the Wisconsin ROI data manager to understand the data structures so that the DCC may harmonize the dataset with those from other sites. A list of data elements that will be sent to the DCC is included in Appendix 3.

Table 6. Quantitative measures collected for Aim 1

Variable	Source	Measure/Operational Definition
Prevalence of HIV, HCV, , syphilis	Point-of-care screening + laboratory confirmation	Number of confirmed active cases / total number screened
Access to 9 prevention services	Participant questionnaire	Perceived accessibility using 5-pt Likert scales
Health insurance	Participant questionnaire	Access to Care Scale†59
Addiction severity	Participant questionnaire	Severity of Dependence Scale60
Barriers to care	Participant questionnaire	Kalichman's Barriers to Care Scale†61
HIV/HCV/STI risk behaviors	HIV/HCV Testing Data Collection Forms	NHME Data Variable Set‡
Demographic characteristics	HIV/HCV Testing Data Collection Forms	NHME Data Variable Set‡

† NIDA STTR Data Harmonization Measure; ‡ NHME=National HIV Prevention Program Monitoring and Evaluation

5.1.1 Additional Data Collection for DHS Linkage Study on COVID-19 Pandemic Impact Among UG3 Participants

We will use data collected by the Wisconsin Department of Health Services (DHS) to estimate the rates of COVID-19 infection, testing, hospitalization, and death, fatal and nonfatal drug overdoses, and vaccination against COVID-19, Hepatitis A and Hepatitis B in the UG3 cohort. To achieve our objectives, we propose a retrospective cohort study that will be facilitated by linking data from several DHS registries with UG3 participants. We propose to provide DHS colleagues with identifiable data from 991 of our prior research participants (identifiers: participant name, date of birth, gender, race, ethnicity, previous address, previous phone number, date of participation in our study) to facilitate linkage with several DHS registries. We are seeking approval for the DHS data linkage via a partial waiver of authorization, waiver of consent, and by maintaining a log of the protected health information provided to DHS per standardized disclosure logs (see here: https://compliance.wisc.edu/wp-content/uploads/sites/102/2019/02/Accounting-for-Disclosures-Log-Research.pdf). The linkage process is described below:

1. UW will provide a dataset containing a unique study identification number and participant name, date of birth, gender, race, ethnicity, previous address, previous phone number, and date of study participation to colleagues at DHS.

2. DHS will link identifiers with vital records data to identify the date (from study participation date through present day) and cause of any deaths that have occurred among participants of our prior study, from study participation date through present day.

3. DHS will link identifiers with COVID-19 data captured in WEDSS to identify the date of any COVID-19 tests, confirmed or probable infections, and hospitalizations.

4. DHS will link identifiers with WIR to identify the dates of all COVID-19 vaccination doses received and type of vaccine (brand or whether an mRNA/adenovirus vector vaccine).

5. DHS will link identifiers with WIR to identify the dates of all vaccine doses for hepatitis A or B received (including doses received before study participation, if possible).

6. DHS will link identifiers with hospitalization data to identify overdose events involving an emergency department visit or hospitalization.

7. DHS will remove and destroy identifiers and return the dataset(s) to UW containing the unique study identification number.

8. UW researchers will link the new dataset with variables collected in our prior cross-sectional survey using the unique study identification number, including sociodemographic (i.e., age, gender, race/ethnicity, housing, education, employment, income, marital status, health insurance coverage) and behavioral correlates (i.e., substances used and mode of use, mental health indicators and symptoms, addiction treatment history, personal and witnessed overdose history, awareness of how to respond to an overdose and access to naloxone, self-reported HIV and hepatitis C infection and treatment, where the participant primarily receives medical care, barriers to engaging in medical care, criminal justice involvement history, access to the internet and a cell phone, and self-stigma).

We will also be requesting that DHS provide an aggregate dataset with COVID-19 data to facilitate comparison of COVID-19 burden between the general population of Wisconsin and UG3 participants. Specifically, we will with monthly age-, sex-, racial/ethnic-, and county-stratified numbers of COVID-19 tests, vaccinations, confirmed or probable infections, hospitalizations, and deaths for Wisconsin (i.e., fully stratified by combined categories of these demographic variables within each county). For the vaccination outcome, we would like to have the number vaccinated with 2 doses of mRNA or 1 dose of Johnson&Johnson and the number with a 3rd mRNA dose or second shot of any type following 1 dose of a Johnson & Johnson vaccine. We hope to obtain the following categories of age (18-29, 30-39, 40-49, 50-59, 60-69, 70+), race/ethnicity (Non-Hispanic/Unknown ethnicity + white, Non-Hispanic/Unknown ethnicity + African American, Non-Hispanic/Unknown ethnicity + American Indian or Alaskan Native, Non-Hispanic/Unknown ethnicity + Other or Multiple races, Hispanic + any race), sex (male, female) within each county in Wisconsin by month, beginning March 1, 2020 to present. We will also request estimates of the monthly population size within each stratum.

5.2. Global Hepatitis Outbreak Surveillance Technology (GHOST).

This research study is part of a collaboration with scientists at other institutions including the U.S. Centers for Disease Control and Prevention (CDC) and the Global Hepatitis Outbreak and

Surveillance Technology (GHOST) Center located at the Ragon Institute of MGH, MIT and Harvard. Blood collected as part of the testing for HIV, Hepatitis and Syphilis may be sent to these other institutions for additional testing. These research tests include, but are not limited to, HIV, HCV, Syphilis and/or other tests for research purposes only. All blood and information will be coded with a number and no directly identifiable information will be shared outside of UW-Madison. The GHOST lab will use specialized technology that identifies transmission links between HCV infected research subjects. The GHOST platform is a secure cloud-based public health research tool to allow state and local health departments to act more quickly to detect and fight the spread of Hepatitis C. Specimens utilized for this laboratory-based initiative will be collected and shared in the context of two complementary protocols:

1. A baseline, retrospective evaluation of HCV transmission clusters using remnant serum specimens currently stored at the Wisconsin State Laboratory of Hygiene.

2. An analysis of prospectively collected blood specimens obtained from individuals who undergo rapid testing for HIV, HCV and syphilis as part of their participation in this study.

5.2.1. Retrospective analysis of HCV transmission clusters in Wisconsin.

We have analyzed data reported to the Wisconsin Electronic Disease Surveillance System (WEDSS) to identify cases of HCV infection that were reported for the first time between January 2016 and December 2017. Approximately 15% of all HCV cases reported to the surveillance system during this time represented individuals who underwent fee-exempt confirmatory HCV RNA testing through WSLH; these instances typically reflect testing done in public health settings such as syringe exchange programs and correctional facilities, and not traditional health care settings. This results in a sample that is enriched for younger people with a history of injection drug use. By contrast, birth cohort testing in WI has been conducted mostly in primary care settings, which utilize commercial or hospital based laboratories for confirmatory testing.

We have identified 241 individuals residing in one of the targeted rural catchment areas who were confirmed to have an HCV RNA+ sample analyzed at WSLH during 2016-17. In addition, we have identified an additional cohort of 218 individuals who we consider likely to represent recent or acute infections because of younger age, higher HCV viral load, or having received a designation of acute HCV infection at the time of reporting to WEDSS. The rationale for including the latter group, who were identified regardless of their geographic area of residence, is that they may enhance the overall likelihood of detecting transmission clusters. Characterization of transmission clusters that include residents of rural and non-rural communities would be highly informative for development of services in the proposed UH3 phase of the study.

Pending approval by the funding agencies and the appropriate institutional review boards, we will identify residual serum specimens corresponding to these 459 cases and ship samples to the GHOST laboratory at MGH. Specimens will be labeled with a unique identifying code and year of collection prior to shipping. GHOST investigators will be sent a corresponding database that specifies the year of collection and quantitative HCV RNA result, but will not receive other information that could be used to identify study participants. After GHOST investigators perform genetic sequencing of

the virus to understand transmission networks, data will be uploaded to a secured web interface in order for researchers and the Department of Health Services to access, according to procedures described below (5.2.2.)

5.2.2. Prospective data collection and analysis of HCV transmission clusters in Wisconsin.

Remnant blood specimens from the confirmatory testing procedures collected from prospectively enrolled study participants will also be used to support the GHOST-related research aims of the multi-site collaborative research program. Upon receipt of a reactive rapid antibody detection test, Vivent Health staff will draw 5 mL of blood into each of up to 3 serum separator tubes (SST), depending on how many of the 3 rapid antibody detection tests had a reactive result.

SST tubes will be centrifuged within 2 hours at the Vivent Health prevention office, according to the Standard Operating Procedures developed between Vivent Health and the Wisconsin State Laboratory of Hygiene. After centrifugation, the SST tubes will be kept cold (4-8°C) and shipped together with the appropriate requisition forms to WSLH via overnight delivery. Confirmatory testing will be performed on specimens on the day of receipt, and aliquots of residual serum will be transferred to secondary tubes and placed in a -80°C laboratory freezer for indefinite storage.

Stored serum specimens for HIV, hepatitis C, and Syphilis positive participants will be shipped to GHOST laboratories for phylogenetic testing on a monthly basis. GHOST laboratories are housed at Massachusetts General Hospital and the CDC. They will perform genetic sequencing of the virus to understand networks. The data will then be uploaded to a secured web interface in order for researchers and the Department of Health Services to access sequence data.

Access to the sequencing data by the Wisconsin Project team will be allowed through the National Healthcare Safety Network's system, known as SAMS. The Centers for Disease Control and Prevention's (CDC) Secure Access Management Services (SAMS) is a federal information technology (IT) system that gives authorized personnel secure access to non-public CDC applications. The SAMS partner portal is a website designed to provide centralized access to public health information and computer applications operated by the CDC. For the National Healthcare Safety Network (NHSN) Program, SAMS will provide healthcare facilities and other partners, such as state health departments and QIOs, with secure and immediate access to the NHSN application.

The UW-Madison-based PI and partners at WI DHS HIV and Viral Hepatitis Program will be granted access to SAMS by CDC after completing the required NHSN training. Data accessed through SAMS will be limited to the viral sequence data derived from the coded HCV RNA-positive samples sent to the GHOST laboratory. No direct identifiers will be associated with data that is accessible through SAMS. Additional information about SAMS is available at https://www.cdc.gov/nhsn/sams/sams-user-faq.html#a1.

5.3. Data collection for Aim 2.

Guided by the social ecologic framework (see Section 1.4), we will assess (a) community-level vulnerability to consequences of injection drug use and (b) availability of essential prevention services through data collection at the county-level, health system and provider-level, and client-level. Interview guides for clients and local service providers will be developed collaboratively by the

research team and Vivent Health staff after the SSP staff interviews have been conducted and analyzed.

Aim 2a. County-level data. We will map out and organize project-related resources within our designated counties. An assessment of service needs and gaps will be conducted. We will identify additional sources of county-level data to complement our preliminary compilation of data that guided the proposal, including use of PDMP and State opioid treatment authority to identify capacity to prescribe MAT and the current level of utilization. Availability of these data sources are reflected in letters of support from WI DHS collaborators.

Aim 2b/Aims 2c. Provider- and client-level data. Semi-structured individual elicitation interviews will be administered to obtain insight from providers of services to injection drug users and clients of these agencies about the context of opioid use and barriers and facilitators of service access and usage.

Aim 2b. Provider interviews will be conducted in person or by phone, and are expected to last 30-45 minutes in duration. They will be audio-recorded and transcribed for later analysis. The goals are to assess (1) services provided to opioid users, (2) barriers and facilitators of access to their services, (3) gaps in service, and (4) strategies to address these gaps. We also will assess the agency's willingness to support a community-based, client-centered prevention home approach to reducing opioid use and infectious disease transmission risk among opioid users. The provider interviews, along with the county-level resource mapping, will inform the readiness and ability of the county to implement a comprehensive prevention program. Agencies will be purposively recruited to represent multiple service domains, including HIV/HCV/STI testing and treatment, medical and mental health, substance misuse treatment, psychosocial assistance, health officials, and law enforcement. The specific provider sample size will depend on the number and variability in the county resources mapped out in Aim 2a.

Aim 2b. Provider mail and email-based surveys. A survey investigating willingness to screen and treat PWID for HCV and opioid use disorder will be developed in collaboration with other UG3 sites. The goals of this mail and email-based survey are to quantitatively asses (1) the willingness of rural primary care providers to provide treatment for HCV infection and/or opioid use disorder as primary prescribers, (2) the prevalence and correlates of failure to provide appropriate screening for HIV, viral hepatitis, and sexually transmitted diseases for people who inject drugs, and (3) negative provider attitudes towards people who inject drugs that may serve as a barrier to effective primary care in rural communities. A cover letter, paper survey, and a $5 incentive will be mailed to selected providers along with materials and instructions for mailing completed surveys back to study staff at UW-Madison. To increase the response rate of the provider survey, providers who have not responded to the survey will be emailed with a web-link to the same survey.

Aim 2c. Client interviews will be conducted in-person in a private setting agreed upon in advance by participants and research staff. Interviews will be digitally audio recorded and transcribed for subsequent qualitative analysis. Respondents will be paid an incentive of $30 for each interview. Interview guides will explore: (1) **Individual characteristics and circumstances**. We will ask people to tell us about themselves, their life circumstances (e.g., housing, employment or school, transportation, financial support), and their daily routine. We also will assess the impact of positive and negative life experiences on their injection drug use. The relationship of these factors to risk behavior will be explored. (2) **Family and other interpersonal relationships.** We will ask participants to tell us about their family and other significant interpersonal relationships they have, including the nature of the relationship, things they do together, and things they talk about. We will explore substance use and sexual risk behavior patterns within the participant's extended family and among significant others. (3) **Community contexts**. We will explore participant's perceptions of the

neighborhood(s) in which they live and socialize, including the types of people that live there, their social interaction patterns, and the places that people go to hang out and use drugs. We also will explore the availability and usage of social services, employment opportunities, and programs that promote community (e.g., churches). (4) **State policy**. We will ask about people's experiences with the legal system, including both incarcerated and non-incarcerated jurisdiction. We will explore the impact that involvement with the legal system has on their injection drug use. (5) **Sexual behavior**. We will explore participant's sexual behavior patterns, and the contexts or factors increasing or decreasing sexual risk likelihood. We also will assess participants' HIV/STD/hepatitis risk perceptions and concerns. Risk reduction behavioral and negotiation strategies will be explored. (6) **Substance use behavior**. We will explore participants' substance use patterns with a focus on injection drug use, and the contexts or factors increasing or decreasing use likelihood. We will assess (un)safe injection practices. We also will assess the saliency and centrality of substance use in participant's lives and the lives of their family and significant others.

A limited dataset of transcripts will be sent to the University of Washington DCC as part of the data harmonization project after the School of Medicine and Public Health's honest broker has reviewed them to assess PHI.

5.4 Data Collection for Aim 3 (Phase 2 - UH3)

Prevention Navigation. The health-related goals for PWID in the context of this study are multi-faceted, reflecting the heterogeneous needs of this vulnerable population. Accordingly, there is not a single, primary outcome which can be measured to evaluate the impact or effectiveness of the intervention. We therefore have proposed a study design that allows us to evaluate the influence of prevention navigation on progress toward a number of health goals. Because no single study design can account for all of the biases inherent in a non-randomized, multi-county intervention trial, we have proposed 2 different types of comparisons in our evaluation strategy (Appendix 1). Prevention Navigators will collect case notes and worksheets as part of the intervention, but this will only be accessible to them. These documents will be analyzed as data or shared with the UW-Madison research team.

The preferred method for intervention sessions is one-on-one in person, with optional one-on-one phone or video interventions when needed (ex: COVID-19 Pandemic). Staff will only contact the participant by their preferred method of contact, getting permission to leave messages before doing so. All virtual interventions and follow up calls will be performed on the navigators' cell phones or laptops provided by Vivent Health. Staff may also text participants to remind them of appointments, request a follow up call, or other short communication purposes. No messages will be sent without consent from the participant while filling out the locator form. Per Vivent Health policy, staff are permitted to communicate with clients about their care and treatment via Facebook messenger utilizing a professional Facebook account that is separate from any personal accounts. Staff are not permitted to use personal accounts to communicate with clients in a professional capacity. No data will be collected over social media accounts. Facebook conversations will not count as an intervention session.

Survey and needs assessment. The primary source of data collection in all three groups of the study will be from the ACASI questionnaire, administered at 0 months (baseline), 3 months, and 6 months from enrollment. All surveys will be administered on a tablet using the ACHESS application, by the participant accessing the survey in ACHESS on their smartphone or web browser on their own time, or over the phone. The data will be securely stored at UW-Madison and erased from the tablet if

applicable. The survey will consist of multiple choice questions designed to efficiently assess drug use history, access and utilization of prevention services, readiness for intervention, and injection related risk behaviors. The final survey a participant takes will include exit questions to help us evaluate and improve the program. Participants enrolled in the intervention between February 1, 2023 and March 31, 2023 will complete the baseline and 3 months ACASI questionnaire only.

ACHESS. All participants will complete study assessments using the ACHESS application. ACHESS can be accessed by downloading the application to a smartphone or via a web browser. Participants may also take part in optional non-research activities within the ACHESS app. These activities include: 1) posting on discussion boards, 2) utilizing the private message function to communicate with study staff or other participants, 3) viewing local community resources and their contact information, 4) viewing and saving motivational quotes of the day and logging thoughts of gratitude, and 5) accessing study staff contact information.

Rapid testing for infectious diseases. Upon enrollment, participants will provide 2 finger stick whole blood samples for rapid testing of HIV and HCV at baseline, 3-months, and 6-month follow up. Participants enrolled in the intervention between February 1, 2023 and March 31, 2023 will complete the baseline and 3-month rapid testing only. Vivent Health prevention staff are trained to perform point-of-care tests for these infections using the Alere Determine™ HIV-1/2 Ag/AB Combo (Alere Inc., Waltham, MA) and the OraQuick® HCV Rapid Antibody Test (OraSure Technologies, Bethlehem, PA. During the 20 minutes while awaiting test results, participants may complete the ACASI questionnaire (described above). If testing by appointment, participants should complete the survey before arriving to their appointment. If both rapid tests are non-reactive, then the study visit will end for non-intervention clients and an appointment will be made for their 3-month visit. Among intervention clients, the study visit will end and an appointment will be made for intervention visit or phone/video call. If either of the 2 rapid tests are reactive, then SSP staff will perform venipuncture to collect a blood specimen to be sent to the Wisconsin State Laboratory of Hygiene (WSLH) for confirmatory testing, and arrange a follow-up visit to review confirmatory test results and provide linkage to care, if needed. In the event that a participant cannot provide a blood specimen for confirmatory testing due to poor venous access, they will be invited to return at a later date for another blood draw attempt. Those confirmed to have active HIV or HCV infection will be linked to a local provider with the assistance of a Vivent Health case manager or Prevention Navigator.

The test results and risk data collected on the HCV and HIV test forms will be entered into Vivent Health's standard of practice database, ServicePoint. Study ID numbers will be included to identify the results as study participants. ServicePoint will securely send data to WEDSS regularly. Only those on the HCV team at WI DHS, which consists of three research team members, will have access to the data. Test forms will be securely faxed to UW-Madison and mailed to DHS, then securely locked at Vivent Health, UW-Madison, and DHS.

Laboratory-based confirmatory testing and specimen handling. Specimens received by WSLH will be processed for confirmatory testing per standard protocols (see Facilities and Resources for details). After completing the required testing and reporting test results to the testing agency and the WI Surveillance System, WSLH staff will store plasma specimens in preparation for shipping to the CDC and/or GHOST laboratories, as described in Section 5.2

Collection of baseline demographic and risk behavior data. Similar to Aim 1, we developed strategies to ensure that research activities are minimally-disruptive to the daily, core prevention activities of Vivent Health staff. Our pilot studies within SSPs have shown that this is essential for ensuring study protocol fidelity, maintaining high-quality data collection, and maximizing client willingness to participate. We will take advantage of existing data collection forms that are used

during HIV and HCV testing encounters to capture necessary individual-level data elements. All publicly-funded HIV testing sites in WI are required to use a uniform data collection and reporting system called Evaluation Web (Luther Consulting, LLC, Carmel, IN). Rapid HCV testing supported by WI DHS requires that agencies report client-level data using the Wisconsin Electronic Disease Surveillance System (WEDSS). With participant consent, the paper data collection forms used to capture the required demographic and risk behavior information will be transmitted to the UW-Madison based study coordinator via secure fax-to-PDF system, and will be stored on an encrypted server in a directory separate from other study data.

Medicaid and Health Care Utilization Analysis. We will link multiple existing datasets at the individual-level to evaluate the effects of the intervention health care use. These include the WI Department of Corrections (DOC) administrative dataset, Medicaid enrollment and claims data, WI State Laboratory of Hygiene (WSLH) HCV test records, WI Department of Health Services HCV Surveillance data, and the new county-level data resource developed through the activities under Aim 2a.

Based on our work with the JCOIN supplement, the UW-Institute for Research on Poverty (IRP) will assist in constructing the study dataset. The IRP has longstanding technical expertise in the construction and secure use of integrated person-level electronic datasets that combine State of Wisconsin administrative data including Department of Corrections and Medicaid administrative and health care claims data. Specifically, the IRP maintains the Multi-Sample Person File (MSPF) dataset which combines data for the universe of individuals interacting with several WI state agencies, including the Department of Health Services (home of the Medicaid program) and the Department of Corrections, at the person-level dating back to the late 1990's through the present. The MSPF is structured at the person-level, and each individual has a unique ID over time and across state agencies (e.g., a person who is incarcerated in a WI state prison and later enrolled in WI Medicaid) which supports longitudinal analysis.

For Aim 3, we will provide the UW IRP programming staff with our sample selection criteria. They will query the MSPF dataset with these criteria to identify possible linkages to our study participants along with a comparison group to evaluate the intervention itself. In addition to basic program participation information (e.g., dates of participation), the MSPF includes identifying variables for each unique person including Social Security number, date of birth, name, and the individual's identification number for each state agency that contributes to the MSPF in which s/he receives or has received services. The IRP will submit a finder file with the relevant identification information to each entity that is providing person-level data for the study. Upon receipt of these data, the IRP will then merge data from all sources at the person level, assign a unique, study number to each subject, and remove the personal identifying information used to match data across sources from the analytic dataset that is provided to the investigators.

The exchange of data between the IRP and state agencies is governed by the Data Use Agreements between the IRP and the respective agencies and follows a strict data security protocol to protect the confidentiality of individuals. The DUA between the IRP and the WI Medicaid program was modified and approved for this study in September 2018.

COVID-19 Pilot Intervention. All data will be collected in REDCap, ServicePoint, Vivent Health's secure server, or on a secure server only accessed by UW research staff. Sessions will happen via phone or Microsoft teams, Vivent Health's approved secure video call resource.

Screening data and locator forms will be stored on the Vivent Health server or secure PHI box and entered into REDCap for analysis by UW staff.

COVID-19 Pilot Navigation Participants will undergo a risk and needs assessment during the first

and last session of the intervention, as well as 30 days after Vivent returns to their full service model (if deemed appropriate post pandemic). The assessment will ask a shortened version of ACASI survey questions specifically relevant to the pandemic. The rest of the assessment will follow the same risk and needs outline as designed for UH3, just with goals specific to the pandemic. Data will be stored on the Vivent Health secure server before being uploaded to a PHI box for analysis. All participant data will be collected by the prevention navigators on their Vivent Health provided devices.

At home testing data will be collected online using Vivent Health's testing protocol. Testing forms will be filled out online, and collected by SSP staff. Individual data will be uploaded to the PHI box, REDCap, or Vivent Heath server by the prevention navigators.

Data Matching We will combine data for participants who completed both Phase 1 and Phase 2 of the study. Combining information across studies could potentially increase the value of individual's participation beyond what is learned in any individual study and increase knowledge about health problems that can result from injecting drugs and ways to reduce the risk of HIV, hepatitis C, and overdose.

6.0 MEASUREMENT CONSIDERATIONS

Data analysis for Aim 1.

The research questions under Aim 1 are descriptive rather than hypothesis-driven. The data collected for this Aim will be used in the UG3 phase to describe burden of infectious consequences of injection drug use, and self-reported access to essential prevention services in the selected rural communities. The same data will be used to establish baseline values in the pre/post analyses for the UH3 phase, if selected to proceed, described below (see Section 3.5.4). We will evaluate baseline statistics for participants recruited from the catchment areas associated with each Vivent Health prevention office, to determine if variation exists among rural regions of the state for each of the key variables of interest.

Prevalence estimates and standard errors will be calculated using RDSAT version 7.1. RDS accounts for a source of bias that is especially severe when sampling hard-to-reach groups; namely, that well-connected individuals tend to be over-sampled because many recruitment paths lead to them. RDS draws statistically valid samples of previously unreachable groups by keeping track of who recruited whom and their numbers of contacts eligible for recruitment. The recruitment process mathematical model weights the sample to compensate for non-random recruitment patterns. Based on Markov chain theory and biased network theory, the analysis provides unbiased population estimates and measures of the precision of the estimates.

Data analysis for Aim 1 DHS Linkage Study on COVID-19 Pandemic Impact Among UG3 Participants.

To estimate the impact of the COVID-19 pandemic on UG3 participants, we will use merged UG3-DHS data to determine several rates and correlates of interest, which are described in detail below.

COVID-19 outcomes. To examine risk and protective factors for COVID-19 related outcomes among people who inject drugs, we will use a time-to-event analysis approach (i.e., Kaplan Meier curves and survival analysis with Cox Proportional Hazards regression models) to quantify COVID-19 testing, infection, vaccination, hospitalization, and mortality rates and predictors of these outcomes among participants of our prior study. This will involve excluding our prior study participants who were deceased prior to the start of the US COVID-19 pandemic (March 1, 2020) and calculating person-

time as the number of days from March 1, 2020 through the date of outcome data provided from DHS.

To describe disparities in COVID-19 related outcomes between the general population of Wisconsin and people who inject drugs, we will create a dataset from the linked dataset and the aggregate dataset provided. Each row of data in the analytic dataset will represent the monthly number and person-time estimate of COVID-19 outcomes within people who inject drugs or the general population in Wisconsin, by strata defined by age group, racial-ethnic group, sex, and county. We will graphically summarize average monthly rates of COVID-19 infections, hospitalizations, deaths, tests, and vaccination among the general population in Wisconsin and among people who inject drugs stratified by age group, sex, racial-ethnic group, and county. We will fit Poisson models (or negative binomial if needed due to overdispersion) with each COVID-19 outcome and the following covariates: age group, sex, racial-ethnic group, county, month/year, and an indicator representing whether the row of data corresponds to data form people who inject drugs vs. general population. The coefficient for the indicator variable will be exponentiated to quantify an incidence rate ratio interpretable as the magnitude of disparity between people who inject drugs and the general Wisconsin population for each COVID-19 outcome, adjusted for age, sex, racial-ethnic group, county, and time. We will additionally examine how age group, sex, and racial-ethnic group status modifies the magnitude of disparity by examining interaction terms between the indicator variable and these sociodemographic variables. We may also describe results by county by creating maps. Any rates or counts involving fewer than 5 individuals will be suppressed (i.e., the results will not be viewable on a map), consistent with confidentiality standards of DHS.

Overdose outcomes. We will use a time-to-event analysis approach (i.e., Kaplan Meier curves and survival analysis with Cox Proportional Hazards regression models) to quantify fatal overdose rates (from vital records data) and nonfatal overdose rates (from hospitalization data) and predictors of these outcomes among people who inject drugs. This will involve calculating person-time as the number of days from study participation date through the date of outcome data provided from DHS. We will examine sociodemographic and behavioral risk and protective factors (covariate list provided in the appendix) by quantifying hazard ratios. We will also examine whether overdose rates changed pre- and post-COVID-19 by including a time covariate with an interaction term indicative of the period (before March 1, 2020 vs. on/after March 1, 2020). If there are a sufficient number of fatal and nonfatal overdose events per county of residence (>5 events), we will also create maps of overdose rates by county. We may also describe results by county by creating maps. Any rates or counts involving fewer than 5 individuals will be suppressed (i.e., the results will not be viewable on a map), consistent with confidentiality standards of DHS.

Hepatitis vaccination outcomes. We will describe vaccination prevalence and use a time-to-event analysis approach (i.e., Kaplan Meier curves and survival analysis with Cox Proportional Hazards regression models) to quantify predictors of hepatitis A and B vaccination among people who inject drugs. We will calculate vaccination prevalence overall (defined as being vaccinated on or before

participation in our prior study). If there are a sufficient number of individuals vaccinated per county of residence (>5 events), we will also create maps of vaccination prevalence by county. For the time to event analysis seeking to understand predictors of vaccination, we will exclude persons vaccinated prior to study enrollment from the predictor analysis to ensure temporality (i.e., that predictors measured during our prior study occurred before the outcome of vaccination). This will involve calculating person-time as the number of days from study participation date through the date of outcome data provided from DHS. We will examine sociodemographic and behavioral risk and protective factors (covariate list provided in the appendix) by quantifying hazard ratios. We may also describe results by county by creating maps. Any rates or counts involving fewer than 5 individuals will be suppressed (i.e., the results will not be viewable on a map), consistent with confidentiality standards of DHS.

Data analysis for Aim 2.

Guided by principles of grounded theory,[62,63] interviews will be analyzed for emergent themes as soon as interviews are transcribed. We will examine study transcripts to identify primary coding categories as well as a range of themes present within each category. Identified coding categories and themes will be organized into a formal code book, and we will extract illustrative quotes. Transcripts then will be formally content coded. If suggested by the data, thematic categories will be refined, merged, or subdivided, and/or new themes created. To ensure coding reliability, summaries will be coded by at least two raters who will discuss discrepancies and reach consensus. Decision trails will be noted and documented.

Quantitative data collected and returned via mail and email by rural primary care providers will be manually converted to an electronic format for data analysis. This data will be used to describe provider-level barriers, such as unawareness of the burden of HIV, HCV and sexually transmitted infections, a related tendency to under-screen for these conditions, and possibly stigmatizing attitudes towards people who inject drugs that may contribute to under-utilization of primary care services by high risk individuals. Insight gained through these surveys may be used for the design of the UH3 phase.

Triangulation of data.

Data from the cross-sectional survey and biological specimen testing (Aim 1) will inform disease prevalence and associated risk behaviors in our initial catchment counties. Data from the quantitative mail and email-based primary care provider survey and qualitative provider and client interviews (Aims 2b/2c) will provide contextual information about drug use, risk behavior, and service access and utilization. These data will be layered onto the compilation of the county-level data and resources (Aim 2a) and a comprehensive summary report will be generated to guide evaluation of which counties are best suited for the implementation phase.

Benchmarks for progressing to UH3 phase.

If the research proposed above is successful, by the end of year 2 we will have established estimates of the burden of infectious diseases in six rural counties, and described service gaps that must be filled in order to ensure that people who inject drugs have access to the complete package of prevention services. We believe that transition to the UH3 phase of the study, which is described below, will be justified if we achieve the following milestones: (1) ***Client reachability:*** We will enroll no fewer than 800 SSP clients who reside in rural communities during the 12-month recruitment period of the UG3 phase. Based on current and historical volume of prevention encounters at Vivent

Health offices, we expect to be able to achieve the recruitment target of 1,200 individuals without difficulty. However, if enrollment is substantially slower than expected, we believe that recruiting at least 2/3 of this number will demonstrate our ability to engage SSP clients in sufficient numbers to answer our research questions and guide implementation of the Client-Based Prevention Home model. (2) ***Local service capacity:*** We will confirm there are sufficient resources in at least 3 of the 6 targeted counties to ensure it is feasible that SSP clients can utilize all 9 of the essential prevention services. For example, we might not be able to move forward with implementation of the service delivery model if we cannot identify providers who provide MAT or are willing to start provision of this service with support and consultation from the UW Addiction Medicine Program (see "Provider-level interventions" below). (3) ***Community stakeholder willingness:*** We will confirm that key stakeholders (e.g., MAT providers, County Public Health Officers, Criminal Justice Agencies, others) are supportive of the new prevention services model participating counties. We will obtain letters of support if requested by funders.

Data Analysis for Aim 3.

There is not a single, primary outcome which can be measured to fully evaluate the impact or effectiveness of the intervention. We therefore have proposed a study design that allows us to evaluate the influence of prevention navigation on progress toward a number of health goals. Appendix 2 shows outcomes we propose to measure.

We will use generalized linear mixed models that will allow us to establish linear growth models. Using quarterly assessments, we will analyze growth rates for each outcome and control for time-variant covariates. Additionally the analysis will allow us to assess the effects of interventions outside of our study that may play a role in our outcome.

Data Analysis for COVID-19 Pilot Cohort.

The objectives of the analysis are consistent with the UH3 study design to evaluate the influence of virtual prevention navigation on progress toward a number of health goals. However, given the restricted timeline for prevention navigation with two assessments one month apart, we will assess pre-and post-changes in factors associated with the risk of HCV, HIV, and overdose death among PWID.

7.0 STATISTICAL CONSIDERATIONS

Sample size and power considerations for Aim 1. Power to detect a significant impact of the client-centered prevention home model is based on the change in proportion of clients in the 3 target counties who receive the 9 essential services (see Table 1, pg. 2) compared to clients in the 3 non-targeted counties. The design effect for respondent-driven sampling is a complex function of the network structure in the population, and thus, it is difficult to precisely estimate the sample size requirements. Nevertheless, simulation research indicates that the design effect for respondent-driven sampling is likely to be 2 or less,[64] which suggests that a sample twice that of simple random sampling should provide adequate power. We estimate that approximately 10% of all clients will have access to all 9 essential services prior to the study. Applying a design effect of 2, and given a sample size of 800-1200 clients, the study will be powered to detect an increase in service provision of 8-10% (424 subjects per group is sufficient to detect a 10% difference in essential service provision rates; 582 subjects per group is sufficient to detect an 8% difference), assuming 80% power and 5% type I error.

Sample size and power considerations for Aim 3. The complexity of our study design requires multiple longitudinal approaches to account for independent and dependent samples. Based on our formative work, an average of 2 clients enrolled per week into the study is feasible for the SSP staff.

With a sample size of 405 (270 intervention and 135 controls), we would have 80% power to detect a difference between 28% and 42% in the same outcome, an effect size that we believe is meaningful and realistic to achieve. In other words, the sample size was chosen to ensure that the Primary Aim 1 comparisons of "Strongly Agree" vs all others of a factor would have sufficient power to detect clinically meaningful increases in accessibility. To address Primary Aim 1, we used preliminary data from the first phase of the study to assume that the base rate of a participant who will strongly agree that it is easy for them to access addiction treatment services is 26%.

COVID-19 Pilot. Given the uncertainty of the timeline for prevention navigation, it is unclear how large our sample size will be. Understanding that there will be two assessments one month apart, we will use matched pair t-test to assess differences between the first and second assessments. Using the same process as above, comparisons of "Strongly Agree" vs all others of a factor would have sufficient power to detect meaningful increases in accessibility. We expect a total sample size of 216 PWID, which provides adequate statistical power (0.83) to detect a 20% difference between three time points of interest (two-sided alpha=0.05).

8.0 RECORDS TO BE KEPT

- Subject demographics & locator forms
- Subject consent forms
- ACASI questionnaires
- HIV testing forms
- Hepatitis C testing forms
- Audio recordings of interviews
- De-identified transcriptions of interviews
- Paper-based primary care provider surveys
- Handwritten notes from individual interviews
- Agency and service provider referral lists
- Participant intervention files (paper and virtual)
- DHS data on UG3 participants
  - COVID-19 infection, death, hospitalization, testing, and vaccination data
  - Fatal and nonfatal drug overdose data
  - Hepatitis vaccine records

9.0 PROTECTIONS AGAINST RISK

A. Characteristics of human participants

Individuals in the cross-sectional and client interview (UG3) phases will be eligible for enrollment if they are 15 years of age or older, have injected any drug in the past 1 month, and reside in a rural community. Rural residence will be determined by ZIP code, which will be programmed in the screening instrument on REDCap. The eligibility form will classify a participant as a rural resident if the ZIP Code's RUCA Approximation is greater than or equal to 4, or if they live in a catchment area of the SSP. ***Providers*** will be eligible if they are employed by an agency that serves opioid users. All study participants must be capable of communicating in English.

Individuals in Phase 2 (UH3) will be eligible if they are 18 years of age or older, have injected any drug in the past 1 month, and reside in a rural community.

B. Inclusion of Women and Minorities

Minorities: The study will include people of all races and ethnicities proportional to rural population of injection drug users accessing services.

Women: Women will be included in the study proportional to rural population of injection drug users accessing services.

C. Participation of Minors

Phase 1 (UG3). Minors ages 15-17 will be eligible to participate if they meet other eligibility criteria. Under the applicable federal regulations (45 CFR § 46.402(a)) "children" are persons who have not attained the legal age for consent to treatments or procedures involved in the research, under the applicable law of the jurisdiction in which the research will be conducted. Under Wisconsin statutes, minors age 15-17 may consent for STI testing and treatment, HIV testing, and alcohol or drug abuse assessment, evaluation, or treatment (outpatient). Thus, minors ages 15-17 are not "children" for purposes of the applicable regulations with respect to these tests. Additionally, the IRB will be asked to determine if this research protocol is designed for a subject population for which parental or guardian permission is not a reasonable requirement to protect participants and may waive the parent/guardian consent requirement. Federal regulation requires an "appropriate mechanism for protecting the children who will participate as subjects" as a substitute for parental consent. This will be accomplished by having an adult counselor from an advocacy organization available by telephone for minors to discuss the consent or other concerns. The consent document will notify minor participants that such resources are available if needed, and all research staff will be prepared to link clients to a local agency belonging to the Child Advocacy Centers of Wisconsin (http://www.cacsofwi.org).

Phase 2 (UH3). No minors will be participating in this phase of the study.

D. Protection of Incarcerated Individuals

For Aim 3, our program is a 12-week intensive case-management program. Therefore we want to ensure that participants who become incarcerated have a way to re-engage with the study and intervention once they are released from jail or prison. If it is learned that a research participant is incarcerated at any time in the study, they will be immediately un-enrolled and research activities will be suspended. Participants in the intervention arm may receive contact from the prevention navigator to notify them of this and explain the process. No data will be collected from the participant during this time. Upon release, participants may contact Vivent Health staff to re-enroll in the study. The consent document will be reviewed with the participant at this time to re-assess willingness to participate. Participants can take their assessment after 2.5-5.5 months from baseline or follow up assessment. If the opportunity to take the assessment is no longer available, then we treat it as missing.

E. Participant recruitment and consent

Provider interviews. Directors or other key contacts at identified agencies providing services to opioid users will be contacted and asked to have one or more designated representatives from their agency participate in the qualitative interview. Providers will not be asked to provide any personal information, and therefore are not considered research subjects.

Provider surveys. Providers that will be invited to participate in the survey will be mailed a survey that will explain the study using a cover letter. The contact information of the study team will be provided for the participant to use, should they have any questions. The consent script will be provided at the beginning of the survey. If a provider agrees to take part in the project, they will simply fill out the survey and mail it back.

The provider survey will be administered by the UW Survey Center (UWSC). UWSC will administer, track, enter, and code the survey data. Questionnaires handled by data entry staff are tracked via case identification numbers only. Completed questionnaires are stored in locked file cabinets or locked storage rooms within their secure data entry facility for up to 7 years as required by Human Subjects protocols. After this period, hard copies of questionnaires will be destroyed. Sample files will be handled only by the UWSC project director and programmer for this study, and will not be merged with study data files for delivery to their clients. UWSC will send us a SAS database of our data using a secured file transmitting system. A last attempt to increase our response rate will include an email explaining the study and a website hyperlink to fill out a survey. The web-based survey will be housed on the same platform of the ACASI survey.

Client interviews. People who participate in the cross-sectional study described above will be systematically invited (e.g., every nth person) to also participate in a qualitative interview. Interested participants will be contacted by study staff to set up an interview appointment. Clients will be asked to sign an additional consent prior to enrollment in this study activity.

Phase 1 (UG3) Participants. Vivent Health prevention staff will meet with the person in a private room to explain more about the study. If they are interested, they will be given a consent document to read, and a phone call will be placed by Vivent Health staff to a study coordinator at UW-Madison. The participant and the researcher will then speak by phone in a private location to complete the eligibility screening and informed consent process. This will be done to minimize the impact of the research activities on the routine prevention activities of Vivent Health staff, and ensure that potential participants have enough time to have their questions answered prior to deciding whether or not to participate. During the initial phone call, potential participants will be provided with a detailed explanation of the study and questions will be answered. People who are willing to participate will be given formal informed consent using an iPad. Participants undergo a comprehension quiz on the iPad that assesses their understanding of the consent documentation. If a person agrees to take part in the project, he/she will be asked to sign the consent and HIPAA forms, which after the conclusion of the phone call with UW-Madison research staff, will be handed to the Vivent Health prevention team member to be filed in a locked file cabinet. Copies of the signed consent documents will be sent via secure fax to the study coordinator in Madison. A signed copy of the consent and HIPAA forms will provided to the participant upon request. For participants ages 15 to 17, the consent form may be used to obtain consent of the minor, provided the study personnel determines that those minors can

comprehend the consent form. The consent form will be modified for participants ages 15-17 by adding a separate authorization section for the minor and the person obtaining assent.

For the retrospective analysis of stored HCV+ serum specimens obtained from WSLH and shared with GHOST laboratory collaborators, a waiver of consent and authorization is requested.

If participants are screened using a paper form at Vivent Health or at an outreach event, a paper copy of the consent document will be given to them and the Vivent Health staff will go over the study procedures. A study coordinator will be on standby to speak to the participant over the phone if they have any questions. If the participant agrees to be part of the study, the participant will be asked to sign the paper copy of the consent form. The form will be kept in the participant's folder in a double locked cabinet. Vivent Health already has a process in place since they work with HIV testing and case management. During outreach events, Vivent Health staff will securely transport screening documents and rapid test forms in a locked briefcase and store the forms in the participant's folders in a double locked cabinet. Once the participant has signed the paper copy of the consent form the iPad will begin at the ACASI survey, therefore the consent documentation will not be replicated.

DHS Linkage Study on COVID-19 Pandemic Impact Among UG3 Participants. For the analysis of the impact of the COVID-19 pandemic on the UG3 cohort, we will be providing DHS with identifiable data on UG3 participants, including participant name, date of birth, gender, race, ethnicity, previous address, previous phone number, date of participation in our study to facilitate linkage with approved registries (vital records, hospitalization, Wisconsin Electronic Disease Surveillance System, Wisconsin Immunization Registry). We are unable to re-obtain consent from participants for this data linkage because of the transient nature of this population and their lack of consistent access to a phone or other communication devices. It is not uncommon for the phone number that was used to initially recruit the participant to be inactive or out-of-date within days. It would be unfeasible to re-obtain consent participants from this cohort more than two years after initial recruitment. Considering this, we seek a Waiver of Consent and a partial waiver of authorization to link original cohort data with DHS data. We have also provided a justification as to how the original study's Certificate of Confidentiality is aligned with this linkage study. These justifications can be found within the Arrow application. Prior to sharing data or receiving data from DHS, we will obtain a signed Data Use Agreement that outlines the terms of the data sharing. A log of disclosures will be maintained in accordance with guidance from the HIPAA privacy officers consulted in the design of this study (Ryan Moze, Staci Lowe; using the template: https://compliance.wisc.edu/wp-content/uploads/sites/102/2019/02/Accounting-for-Disclosures-Log-Research.pdf).

Phase 2 (UH3) Participants. Vivent Health staff will meet with participants in a private location within the SSP office for all aspects of the study. All forms will be delivered in person, and staff will gauge comprehension throughout the enrollment and verbal consent process. Participants will be given a copy of the verbal consent if they choose to participate. Paper copies of all documents will be stored in a locked cabinet, only accessible by the research team. Protections for the ACASI survey and blood specimens will be protected in the same manner as phase 1. The screening questionnaire will be the first document with both a name and study ID on them, and subsequent documents will only have one or the other, aside from testing documents. If necessary, all of the above activities may take place virtually, with electronic record keeping privacy considerations.

COVID-19 Pilot. All activities related to recruitment and consent will be conducted virtually either over the phone or via Microsoft Teams video call. Prevention navigators will hold responsibility for recruitment, unless UW staff assist by calling UG3 participants if necessary. UG3 participants who consented to future contact will be called using a random list by navigators. Additionally, participants will be passively recruited by study fliers distributed in prevention kits to clients, and by Vivent staff services. Those who are interested will be given a detailed description of what virtual navigation would look like, and will be screened for eligibility. If eligible, verbal consent will be taken only after the participant answers a series of questions about what the study involves to confirm comprehension. If ineligible, name and demographics will be retained on REDCap and a DOM secure drive to monitor duplicate screens and compare ineligible participants to those who enrolled. A paper copy of the consent form will be mailed to the participant upon authorization to do so or sent by text message/email if that is the client's preferred method of contact.

ACHESS. Upon account setup, participants will be able to choose a unique username that does not need to include their name or any other identifiable information. This username will be the name that appears in the pick list of participants available to private messaging, and listed on any discussion board posts. To protect participant's identity, it will be recommended that participants choose a username that will not include identifiable information such as first or last name, etc.

All subjects will have the option to contact study staff to turn off private messaging. This would prevent any incoming private messages, along with removing the participant's username from the picklist of participants who can be contacted by private message. Study staff will be able to monitor private messages, and participants can report any inappropriate or unwanted messages to study staff. The study team also has the option to turn off the private messaging function to those who send inappropriate or unwanted content to other participants to prevent future unwanted content.

F. Sources of research data

The source of research data is clients' (injection drug users) biological specimens and their self-reported survey data (all clients); and the qualitative interview (for people who complete this activity). Provider participant data will be limited to their qualitative interview and quantitative mail and email-based survey. For phase two we will also be collecting demographic information, program data from intervention sessions (upon completion of the study), testing data, and contact information from all participants.

DHS Linkage Study on COVID-19 Pandemic Impact Among UG3 Participants. For this analysis, we will obtain external data from Wisconsin DHS via linkage of identifiable data from UG3 participants will several DHS registries, as described in detail above.

G. Potential risks

Potential psychological risks to participants in this study are: (1) negative consequences if confidentiality of information obtained in this study were violated; (2) embarrassment, discomfort, or distressed emotional reactions to the study assessment measures; (3) increased anxiety about personal safety and wellness resulting from the interview or survey; and (4) potential for minor bruising or irritation from a phlebotomy blood draw if confirmatory HIV test is required due to a

reactive rapid test. Emotional distress is common after a person learns he or she is HIV or HCV-positive.

COVID-19 Response. In addition to the above risks, if a participant may go into the community for treatment, confirmatory testing, or any other reason related to the study there is a risk of COVID-19 transmission. In order to mitigate this, Vivent Health is providing as many virtual services at possible, at home testing, and referrals to tele-medicine sources when available.

H. Steps to protect against or minimize potential risks

Confidentiality protections. A number of steps will be taken to protect the confidentiality of participants' data and their identity. All investigators have extensive experience in the safe collection, handling, and storage of sensitive and highly confidential data. All name-identified information (e.g., informed consent) will be kept in a locked file, separate from any data. Data-related materials will be identified by a unique Research Identification Number (RIN) and stored in a second locked file. All materials will be kept in a locked room, ensuring two locking measures. Access to these two files will be limited to the research team. All data files will be securely transferred using encryption. Computer databases will be password protected and accessible only to the research team. No individual identities will be used in any reports or publications that may result from this research project. Data requested from researchers from organizations not formally collaborating on this research project will only be shared in aggregate form per NIH and federal data sharing regulations.

Prevention Navigation materials will utilize study ID only, and will not include a name on them, as to prohibit this link from being made again in another location and to protect the individual's identity should a breech occur. Navigation files will be double locked and stored separately from any forms containing the participant's name if a physical copy. All virtual copies will be stored in a secure Vivent Health server. Because of the nature of the participant's lives, navigation sessions may need to occur outside of the office in a public location. Only essential documents will be brought with the navigator in a locked binder with a secure code. Documents will be immediately returned to the office to be double locked and stored properly. Should a prevention navigator need to work from home (for example, due to COVID-19 restrictions) essential files with study IDs and not names may be brought home in a secured binder and locked in a secure location inside their home. Files may not be left in a vehicle or outside of a locked room or cabinet.

We recognize that we are asking participants to provide sensitive information about private behavior and health. Our research team is experienced in the collection of this type of information, and we will implement multiple safeguards to protect participants' confidentiality. All project protocols will be subject to review by the institutional IRB at the University of Wisconsin-Madison. The UW-Madison IRB will approve research involving children only if the IRB finds that the research includes any required additional safeguards outlined in ethical principles and applicable federal regulations, state laws and institutional policies. An inter-institutional agreement will be signed between the University of Wisconsin-Madison and Tulane University for IRB oversight; and a data sharing agreement will be obtained for any information shared with the Wisconsin Department of Health Services AIDS/HIV

Program, the Wisconsin Division of Care and Treatment Services, and any outside jurisdictions (e.g., GHOST lab) with which data will be shared. Vivent Health staff will be included in the University of Wisconsin-Madison IRB protocol. A Certificate of Confidentiality has been obtained as a condition of the NIH grant award. All study participants will be fully informed of the project goals and procedures, and of their rights as research participants, including the right to not participate without penalty. Signed consent will be obtained prior to the collection of any data, or the conduct of any research activities.

Pregnant women are a vulnerable population whose inclusion in this research is justified by the increasing incidence of neonatal abstinence syndrome, and increased prevalence of opioid use among women of childbearing age. Although drug use in pregnant women does not require mandatory reporting under state law, study team members may choose to voluntarily report it. The possibility of this and the risks if this were to be reported will be clearly outlined in the consent form. Prevention navigators will also communicate with the participant the risk of medical providers reporting such drug use when initiating referrals for care.

Per HIPAA, participants will be advised during the consent process of our intent to collect biological specimens to test for HIV, HCV, and other STIs. Positive tests will be reported to the health department per state and local regulations.

Follow up contacts will be performed with participants in both the intervention and control groups. Vivent Health study staff will perform all follow up contacts with intervention participants. These follow ups include appointment reminders, appointment scheduling, checking in after an important appointment, booster sessions via phone, and discussing test results. These contacts will be made in accordance to the participants' preferred contact method. Contacts with the control group will all be performed by the project manager on the designated study phone to enhance trust with participants who may not want calls from strangers. Calls will be made to remind them to schedule follow up visits. Control participants will be called no more than 3 times between each research visit to eliminate disruption to their daily lives. All social media interactions will occur using a professional Facebook account separate from personal accounts. Facebook's privacy policy will be given to the participant if they choose to contact their PN via Facebook, and they will be reminded that it is not a secure form of communication. PNs will suggest alternative ways to privately discuss treatment and care in detail. All phone calls and text messages performed by Vivent Health staff will be done on a Vivent Health provided work phone, separate from staff's personal information. These phones have secure codes and laptops have two-factor authentication. Phone calls and text messages sent by the UW research team will be performed on a study phone only accessed by one person with a secure code. No names will be stored in the phone.

DHS Linkage Study on COVID-19 Pandemic Impact Among UG3 Participants. Given the transient nature of people who inject drugs, re-consenting participants for this data linkage study and analysis would not be feasible, as the proposed analysis will occur at least two years after original recruitment of UG3 participants when contact information is no longer valid. Moreover, the need for this analysis stems from the COVID-19 pandemic emergency, which was not foreseeable at the time of original recruitment. As such, we will carry out the linkage via a waiver of consent and partial waiver of

authorization. Identifiable information that will facilitate the linkage will be shared within the purview of Data Use Agreements that will be established prior to any data transfers. Study activities for this data linkage have been reviewed and approved by the Data Governance Board at DHS, pending subsequent IRB approval and the establishment of the aforementioned agreements. Once the linkage is completed, participant data will be destroyed and not kept on file by DHS. Our study team will receive the linked dataset containing only a unique research identification number (identifiers will be removed before DHS provides the linked dataset).

Steps to reduce discomfort or anxiety resulting from study participation. Assessment measures involve sensitive topics related to safety and wellness. Some participants may feel awkward or embarrassed when discussing, hearing about, or being asked to provide information related to their safety and wellness. Staff are trained to employ techniques that prevent, reduce, or minimize embarrassment, discomfort, or atypical stress associated with study participation. Staff will be trained to observe for any evidence that a participant may be overly anxious and to assess whether threat sensitization and vulnerability perceptions are realistic. Vivent Health and research field staff will be required to have extensive research- or program-based experience with the conduct of HIV-related research. The project will be guided by a detailed procedural manual, and field staff will receive intensive training focused on the specific project protocols and materials to ensure that they are being rigorously and consistently implemented, including extensive role-play rehearsal of recruitment, enrollment, and consent procedures and assessment procedures and materials. Staff will be required to demonstrate competence with project protocols prior to implementation. Investigators and field staff have or will be required to complete the NIH required CITI web-based ethics training. Interviews will be supervised by the lead project investigators to ensure protocol adherence. The field team will meet regularly to discuss implementation issues and areas warranting additional training. If research personnel change during the course of the study, new staff will be required to complete the training described above prior to conducting any research activities.

HIV, HCV, and syphilis testing and counseling safeguards. All testing staff have completed the Wisconsin AIDS/HIV Program state HIV test counselor training to ensure that HIV pre- and post-test counseling is conducted in accordance with state guidelines. Testing staff will be further required to complete training and demonstrate competence with the fingerstick collection of whole blood specimens (i.e., rapid HIV, HCV, and syphilis point-of-care testing methodology) and phlebotomy blood draws prior to study Implementation; and complete annual training in blood borne pathogen control (“universal precautions”) to ensure adherence to the Occupational Safety and Health Administration Occupational Exposure to Blood borne Pathogen standards. Any new staff who are hired will be required to complete the training package described above, and demonstrate competency with HIV, HCV, and syphilis testing and counseling. James Sosman, M.D., will provide on-going review of counseling and testing procedures, as well as the interpretation and provision of test results to study participants. If any adverse physical harm results from the administration of the rapid HIV, HCV or syphilis tests, free medical follow-up will be provided to participants. Vivent Health is a CLIA-certified HIV test site funded, in part, by the Wisconsin Division of AIDS/HIV’s HIV testing program.

Specimens will only be sent for confirmatory testing for those rapid tests that they are already positive for, therefore, no new health information will be generated by analysis of these samples.

COVID-19 Pilot. All data collected from participants will be stored on a secure server, REDCap, Qualtrics, and/or Client Point. Participants will be assigned a unique study ID, which will be linked to their name in on the screening form, housed on the Vivent Health server, PHI box, and REDCap. All other forms used for these participants will only have their study ID attached. Testing forms will follow Vivent Health's virtual testing protocol.

All calls for virtual navigation, and originally proposed UH3 navigation performed virtually, will be conducted through a cell phone provided by UW or Vivent Health, or on Vivent Health's approved video conferencing platform, Microsoft teams. Staff may conduct reminders or follow ups via their work telephone. Facebook messenger from a business profile, or mail if the client consents to that form of contact.

All other privacy and protection safeguards listed in above sections involving testing, staff training, and reducing anxiety related to the study will be followed as outlined above.

I. Data safety and monitoring plan

See Appendix 1.

J. Data Safety Monitoring Board (DSMB)

For the second phase (UH3), a DSMB will be convened for this study in collaboration with the University of Wisconsin Institute for Clinical and Translational Research (UW ICTR). The ICTR Data Monitoring Committee (DMC) meets the requirements for an independent Data and Safety Monitoring Committee or a Data and Safety Monitoring Board. The committee is comprised of experienced clinical researchers representing a diversity of backgrounds, skills and knowledge. The DMC helps investigators ensure subject safety, research integrity, and compliance with federal regulations and local policies. The DMC also makes recommendations to the PI that could include actions of continuation, modification, suspension, or termination. Prior to submission of the final protocol and IRB application to the UW Health Sciences Institutional Review Board, the PI will request a DMC consultation using the online application form. Once convened, the DMC will meet annually to review study procedures and provide a report to the PI, which will be then submitted to the UW IRB and the NIDA PO within a month after each meeting.

K. Costs and alternatives

There are no costs to the participants for taking part in this research project. The participants have the alternative NOT to participate in this project or seek services independently from other agencies.

L. Incentives

Aim 1 and 2. Participants will receive $20 remuneration for survey participation on the day of enrollment, and will receive a smaller incentive of $10 for each eligible peer recruit who enrolls in the study. For participants who have a reactive HCV rapid test and are unable to provide a blood sample for HCV confirmatory testing due to phlebotomy difficulties, a one-time incentive of $10 will be provided if they return at a later date and attempt a second blood draw. Syringe program clients and local service providers who agree to participate in qualitative interviews will be paid an incentive of

$30 each for one hour-long interview. All primary care providers who are selected to participate in the quantitative mail-based survey will receive an incentive of $5 at the time the survey is mailed to them.

Aim 3. Participants will receive $20 remuneration for survey participation and rapid testing on the day of enrollment, and will receive an additional incentive of $20 for 3-month, and 6-month assessments. Participants may also receive a monthly incentive of $5 to update their contact information so we have the most up to date information to decrease the risk of loss to follow up if it is deemed necessary to do so. For participants who have a reactive HCV rapid test and are unable to provide a blood sample for HCV confirmatory testing due to phlebotomy difficulties, a one-time incentive of $10 will be provided if they return at a later date and attempt a second blood draw. Additionally, participants will receive $10 for each eligible peer recruit who enrolls in the study.

COVID-19 Pilot. Participants will receive $10 for each research assessment (baseline, 4 weeks, and 30-days post service resumption). There will be no incentives for testing during this sub-phase of the study.

L. Potential benefits in relation to risk of the proposed research to the participants and others

There are no direct intended personal benefits from participation in the **UG3 phase** of this study. Although participants may not individually benefit from the study, the information obtained will guide the development of a comprehensive program aimed at protecting the health of PWID. In the **UH3 phase** of the study who receive the Client-Centered Prevention Home intervention are expected to achieve more positive health outcomes and better linkages to services and care than people who do not receive this intervention.

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APPENDIX 1: DATA AND SAFETY MONITORING PLAN

PI Name: Westergaard, Seal (MPI)
Grant Number: UH3DA044826
Grant Title: Community-based client-centered prevention homes to address the rural opioid epidemic
Institution: University of Wisconsin - Madison

1.0. Project Overview

1.1. PI Statement of responsibility for developing and executing DSMP. As contact PI for this application, Dr. Westergaard accepts responsibility for implementation of the data and safety monitoring plan, and acknowledges the requirement to request and receive permission from the PO for protocol or DSMP changes in advance of their implementation.

1.2. Brief protocol description. In response to RFA-DA-17-014, HIV, HCV and Related Comorbidities in Rural Communities Affected by Opioid Injection Drug Epidemics in the United States: Building Systems for Prevention, Treatment and Control (UG3/UH3), our research team proposed a multi-phase, mixed-methods study that aims to implement and evaluate a novel community response model, which we have named the Community-Based, Client-Centered Prevention Home, or Prevention Navigation.

Using the organizational infrastructure of Vivent Health, a geographically dispersed population of people who inject drugs in rural communities across Northern Wisconsin, we are building locally responsive systems to facilitate uptake of evidence-based prevention services for high-risk clients. The Client-Centered Prevention Home (CCPH) model incorporates prevention case management (called Prevention Navigators) into traditional harm-reduction services delivered at syringe service programs, which we hypothesize will increase use of treatment and prevention services. During the first 2 years of the project (UG3 phase), we performed needs assessments in six rural Wisconsin counties in partnership with local stakeholders, and conducted a survey among people who inject drugs. In the next three years of the project we will deploy and evaluate the CCPH model. The growing problem of opioid injection in rural Wisconsin is highly significant because it exemplifies trends observed nationally indicating severe vulnerability to worsening epidemics of HIV, HCV, and opioid overdose deaths in rural communities that are substantially underserved by evidence-based prevention interventions.

1.3. Study aims and study outcomes. The aims of the intervention is to evaluate the impact of the Client-Centered Prevention Home model, deployed within syringe service programs in counties with high burden of opioid injection, on the proportion of clients who receive the package of essential preventative services to prevent HIV/HCV in PWID.
The goal of the Client-Centered Prevention Home program is to increase the knowledge of people who inject drugs on navigating prevention and treatment services for HIV, HCV, and drug overdose. We describe measures for our study population in the Appendix. Key sources for measurement will come from the ACASI survey that will be adapted from the ROI Harmonized UG3 survey, surveillance data gathered from the state of Wisconsin, and Medicaid health utilization data.

1.4. Study data collection sites. The main community partner, Vivent Health, will serve as the data collection and study site. Vivent Health is a statewide organization that provides harm reduction services, including syringe services and confidential HIV and HCV testing. As shown in Figure 1, three sites will be used for the intervention of the study: Brown County (Green Bay), Marathon County (Wausau), and La Crosse County (City of La Crosse). The 3 other Vivent Health offices that participated in the UG3 study phase, including Outagamie County (Appleton), Eau Claire County (City of Eau Claire), and Douglas County (Superior), will serve as recruitment sites for control group participants during the UH3 phase, but will not provide the prevention navigation intervention.

1.5. Study sample description and inclusion and exclusion criteria. Leveraging relationships developed among Vivent Health clients and community partners during the UG3 phase, we will recruit participants using Vivent Health staff at all six counties. In order to be part of the study, participants must meet the following eligibility criteria: 1) clients must be at least 18 years old, 2) have injected drugs to get high in the past 30 days, and 3) reside in one of the participating communities in or around one of the six participating counties.

Exclusion criteria are: (1) not speaking English fluently, (2) residing outside or being unwilling or unable to travel for study visits at one of the participating communities.

1.6. Sample size. A total of 405 participants will be enrolled to evaluate the intervention (Figure 1). Study procedures will vary for participants based on enrollment into 2 study groups, as follows:

(a) 270 participants enrolled at intervention sites, who will receive prevention navigation.

(b) 135 participants enrolled across the 3 non-intervention sites, who will serve as a contemporaneous control group.

1.7. Study design. In order to measure the impact of the Client-Centered Prevention Home we will prospectively assess the 12-week intervention by measuring outcomes at baseline, 3-months, and 6-months. We will target participants who engage in syringe services at Vivent Health and may be interested in additional services that may be offered in our multilevel harm reduction intervention. At intervention sites, the Prevention Navigator will engage prospective clients by screening them for the study, having the participant sign the consent form and performing baseline assessments along with rapid testing for HIV, HCV, and syphilis Using the same infrastructure used in the UG3 phase, a second group of controls will be enrolled at the three non-intervention sites. Syringe service program staff at the non-intervention sites will recruit participants for baseline, 3-month, and 6-month assessments during the two year study period.

The health-related goals for PWID in the context of this study are multi-faceted, reflecting the heterogeneous needs of this vulnerable population. Accordingly, there is not a single, primary outcome which can be measured to evaluate the impact or effectiveness of the intervention. We therefore have proposed a study design that allows us to evaluate the influence of prevention navigation on progress toward a number of health goals. Because no single study design can account for all of the biases inherent in a non-randomized, multi-county intervention trial, we have proposed 2 different types of comparisons in our evaluation strategy:

(A) **A within-person comparison using a pre/post study design**
Participants among intervention sites will serve as within-person comparisons as they will participate in baseline assessments, including self-reported outcomes evaluated using ACASI questionnaire, and then again in 3 and 6 months This is ideally suited for short-term outcomes that we hypothesize will be immediately influenced by prevention navigation, such as perceived accessibility of services, and readiness/motivation to initiate addiction treatment. These self-reported outcomes are listed in Appendix 2.

(B) **A comparison of participants enrolled at sites with and without prevention navigation**
In separate analyses, we will compare the self-reported outcomes of individuals enrolled at Vivent Health offices offering only standard prevention services without prevention navigation. This is advantageous for detecting changes over 6 months of follow-up.

(C) **A cohort-study design comparing longer term outcomes using external data sources**
To detect changes in so-called “hard” outcomes such as enrollment in insurance, HCV cure, hospitalization, and initiation of medication assisted treatment, we will access sources such as the Wisconsin Medicaid data for all enrolled participants for up to 2 years after enrollment. This strategy is enabled by the data sharing agreements and database resources created through our JCOIN Supplement award in 2018-19. Additional data sources include the Wisconsin Electronic Disease Surveillance System and the Wisconsin Immunization Registry.

1.8. Consent documents. When a client agrees to participate in the Client-Centered Prevention Home, he or she will be informed about the research aims of the project by the Prevention Navigator during the intake encounter, they will be asked to provide informed consent to participate, and authorize the research team to use their health information. The consent form will cover information on the protocol, risks, benefits, and protections for the participant. It will also note the existence of a Certificate of Confidentiality for the intervention. The consent document will remind participants that their participation is voluntary, and that their decision of not participating will not jeopardize their relationship with ARCW and UW-Madison. Consenting participants will verbally consent, and a copy of the consent form will be available to them upon request. Additional consent documents will be signed for rapid HIV and HCV testing as per procedures from the Wisconsin Department of Health Services.

1.9 Collection of data for research/evaluation, In order to evaluate the effectiveness of the Client-Centered Prevention Home, data will be collected data using various tools throughout the UH3 phase. Interested participants will first be screened for the study by the Prevention Navigator or research staff by phone or in person, respectively. Once screened eligible, participants will be tested for HIV, HCV, and syphilis at baseline, 3-month, and 6-month follow up. Testing forms

provided by Wisconsin Department of Health Services for routine testing will be used and information from the forms will be collected for research. At baseline, 3-month, and 6-month follow up, participants will complete an audio computer-assisted self-interview (ACASI) survey that will assess substance use, injection behavior, past overdoses, addiction treatment, stigma, infectious diseases, access to health care, sexual risk behavior, mental health, criminal justice, and basic demographics.

1.10. Collection of data for intervention implementation. The RE-AIM framework will be used to measure adoption and implementation of the intervention. In order to assess whether Prevention Navigators' fidelity to the various elements of the intervention's protocol are met, we will use program data to measure consistency of delivery as intended for the intervention. After the participant has screened eligible and have provided informed consent, participants will engage with the Prevention Navigator at their first intake. During that time, participants will be asked to sign an agreement of services, fill out a locator form, release of information form, and service request form. At the second session, participants will come back to assess their risk for infectious diseases and overdose, and will develop a service plan using a problem solving worksheet and goals sheet. The problem solving and goals sheet will be amended at each session to assess progress to goals. Once the participant is ready to be discharged from the program, Prevention Navigators will fill out a discharge form that will consist of a checklist to make sure that there is plan in place for each goal that was set. Communications logs will document every successful and unsuccessful attempt in contacting participants and will be used to measure fidelity of the protocol.

1.11. Projected timetable. During the three year study period, the first quarter will be used for protocol development, hiring, and training of staff. Open enrollment for recruitment will begin during the second quarter and will continue through the second year. Enrollment for the study will end during the summer of the second year in order to have a full 6-month assessment for each participant. The last year will be used to close out the intervention, analyze the data, and disseminate our findings. The timetable is presented in Table 1.

Table 1. CCHP Project Timetable

Activity	UH3 Phase											
Quarter	1	2	3	4	5	6	7	8	9	10	11	12
Develop protocol and IRB	▲											
Hire and training staff	▲	▲										
Collect county-level data							▲	▲	▲	▲	▲	▲
Recruitment of intervention and control participants		▲	▲	▲	▲	▲	▲	▲	▲			
Test for HIV, HCV, ,		▲	▲	▲	▲	▲	▲	▲	▲			
Resource mapping in 6 counties							▲	▲	▲	▲	▲	▲
Develop PCM manual	▲											
Implementation coaching	▲	▲										
Enroll clients in CCPH		▲	▲	▲	▲	▲	▲	▲	▲			
Analysis of intervention effect									▲	▲	▲	▲
Manuscripts and dissemination									▲	▲	▲	▲

2.0. Data Security

2.1. Data collection. The source of research data is clients' biological specimens and their self-reported survey data along with all intervention materials used. For all research components, data will be gathered remotely on personal devices or in private spaces where white noise machines will be placed outside the door to reduce the risk that others will overhear data collection activities. Self-administered surveys will be conducted using ACHESS and will be administered via the ACHESS app on a smartphone or web browser, or using wifi-enabled iPads with headphones. Data from the self-administered survey are automatically stored in a password protected, HIPAA-compliant server that is accessible to UW-Madison research staff. Information from rapid tests for HIV and hepatitis will be securely faxed to UW-Madison and entered into a secured HIPAA-compliant database.

Each participant will receive a unique identifying number that will be used in all materials related to the study. A master list matching identifiers to participants will be maintained on a database that is only accessible to research staff. All staff will be trained in HIPAA compliance and best practices for human subjects research data in order to ensure that they will not disclose information about participants to others outside of the study team.

2.2. Data management and storage. The Project Manager and shall be responsible for ensuring that the data for the project are securely stored, that storage is in compliance with University and federal regulations and that no unauthorized persons have access (electronic or physical) to any participant-identifiable data. All HIPAA regulations and guidelines will be followed, and all study staff must complete approved human subjects and HIPAA training programs.

Inter-site data transfers are accomplished via secure file transfer protocols (SFTP) using an internet server maintained by the UW School of Medicine and Public Health (UWSMPH) Department of Medicine. To protect the privacy of database records and the integrity of the network, this server is firewall-protected and is stored in a locked server room with a numeric keypad to restrict entry. The server is continuously scanned for the presence of viruses. A complete virus scan of all workstations also takes place once a week. Server system log files are scanned for unusual activity, which is immediately investigated. Network and Server Administration staff members apply critical and non-critical patches as needed. In addition, the study staff also have multiple mechanisms for preserving confidentiality of research participants and providing data security in the transfer of data from participant machines to the SFTP server. The Department of Medicine web servers use Secure Socket Layer (SSL or https) technology to encrypt data exchanged between the client and the server. In addition, all online and offline components of the data systems described in the proposal will be accessible only through a login and password unique to each user. The security access levels for these login accounts are tiered and the features and privileges given to each staff member will be determined by the PIs and data Manager. To further protect confidentiality, only the PI and data manager will be permitted to transmit data to the SFTP server. Finally, the Department of Medicine employs extensive data backup and server redundancy procedures and performs full backups to tape weekly of all servers, along with incremental and daily backups.

2.3. Data entry methods. The PIs will develop and implement protocols for assuring data collection accuracy and protocol compliance. Data will be entered through REDCap. Data entry staff will be automatically logged out after a specified time of inactivity. Consent forms and rapid testing forms will be securely faxed using a HIPAA compliant, confidential fax line located at the University of Wisconsin-Madison.

2.4. Quality assurance plan. Investigators and staff will have weekly team meetings to update study progress, discuss and problem-solve barriers to successful field implementation, and receive group training on cross-cutting QA issues. Staff also will receive individual training as needed.
To monitor assessment quality assurance, staff will record process notes on a standardized form, including documentation of any questions or problems raised by the participant during the interview or survey.

3.0. Participant Safety and Monitoring

3.1. Potential risks and benefits to study participants.

Potential psychological risks to participants in this study are: (1) negative consequences if confidentiality of information obtained in this study were violated; (2) embarrassment, discomfort, or distressed emotional reactions to the study assessment measures; (3) increased anxiety about personal safety and wellness resulting from the intervention or survey; and (4) potential for minor bruising or irritation from a phlebotomy blood draw if confirmatory HIV test is required due to a reactive rapid test. Emotional distress is common after a person learns he or she is HIV or HCV-positive.

Confidentiality protections. A number of steps will be taken to protect the confidentiality of participants' data and their identity. All investigators have extensive experience in the safe collection, handling, and storage of sensitive and highly confidential data. All name-identified information (e.g., informed consent) will be kept in a locked file, separate from any data. Data-related materials will be identified by a unique Research Identification Number (RIN) and stored in a second locked file. Access to these two files will be limited to the research team. All data files will be securely transferred using encryption. Computer databases will be password protected and accessible only to the research team. No individual identities will be used in any reports or publications that may result from this research project. Data requested from researchers from organizations not formally collaborating on this research project will only be shared in aggregate form per NIH and federal data sharing regulations.

We recognize that we are asking participants to provide sensitive information about private behavior and health. Our research team is experienced in the collection of this type of information, and we will implement multiple safeguards to protect participants' confidentiality. All project protocols will be subject to review by the institutional IRB at the University of Wisconsin-Madison. The UW-Madison IRB will approve research involving children only if the IRB finds that the research includes any required additional safeguards outlined in ethical principles and applicable federal regulations, state laws and institutional policies. An inter-institutional agreement that was used during the first phase of the study between the University of Wisconsin-Madison and Tulane University for IRB oversight; and a data sharing agreement for any information shared with the Wisconsin Department of Health Services AIDS/HIV Program, the Wisconsin Division of Care and Treatment Services, Vivent Health, and the GHOST lab will be used. CCHP staff will be included in the University of Wisconsin-Madison IRB protocol. A Certificate of Confidentiality will be obtained as a condition of the NIH grant award. All study participants will be fully informed of the project goals and procedures, and of their rights as research participants, including the right to not participate without penalty. Consent will be obtained prior to the collection of any data, or the

conduct of any research activities.

Pregnant women are a vulnerable population whose inclusion in this research is justified by the increasing incidence of neonatal abstinence syndrome, and increased prevalence of opioid use among women of childbearing age. Although drug use in pregnant women does not require mandatory reporting under state law, study team members may choose to voluntarily report it. The possibility of this and the risks if this were to be reported will be clearly outlined in the consent form.

Per HIPAA, participants will be advised during the consent process of our intent to collect biological specimens to test for HIV and HCV. Positive tests will be reported to the health department per state and local regulations.

Steps to reduce discomfort or anxiety resulting from study participation. Assessment measures involve sensitive topics related to safety and wellness. Some participants may feel awkward or embarrassed when discussing, hearing about, or being asked to provide information related to their safety and wellness. Staff are trained to employ techniques that prevent, reduce, or minimize embarrassment, discomfort, or atypical stress associated with study participation. Staff will be trained to observe for any evidence that a participant may be overly anxious and to assess whether threat sensitization and vulnerability perceptions are realistic. Vivent Health and research field staff will be required to have extensive research- or program-based experience with the conduct of HIV-related research. The project will be guided by a detailed procedural manual, and field staff will receive intensive training focused on the specific project protocols and materials to ensure that they are being rigorously and consistently implemented, including extensive role-play rehearsal of recruitment, enrollment, and consent procedures and assessment procedures and materials. The field team will meet regularly to discuss implementation issues and areas warranting additional training. If research personnel change during the course of the study, new staff will be required to complete the training described above prior to conducting any research activities.

HIV and HCV testing and counseling safeguards. All testing staff have completed the Wisconsin AIDS/HIV Program state HIV test counselor training to ensure that HIV pre- and post-test counseling is conducted in accordance with state guidelines. Vivent Health is a CLIA-certified HIV test site funded, in part, by the Wisconsin Division of AIDS/HIV's HIV testing program.
Specimens will only be sent for confirmatory testing for those rapid tests that they are already positive for, therefore, no new health information will be generated by analysis of these samples.

In the UH3 phase of the study, participants who receive the Client-Centered Prevention Home intervention are expected to achieve more positive health outcomes and better linkages to services and care than people who do not receive this intervention.

3.2. Potential adverse events (AEs) and Serious adverse events (SAEs). Unanticipated problems will be reported to the IRB in accordance with posted guidance. SAEs also may constitute unanticipated problems, depending on the nature of the event. In general, SAEs do not require reporting to the IRB unless they also potentially meet the definition of an unanticipated problem.

An unanticipated problem is an event that meets all of the following criteria:

- Reasonably related to the research;
- Unexpected (in terms of nature, severity, or frequency) given the research procedures that are described in the study-related documents, such as the IRB-approved research protocol and informed consent document, and the characteristics of the participant population being studied; AND
- Suggests that the research places subjects or others at a greater risk of harm (including physical, psychological, economic, or social harm) related to the research than was previously known or recognized

Adverse events (AEs) may occur during data collection may include:

- Violation of confidentiality,
- Discomfort due to assessment procedures,
- Embarrassment in disclosing sensitive personal information,
- Disclosure of information about current and/or intended physical harm persons,
- Current and/or intended abuse of children (that would be reported to child welfare agency)
- Dissatisfaction with the assessment procedures or intervention activities.

The population of focus in this research is at high risk for multiple health consequences that are associated with

substance use disorder, which may constitute serious adverse events. These include development of bacterial infections, blood-borne viral infections including HIV and hepatitis, and sexually transmitted infections. This population is also known to have an elevated risk of drug overdose and death from all causes.Because of this, we will only be reporting death as an adverse event.

Adverse events will be solicited from the study participants using a standardized case report form. Study document review will be performed to abstract additional information as necessary. A contact number for the research program manager and PI will be provided to each subject to contact the study in case of an unanticipated serious adverse event (SAE).
Potential adverse events will be reviewed as to the assigned treatment group and further classified by severity (life-threatening, serious, non-serious) and expected vs. unexpected. Expected and unexpected adverse events will be monitored at each enrolling site and reported to overseeing agencies as required by federal regulations and local requirements.

3.6. Staff training. Staff will be required to demonstrate competence with project protocols prior to implementation. Investigators and field staff have or will be required to complete the NIH required CITI web-based ethics training. Interviews will be supervised by the lead project investigators to ensure protocol adherence. Testing staff will be further required to complete training and demonstrate competence with the fingerstick collection of whole blood specimens (i.e., rapid HIV, HCV, and syphilis point-of-care testing methodology) and phlebotomy blood draws prior to study Implementation; and complete annual training in blood borne pathogen control ("universal precautions") to ensure adherence to the Occupational Safety and Health Administration Occupational Exposure to Blood borne Pathogen standards. Any new staff who are hired will be required to complete the training package described above, and demonstrate competency with HIV, HCV, and syphilis testing and counseling. Adverse event assessment, recording, reporting, and investigation will be accomplished through staff training, structured/standardized assessments of untoward occurrences/events, and regular monitoring by the study team.

4.0 Reporting Procedures to NIDA

4.1. Procedures and timeline for reporting AEs and SAEs to NIDA. Reportable adverse events will be submitted to NIDA annually as part of the annual progress report. This report will describe the event, when it occurred, whether the participant was part of the control of intervention arm, and the outcome/resolution. If there were no AEs that year, a statement that no AEs occurred will be included in the progress report or communicated to NIDA in writing.

In this research, all deaths and unanticipated SAEs determined by the PIs to be likely directly related to study participation will be reported to the IRB and NIDA within 24 hours after the PIs are made aware of the incident. The notification will include a brief explanation of the SAE and when it occurred. A written follow up will be sent within 72 hours of the event. The written follow up will include information on the date of the event, what occurred, actions that were taken by the field staff, any planned follow up, whether the participant was part of the intervention or control arm, whether the event appears to be related to the intervention, and whether the participant will continue in the study. Additionally, the IRB will receive an annual report of all SAEs and AEs meeting the criteria listed above.

4.2. Reporting of IRB actions to NIDA. After the IRB has reviewed and determined the course of action for reportable SAEs, the PIs will inform NIDA within 24 hours of the course of action.

5.0 Data Safety and Monitoring Board. A DSMB will be convened for this study in collaboration with the University of Wisconsin Institute for Clinical and Translational Research (UW ICTR). The ICTR Data Monitoring Committee (DMC) meets the requirements for an independent Data and Safety Monitoring Committee or a Data and Safety Monitoring Board. The DMC is available for UW-Madison investigators when a funding agency, the PI, or IRB requires such a committee or board. The committee is comprised of experienced clinical researchers representing a diversity of backgrounds, skills and knowledge. The DMC helps investigators ensure subject safety, research integrity, and compliance with federal regulations and local policies. The DMC also makes recommendations to the PI that could include actions of continuation, modification, suspension, or termination. Prior to submission of the final protocol and IRB application to the UW Health Sciences Institutional Review Board, the PI requested a DMC consultation using the online application form. After an initial consultation with the DMC, there are no conflicts of interest with the current committee. None of the current board members has no financial and/or scientific ties to the outcome of the study. A list of current voting members are provided in the Appendix. The DMC will alert the investigation team if there is change in membership. If a conflict of interest arises, the PIs will inform NIDA within 24 hours of becoming aware of it. That member will abstain from voting or providing input to the study. As the protocol is refined and/or if a serious adverse event occurs, the DMC will work with the PIs and research team to determine whether or not there is a need to meet more than annually. After

each meeting, the DMC will review emerging data, make recommendations about the trial's conduct, including possibly stopping the trial. At the close of each meeting, the DMC will make one of four recommendations: continue as is, continue but with specific modifications; stop temporarily until specific conditions are met; or terminate. The PIs will report DMC activity as part of their annual project progress report to NIDA.

A report on DMC meetings and activities will be sent to NIDA within 30 days of the meeting. The update will include the following: meeting dates (past and upcoming if known), meeting minutes or summary, current board membership, changes in membership (if applicable), information about any new member(s) (if applicable) including statement that new members have no conflict of interest, and specific board recommendations regarding the research project (if any).

APPENDIX 2. Proposed outcome measures for Aim 3

	Outcome Type	Data Source±	Unit of Analysis	Measure for Cost Analysis	Time Period for Analysis*
Addiction treatment accessibility and utilization					
If I wanted to start a medical treatment for opioid or heroin addiction, I could easily get into a methadone program.	Short-term Client-level	ACASI Survey	Change in Likert-scale		T_0, T_1, T_2
In the last 3 months, have you gone to a self-help group like Narcotics Anonymous, Alcoholics Anonymous, Celebrate Recovery, or Rational Recovery?	Intermediate Client-level	ACASI Survey	Change in frequency	✓	T_0, T_1, T_2
In the past 3 months, have you received outpatient counseling from a provider or program?	Intermediate Client-level	ACASI Survey	Change in frequency	✓	T_0, T_1, T_2
In the past 3 months, have you stayed overnight at a residential or inpatient drug treatment facility?	Intermediate Client-level	ACASI Survey	Change in frequency	✓	T_0, T_1, T_2
In the past 3 months, have you been in detox?	Intermediate Client-level	ACASI Survey	Change in frequency	✓	T_0, T_1, T_2
In the past 3 months, have you stayed overnight at a sober house?	Intermediate Client-level	ACASI Survey	Change in frequency	✓	T_0, T_1, T_2
In the past 3 months, have you gotten buprenorphine maintenance medication–like Suboxone or Subutex–from a doctor or program?	Intermediate Client-level	ACASI Survey	Change in frequency	✓	T_0, T_1, T_2
In the past 3 months, have you gotten methadone maintenance from a clinic?	Intermediate Client-level	ACASI Survey	Change in frequency	✓	T_0, T_1, T_2
In the past 3 months, have you gotten buprenorphine shots – like Sublocade – from a doctor or program?	Intermediate Client-level	ACASI Survey	Change in frequency	✓	T_0, T_1, T_2

If I wanted to start medical treatment for opioid or heroin addiction, I could easily get buprenorphine or Suboxone or Subutex.	Short-term Client-level	ACASI survey	Change in Likert-scale		T_0, T_1, T_2
If I wanted to start a medical treatment for opioid or heroin addiction, I could easily get into a methadone program	Short-term Client-level	ACASI survey	Change in Likert-scale		T_0, T_1, T_2
Any outpatient visit for MAT for opioid use disorder post initiation of CCPH or control	Intermediate Client-level	Medicaid	Change in frequency	✓	T_{-2}, T_0, T_2
Prescription fill for methadone, buprenorphine, naltrexone, probuphine post initiation of CCPH or control	Long-term community-level	Medicaid	Change in frequency	✓	T_{-2}, T_0, T_2
Treatment for hepatitis C					
Utilization of HCV treatment among participants	Intermediate Client-level	Medicaid	Change in rate of HCV treatment	✓	T_0, T_1, T_2
Successful HCV treatment among participants	Long-term Client-level	WEDSS	Change in cure rate of HCV treatment		T_{-4}, T_0, T_4
Decrease in prevalence of HCV	Long-term County-level	WEDSS	Change in rate of HCV by county		T_{-4}, T_0, T_4
Do you currently have health insurance or health care coverage?	Short-term Client-level	ACASI Survey	Change in rate of health insurance		T_0, T_1, T_2
If I ever tested positive for hepatitis C, I'm confident I could get linked to a medical expert and start hepatitis C treatment.	Short-term Client-level	ACASI Survey	Change in Likert-scale		T_0, T_1, T_2
Number of appointments made for HCV treatment	Short-term Client Level	CCPH Program data	Change in frequency		T_0, T_1, T_2
Prescription fill for DAAs post initiation of CCPH or control	Intermediate Client-level	Medicaid	Change in frequency	✓	T_{-2}, T_0, T_2
Lower risk of viral hepatitis					
Uptake of hepatitis A immunization	Long-term County-level	WIR	Change in rate of hepatitis A immunization among 15-39 year olds		T_{-4}, T_0, T_4
Uptake of hepatitis B immunization	Long-term County-level	WIR	Change in rate of hepatitis B		T_{-4}, T_0, T_4

			immunization among 15-39 year olds		
I am certain that I got all 3 recommended shots for Hepatitis B.	Intermediate Client-level	ACASI survey	Change in Likert-scale		T_0, T_1, T_2
Health department referrals for hepatitis A and B immunization	Short-term Client-level	CCPH Program data	Number of referrals		T_0, T_1, T_2
Any outpatient visit that includes immunization for hepatitis A or B	Long-term Client-level	Medicaid	Change in frequency	✓	T_{-2}, T_0, T_2
Lower risk of HIV					
Have you ever heard of medicine people can take to prevent HIV?	Short-term Client-level	ACASI survey	Change in rate of knowledge of PrEP		T_0, T_1, T_2
It's easy for me to get new, clean syringes or needles.	Short-term Client-level	ACASI survey	Change in Likert-scale		T_0, T_1, T_2
It's easy for me and my sex partners to get condoms.	Short-term Client-level	ACASI survey	Change in Likert-scale		T_0, T_1, T_2
PrEP utilization	Long-term County-level	IQVIA	Change in number of prescriptions for PrEP		T_{-4}, T_0, T_4
Safe injection drug use practices	Intermediate Client-level	ACASI survey	Change in rate of safe injection drug use practices		T_0, T_1, T_2
Have you had sex without a condom?	Intermediate Client-level	ACASI survey	Change in rate of sex without a condom		T_0, T_1, T_2
Were you diagnosed with an STD in the past?	Intermediate Client-level	ACASI survey	Change in rate of STD diagnoses		T_0, T_1, T_2
Have you had sex with more than one person in the past 6 months?	Intermediate Client-level	ACASI survey	Change in rate of sex with more than one person		T_0, T_1, T_2
Syringe distribution	Intermediate County-level	Lifepoint	Change in rate of syringe distribution		T_{-2}, T_0, T_2
HIV prevalence	Long-term County-level	WEDSS	Change in rate of HIV incidence		T_{-4}, T_0, T_4
Lower risk of drug overdose					
If I wanted the overdose reversal drug naloxone or Narcan, I could easily get it.	Short-term Client-level	ACASI survey	Change in Likert-scale		T_0, T_1, T_2
Narcan distribution	Intermediate County-level	Lifepoint	Change in narcan distribution		T_{-2}, T_0, T_2
Overdose hospitalizations	Long-term County-level	Wisconsin Hospital Administration Data	Change in rate of overdose-related hospitalizations		T_{-4}, T_0, T_4

Probable opioid overdose	Long-term County-level	Wisconsin Ambulatory Run Data System	Change in rate of overdose-related ambulatory run	T_{-4}, T_0, T_4
Overdose death	Long-term County-level	Wisconsin Mortality data	Change in rate of overdose-related death	T_{-4}, T_0, T_4
Smoking cessation				
Quit-line encounters	Short-term Community-level	Quit-line database	Change in number of quit-line uses	T_{-4}, T_0, T_4
Do you smoke cigarettes?	Intermediate Client-level	ACASI Survey	Change in prevalence	T_0, T_1, T_2
On average, how many cigarettes do you smoke a day?	Intermediate Client-level	ACASI Survey	Change in median number of cigarettes	T_0, T_1, T_2
Overall smoking prevalence by county	Long-term County-level	BRFSS	Change in prevalence	T_{-4}, T_0, T_4
Self-stigma				
How much do you feel ashamed of using drugs?	Intermediate Client-level	ACASI Survey	Change in Likert-scale	T_0, T_1, T_2
How much do you feel people avoid you because you use drugs?	Intermediate Client-level	ACASI Survey	Change in Likert-scale	T_0, T_1, T_2
How much do you fear you will lose your friends because you use drugs?	Intermediate Client-level	ACASI Survey	Change in Likert-scale	T_0, T_1, T_2
How much do you fear family will reject you because you use drugs?	Intermediate Client-level	ACASI Survey	Change in Likert-scale	T_0, T_1, T_2
How much do you think other people are uncomfortable being around you because you use drugs?	Intermediate Client-level	ACASI Survey	Change in Likert-scale	T_0, T_1, T_2

‡Data sources used to measure the effectiveness of intervention include:
ACASI Survey: the harmonized survey used in the UG3 phase
WEDSS: Wisconsin Electronic Disease Surveillance System
Medicaid: Wisconsin Medicaid Program
IQVIA: Purchased prescriber data
WIR: Wisconsin Immunization registry
Lifepoint: Syringe service program database of needle exchange encounters and narcan distribution
BRFSS: Behavioral Risk Factor Surveillance System
SAMHSA: Database of DATA-Waived Practitioners

*Time is measured in 3-month intervals based on the intervention assessment phases
T_{-4} a year prior to the intervention
T_{-2} 6 months prior to the intervention
T_0 Start of the intervention
T_1 3 month follow up
T_2 6 month follow up
T_4 12 month after intervention

APPENDIX 3. Data elements to be shared with University of Washington Data Coordinating Center

Please refer to the ACASI questionnaire for review of exact wording of questions. Identifiers are highlighted in yellow.

Screener data	
Variable Name/Category	**Description of Variable/Category**
RECORD_ID	Participant's ID Number
SCRDATE	Date of screening
REFERRAL CODE	Code number that traces participant to their recruiter
RELATIONSHIP TO RECRUITER	We ask how the participant is related to the recruiter
AGE	Two digit age
GENDER	The participant's gender
SCREDU/SCRGRDE	The highest grade or degree the participant attained
SCRRACE/SCRHISP	The participant's race and ethnicity
SCRZIP/SCRCO	Participant's zipcode and county of residence
SCR10	Drugs taken in the past 30 days
INJECTED_DRUGS/SCRINJDT	Date of the last time participant injected drugs to get high
Quantitative Survey Data (ACASI)	
Variable Name/Category	**Description of Variable/Category**
ID	Same as RECORD_ID
SCRGEN	The participant's gender
EVERUSED (SCR SERIES)	Ever used drugs
SUBDRCH	Drug of choice
USED PAST 30 DAYS (SUB SERIES)	Used drugs in the past 30 days
SUBALCMD/SUB_ALC_B30	Alcohol use in the past 30 days
CIGARETTE USE	Cigarette use, number of cigarettes, type of tobacco products
SUBSTANCE DEPENDENCY	Questions regarding whether or not participants worry about their drug use, and whether or not they wish to stop
INJECTED PAST 30 DAYS	Injected drugs in the past 30 days
AGE FIRST INJECTED	Age first injected heroin, methamphetamine, and cocaine
SYRINGES LAST 30 DAYS	Where participant received syringes in the last 30 days
INJECTING BEHAVIOR	Questions on whether or not participant used clean syringes, shared syringes, had someone else prepare their drugs, injected more than one time in one sitting.
SKIN PREPERATIONS	Questions on how participants cleaned their skin, water source, whether they injected into muscle or skin, and whether they've had a skin infection in the past
OVERDOSE	Ever overdosed, times overdosed, trained to recognize and respond to an overdose, ever call 911, number of people that have died from an overdose
SUBSTANCE USE TREATMENT	Ever used a self help group, received outpatient counseling, stayed overnight at a residential drug treatment center, etc
REASONS FOR TREATMENT	Reasons why the participant has not used buprenorphine, methadone, and/or Vivitrol
STIGMA (STG SERIES)	Questions address self shame for using drugs
HIV DIAGNOSIS AND TREATMENT (HHIHIV SERIES)	Questions on whether participant has been tested for HIV, last HIV test date, test results, date of diagnosis, HIV treatment
HCV DIAGNOSIS AND TREATMENT (HHIHCV SERIES)	Questions on HCV diagnosis, treatment for HCV, and main place for medical care for HCV
BACTERIAL INFECTIONS	Hospitalization of serious bacterial infection, date of hospitalization
ACCESS TO MEDICAL CARE	Main place participant received medical care, barriers to care

KESSLER DISTRESS SCALE (KES SERIES)	Questions on participants anxiety and depressive symptoms in the last 30 days
PTSD SCALE	Questions on whether participant experienced adverse event, and symptoms experienced after adverse event
ACCESS TO PREVENTION AND TREATMENT (ACC SERIES)	Questions on accessibility to condoms, HIV treatment, HCV treatment, STI treatment, buprenorphine, naloxone, clean syringes, vaccinations, infection information
CRIMINAL JUSTICE	Times law enforcement has stopped and searched participant, number of arrests, probation in the last 6 months, days they were in jail
SEXUAL RISK (SXR SERIES)	Number of partners in the past 30 days, trade sex for drugs, last time they had vaginal or anal sex, sex without a condom, sex without a condom and injected drugs, sex with HIV+
DEMOGRAPHICS	Main source of income, services received, relationship status, student status, pregnancy status, forms of birth control, homelessness, transportation, health insurance
RDS	Questions on their network of people who inject drugs
RAPID RESULTS	Results from HIV, HCV, and Syphilis testing that was done that day
DUP_ID	Possible participants that entered the study more than once
Qualitative Participant Interviews	
All transcripts were stripped of the following information:	Names Geographic subdivisions smaller than a state All Dates Telephone numbers FAX numbers Email addresses Social security numbers Medical record numbers Health plan number Account number Certificate/license number License plate number Device identifiers/serial numbers Web urls Internet protocol addresses Biometric identifiers Full face photos and comparable images