Study Protocol

Ending transmission of HIV, HCV, and STDs and overdose in rural communities of people who inject drugs (ETHIC)
Including the ECHO addendum

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Principal Investigator:
Mai Tuyet Pho, MD MPH
Assistant Professor
Department of Medicine
University of Chicago
5841 S Maryland Ave, MC 5065
773-834-3689

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1) Background

Opioid use in rural areas has reached epidemic proportions in the United States.[1-3] Outbreaks of HIV and HCV have been associated with syringe sharing among partners injecting prescription opioids in rural Indiana, and increases in heroin and fentanyl-related drug overdose deaths have been reported throughout the Midwest.[2, 4, 5] Illinois ranked as the third highest state in percentage increase in death rates involving synthetic opiates between 2014-2015.[3] Rural areas in southern Illinois may be disproportionately affected by the epidemic. The southernmost 16 counties in Illinois are part of the federally designated Delta Regional Authority (Illinois Delta Region; IDR), an area of 252 counties and parishes described as the most economically distressed area of the country.[6] These areas have been adversely affected by loss of coal mining and agricultural employment, population decline, and defunding of public services, and they are both geographically proximate to and share many of the demographic characteristics as Scott County, IN. Public health surveillance data indicate that some Illinois counties in this largely rural and poor area have seen tremendous increases in opioid use, overdose, and HCV and STD transmission. However, the epidemiological factors underlying this increase, including demographic factors, sociocultural influences, healthcare access, and community resources are largely unknown. Our previous work in rural communities has demonstrated substantial variation in a number of these factors.[7]

A deeper understanding of community characteristics, transitions from oral to injection opioid use, circumstances for high-risk injection practices, and accessibility to existing and potential health-related resources will be essential to developing models of disease prevention and treatment.[8] In this study we will utilize mixed analytical approaches including a) predictive modeling and GIS hotspot analysis to identify high risk counties / zip codes, b) qualitative and survey analysis to examine HIV/HCV risk practices and prevention barriers/ opportunities and, coupled with respondent-driven sampling (RDS), delineate injection and sexual networks, and c) HCV molecular epidemiology to understand overlaying transmission dynamics. These data will inform community response projects including evidence-based interventions to strengthen access to HIV/HCV/STD screening and linkage to care and treatment, expansion of syringe services and naloxone-based overdose programs, screening and referral to substance use treatment, and expanded telehealth capacity regarding PrEP, HCV management, and medication-assisted drug treatment.

Background on social network aims

Traditional infectious disease models of HCV disease are often based on assumptions about mixing, i.e. that individuals who are infectious and susceptible have contact with all other members of the population. Such models that are not informed by empirically based contact patterns and fail to capture the heterogeneity in individual interactions.[35] In our study, the ability to collect data on using both blood sampling and social network will allow us to estimate incidence rates in conjunction with estimating the network itself. Our goal is to explore the network role in HCV transmission, including an examination of independent risk factors for transmission. For example how to network size, connectivity or geographic spread impact risk? What are the potential protective network effects? For example, in the rural Appalachian setting, injection drug use network studies revealed that injection of prescription opioids, cocaine, needle sharing, and degree centrality (i.e. connected network position) were associated with increased HCV risk.[36] Public health and policy intervention that could impact HCV transmission in this case could include prevention of transition to injection among prescription opioid, as well as increased access to opioid maintenance treatment, and syringe exchange. Network position can be useful when employing network-based interventions via dissemination of information, clean needles, and naloxone.

In ETHIC, injection, sexual and social support network data will be collected from participants. Participants will also undergo HIV, HCV and STI screening. Data collected will not be used to attempt to contact network partners (see section "Protection of Third Party Data below). Respondent driven sampling (RDS), a voucher based snowballing type of recruitment will be used. An augmented social network will be generated using matching protocols between participant self-reported networks and RDS connections. Having better connection information than would be obtained through RDS in isolation allows for more variety of network indices to be examined for relevance in interventions. The accuracy of network structure is critical to appropriately inform the universe of available prevention and treatment interventions.

2) Specific aims: The goals of 'Ending transmission of HIV, HCV, and STDs and overdose in rural communities of people who inject drugs' (ETHIC) are to:

1. UG3 Aim 1. Determine the geographic areas in the rural Illinois Delta Region at greatest risk for opioid misuse and infectious diseases in the IDR based on disease surveillance, healthcare utilization, prescription drug monitoring, arrest and drug seizure, and resource scarcity using epidemiological analysis and GIS hot-spot mapping.
2. UG3 Aim 2. Understand how sociocultural factors impact risk and health-seeking behaviors, social networks, and disease transmission of people who inject drugs in the IDR.
3. UG3 Aim 3. Integrate and apply the epidemiological, geospatial, qualitative and network data to inform expanded harm-reduction services and targeted telehealth capacity building for related clinical care.

4. Expand harm reduction services **(HRS)** including syringe services, naloxone overdose prevention, substance use treatment referral, HIV, HCV, and STD testing and referral and linkage to care through capacity building of existing programs.

a. Evaluate using RE-AIM framework

3) Methods

a) Study Staff Training: There are a variety of skills that study personnel will either have to possess or acquire through training, and specific skills are dependent upon individual staff functions. All research staff will be trained in the proper conduct of research, eligibility screening procedures, the process for obtaining informed consent, and data entry. Research staff will be involved in eligibility screening, consent, interviewing and administration of the surveys using Computer-Assisted Personal Interviewing (CAPI) where the research staff assists participants in the completion of the survey using computers or tablets. Those involved in biospecimen collection, disease counseling, and results return and follow up will need documentation of training as a Disease Intervention Specialist (DIS) and also receive instruction on study-specific procedures for oral swab specimen collection and storage, phlebotomy, and specimen storage.[9, 10]

b) Community Advisory Board: A Community Advisory Board (CAB) will be convened with the goals of co-learning between the investigators, patients and other stakeholders through an iterative process of elicitation of key priorities regarding addressing the opioid overdose epidemic, review of study implementation and dissemination of results. Additionally, the transition plan for implementation the community response projects (such as expanded harm reduction services and capacity building for addiction and HCV treatment) that will arise from the work performed in this UG3 period will be informed by input from the CAB. The CAB will meet every 3-6 months depending on the study stage and will consist of individuals residing in the IDR with lived experience with addiction, family members, primary health care providers, community advocates, and drug coalition members. In the event of state-wide or regional shut down due to COVID-19 CAB meetings will be held over videoconferencing.

c) Descriptive epidemiological analysis: Epidemiological analysis related to the opioid overdose epidemic and associated infections will be performed to examine the temporal and geographical trends of these outcomes in the IDR, as well as inform the GIS hot spot analysis (described in section b). We will perform secondary data analysis using public health datasets, including vital registry, hospital and emergency department discharge data, HCV, STI and HIV surveillance data, syndromic surveillance data of emergency room visits, and emergency medical services data from the Illinois Department of Public Health under the authority of Pursuant to Part 21, Medical Studies, Article VIII, Code of Civil Procedure, 735 ILCS 5/8-2010 et seq., commonly known as the “Medical Studies Act” as well as a Data use Agreement between IDPH and the University of Chicago and between IDPH and SIU School of Medicine. Analysis will include the prevalence of fatal and non-fatal opioid overdose, neonatal abstinence syndrome, HIV, HCV and STIs

including Neisseria gonorrhea and Chlamydia trachomatis between 2012-2017 and will be reported at the zip code or County level.

Additional analysis will be performed using de-identified, aggregate data from the Illinois Prescription Monitoring Program (PMP) under a Data Use Agreement between the University of Chicago and the Illinois Department of Human Services. This analysis will include zip code level data on opioid prescribing, including total morphine milligram equivalents (MMEs), buprenorphine prescribing and high-risk practices (benzodiazepine – opioid co-prescribing, multiple prescribers / pharmacies) at the zip code or county level. No patient or prescriber identifying information will be analyzed.

Publically available data from the Illinois Youth Survey (https://iys.cprd.illinois.edu/), the SAMHSA Buprenorphine Treatment Locater (https://www.samhsa.gov) and the Illinois Criminal Justice Authority http://www.icjia.state.il.us/research/overview#tab_research-data) will be analyzed to understand self-report opioid use among school age children, number of buprenorphine-waivered prescribers and drug index arrest data in the IDR.

d) GIS Mapping:
We will use geographic information system (GIS) methods to create zip code-level measures of accessibility scores for the following service types in the IDR: 1) local health department services (in aggregate and for each relevant service, including STD clinics, HIV testing, PReP clinics, needle exchange services, naloxone training sites, etc) 2) pharmacies and veterinary supply retail (i.e. locations where clean syringes can be purchased); 3) mental health services; 4) hospitals; 5) safety net clinics. This GIS method, the two step floating catchment area (2SFCA) method[9], which will utilize data on geocoded addresses of services relative to the population who may need those services. We will utilize zip code tabulation area estimates of population who may utilize these services (e.g. those aged 15 and older). Zip code tabulation areas are generalized representation of U.S. zip codes developed by the U.S. Census Bureau. These population estimates will be obtained from the publicly available U.S. Census Bureau's American Community Survey.

e) PWUD Interviews: Key informants who are people residing in the IDR and who use drugs (PWUD), specifically stimulants, or opioids such as heroin, fentanyl, or prescription analgesics, identified through harm reduction staff, will participate in semi-structured, narrative interviews to explore the sociocultural contexts underlying nonmedical prescription, stimulant, and other opioid drug use, transition to injection, needle sharing, condom-less sex, social network composition, and factors impacting health care and social services utilization including cancer screening (Appendix 2). A subset of these interviews will focus specifically on how COVID-19 and related shelter-in-place and business closure policies impact PWUD's behaviors, access to care, and preferences for research participation in order to inform study implementation as the environment shifts due to the crisis. The analytical approach for interview guide development is guided by two conceptual frameworks, the Galea 'contextual determinants of drug use

risk behavior' and the Auerbach 'social drivers' models, with special focus on the social networks, norms, health and social resources and the physical environment that may be unique to rural settings.[10, 11] The guide is also informed by harmonization efforts from the larger UG3 group of grantees under the guidance of the National Institute on Drug Abuse (NIDA, primary funder).

Ninety (90) interviews will be performed to reach theme saturation, with 30 interviews focused on COVID-19 and related policies. Interviews will last approximately 60 minutes. Interviews will be audio-taped, transcribed verbatim, and then edited to remove personal identifiers from the finished copy. Interviews will be performed by trained study staff, including Dr. Larry Ouellet (Consultant) who has had 30 years of experience working with PWUD in the areas of ethnographic and qualitative research. Interviews may also be conducted via phone when necessary.

f) Stakeholder Interviews: Stakeholders including harm reduction organization staff members, law enforcement including communication corrections officers, clinical providers, and local public health administration will be interviewed to explore the community level barriers to care facing PWUD in accessing care (Appendix 3) Stakeholders who have membership in the Southern Illinois Opioid Taskforce or who have been referred by members of the Taskforce or local health departments will be invited by email to take part in the study interviews. Flyers will be handed out by the staff at the Center for Rural Health and Social Services Development (CRHSSD) at the Southern Illinois University School of Medicine as well as posted at local health departments. Interviews will be performed by trained study staff. Interviews will last approximately 60 minutes. Interviews will be audio-taped and transcribed verbatim.

g) Stakeholder Demographic Survey: Following the interviews, stakeholders will be asked to complete a brief demographic survey. The information captured through this survey will be used to help us contextualize the background and general traits of these participants.

h) PWUD Survey: We will use Respondent Driven Sampling (RDS) to recruit PWUD and people who use opioids through harm reduction organizations operating in the Delta region to perform a survey analysis to understand risk behaviors, health services preferences, social network estimates and estimates of population size and demographics. Further discussion of RDS methods and sample size are discussed in the section 4b "Method of participation selection" below. In distinction from the interviews, we will include participants who inject any psychoactive drug including non-opioids given the high proportion of methamphetamine users in the region, as well as individuals who use opioids or stimulants to get high through intranasal, smoke, or ingestion route. A survey instrument will be used to gather information related to the following domains: demographics, drug use behavior, overdose experience, sexual risk behavior, HIV/HCV/STI testing history, health care utilization and preferences, barriers to care, and egocentric network data. The survey instrument is adapted from the Social

Networks among Appalachian People (SNAP) instrument developed by the University of Kentucky, including investigators who are members of the larger UG3 cooperative agreement, Kentucky site.[12] The survey is attached as Appendix 4. Surveys will be programmed and administered using REDCap and will take approximately 60-90 minutes to complete. Surveys will be performed at the baseline study encounter and then every 6 months until the beginning of the draw down period of the study. Surveys may be performed over videoconferencing, telephone, or through an encrypted link to the REDCap survey.

i) Biosurveys / HIV, HCV, HBV and STD Burden Screening:

Specimen collection and analysis will be based on the standard of care and coordinated with the harm reduction partners and IDPH per existing contracts and provider arrangements. Thus, all aspects of HCV and HIV screening and confirmation that are current standards of care for the harm reduction partners (HRP) will remain unchanged (e.g. obtaining kits, referral to care, results reporting). Screening will be performed at the baseline study encounter and then every 6 months until the beginning of the drawn down period of the study. In the event of state-wide or regional shut down due to COVID-19 CAB specimen collection will be deferred until in-person data collection is possible.

PWUD enrolled for the surveys will be screened at baseline and follow-up to determine disease prevalence and incidence in the population. Participant demographic data, survey responses, and specimen analysis results will be utilized to characterize the disease burden in the rural PWUD population versus the rest of the IDR and national trends and be applied to models of individual factors associated with increased risk.

All participants will provide as part of routine services provided:

- Finger stick sample and/or oral swabs at the time of participation for rapid screening for HIV ,and HCV using commercially-available and FDA-approved rapid assays provided by IDPH.
- Urine specimens for urine toxicology testing using the 10-panel Alere iCup urine toxicology test (point-of-care, with results within 5 minutes) as part of the eligibility screening (see section 4)d. below)
- Urine specimens for FDA-approved procedures to analyze for the presence of Chlamydia trachomatis (CT) and Gonorrhea (GC) by the IDPH State Laboratory.
- Oral swabs to test for CT/GC using a combination of FDA-approved and internally-validated procedures as performed by the IDPH State laboratory

Rapid assay preliminary results will be reported directly to the participant during the visit according to standard procedure. In the event that the HIV and/or HCV finger stick or oral swab screen is positive, phlebotomy for serum samples for HIV RNA

(confirmatory to rapid assay), and blood for HCV RNA (confirmatory to rapid assay) will be obtained. Additional serum will be sent to the NIH/NIDA-funded GHOST laboratory to perform HCV sequencing (see Section i below) sometime after collection (weeks/months; non-diagnostic) Samples sent to the GHOST lab will be de-identified. Biospecimen analysis results will be reported to a study PI (Jenkins), the Harm Reduction partner from whom the participant was recruited, and the proper local health department (according to standard IDPH procedure). The HR partner will be responsible for contacting all participants with their screening results. Study personnel will facilitate linkage to care, providing the introduction of the participant to the local health department staff. Additionally, we will provide the participant with transportation, if required, and will confirm that they attended their first confirmatory testing appointment. Positive results for any disease will also be reported to the appropriate local health department for follow up by a DIS and provision/referral to appropriate services according to standard procedures.

- For CT/GC - The LHD will follow up first with the provider. If they have not treated, then they contact the patient if they are age 18 or older and can treat since they have the lab result. Those under age 18 can only be contacted by the original HR partner.

- For HCV - For participants who test positive for HCV, we will assist them with attending their first confirmatory testing appointment, which will be with their primary care physician or a local infectious disease specialist.

- For HIV - Treatment and follow up is arranged through Southern Illinois Care Connect for services through the Ryan White Program which is operated by the Jackson County Health Department HIV Care Connect Grant.

j) HCV sequencing: Serum samples will be collected from HCV and HIV rapid screen positive cases to facilitate viral sequencing of HCV strains by a funded center through NIH-DA-17-023. These centers will be conducting HCV next-generation sequencing (advanced molecular detection) using Global Hepatitis Outbreak and Surveillance Technology (“GHOST”) developed in collaboration with CDC’s Division of Viral Hepatitis. Standard protocols developed by these centers will be used for the collection and preparation of samples. Genotypes will be classified by comparing sequences obtained in this study with representative GenBank sequences.

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 may be sent to these other institutions for additional testing. These research tests include, but are not limited to, HIV, HBV, HCV and/or other tests for research purposes only. All blood and information will be coded with a number and any directly

identifiable information will not be shared outside of the [research study site]. 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 act more quickly to detect and fight the spread of Hepatitis C. All results will be uploaded by the GHOST center and transmitted securely via the web-based portal and/or secure email to the [research site] and/or the relevant state and local health departments. The results of HIV and or other testing performed by the CDC will be directly transmitted back to the [research site] by the CDC using secure means. Since all tests are for research purposes only no individual results will be given back to the subjects.

k) Referral to harm reduction services (HRS) . For those participants not engaged in harm reduction (ie not directly referred by CAP), a referral will be made to these services. Evidence-based services offered through CAP will include five core services: syringe services; naloxone training and dispensing; referral to substance use treatment; infectious disease screening and referral to treatment and vaccination; and education/counseling around sexual/injection drug risk behavior, including condom and fentanyl test strip distribution. Initial engagement/enrollment in the harm reduction intervention will be defined as acceptance of any service at the time of referral. Participants who refuse initial referral will be offered referrals at each of the 6 month follow up encounters.

l) Evaluation of Harm Reduction Service provision using qualitative data collection. We will interview the harm reduction staff at Community Action Place, Inc. (CAP) (3). These interviews will be performed as part of the implementation analysis to identify barriers and facilitators to provision of harm reduction services, including factors impacting participant outreach, engagement, retention, linkage, and referral to treatment services. The interview guide will be developed using the Consolidated Framework for Implementation Research (CFIR) conceptual framework developed to guide systematic assessment of multilevel implementation contexts to identify potential determinants of intervention implementation. Interviews will last approximately 60 minutes. Following the interviews, staff members will be asked to complete a brief demographic survey. The information captured through this survey will be used to help us contextualize the background and general traits of these participants. Interviews will be audiotaped, transcribed verbatim, and then edited to remove personal identifiers from the finished copy.
m) Evaluation of Harm Reduction Service engagement through analysis of Community Action Place, Inc. client services data. Data to be used for the analysis includes number of client visits, syringes / equipment / condoms distributed, naloxone training and kits distributed, referrals and linkages to treatment.

Figure 1. Flowchart for Study Enrollment and Procedures for PWUD

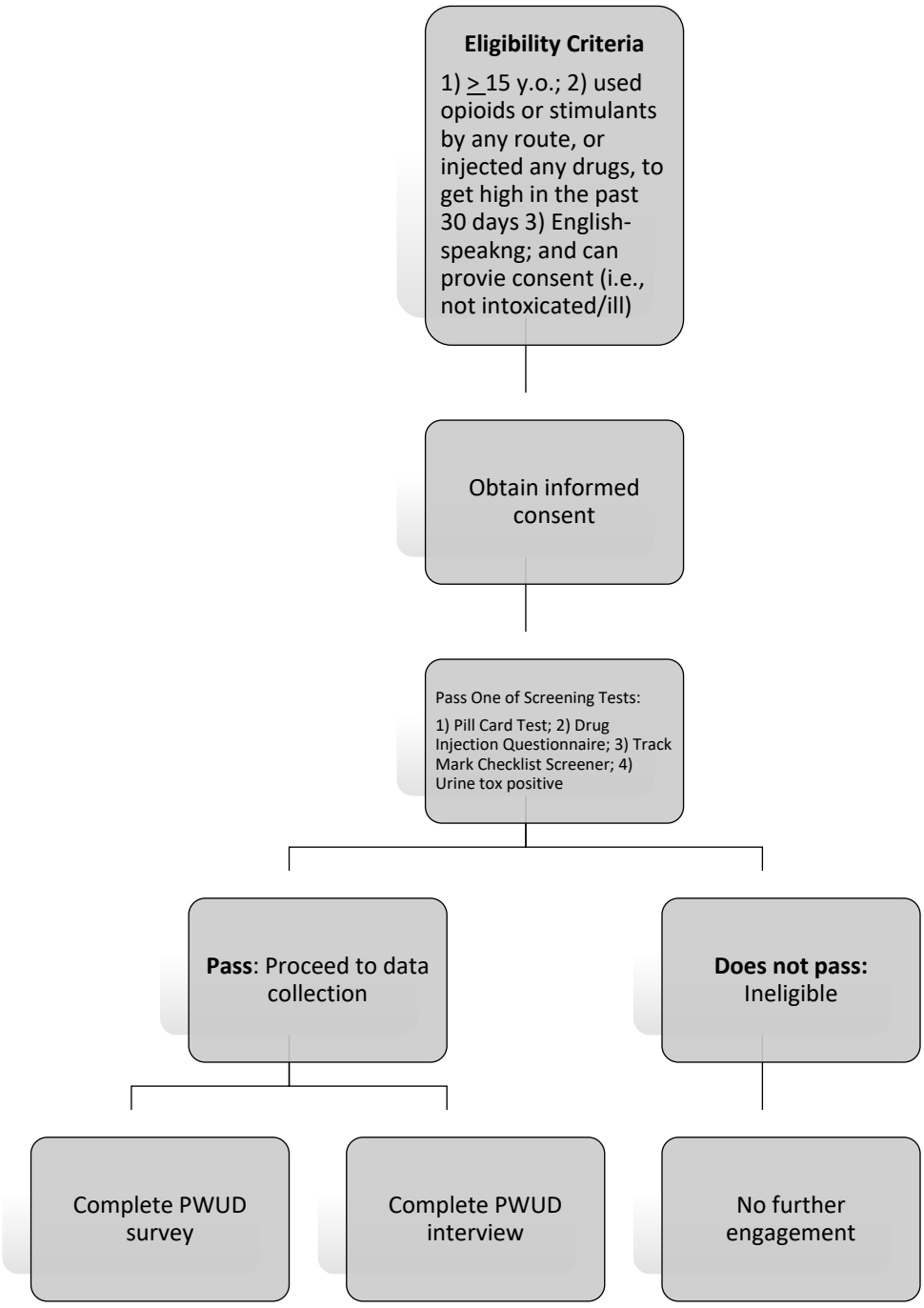
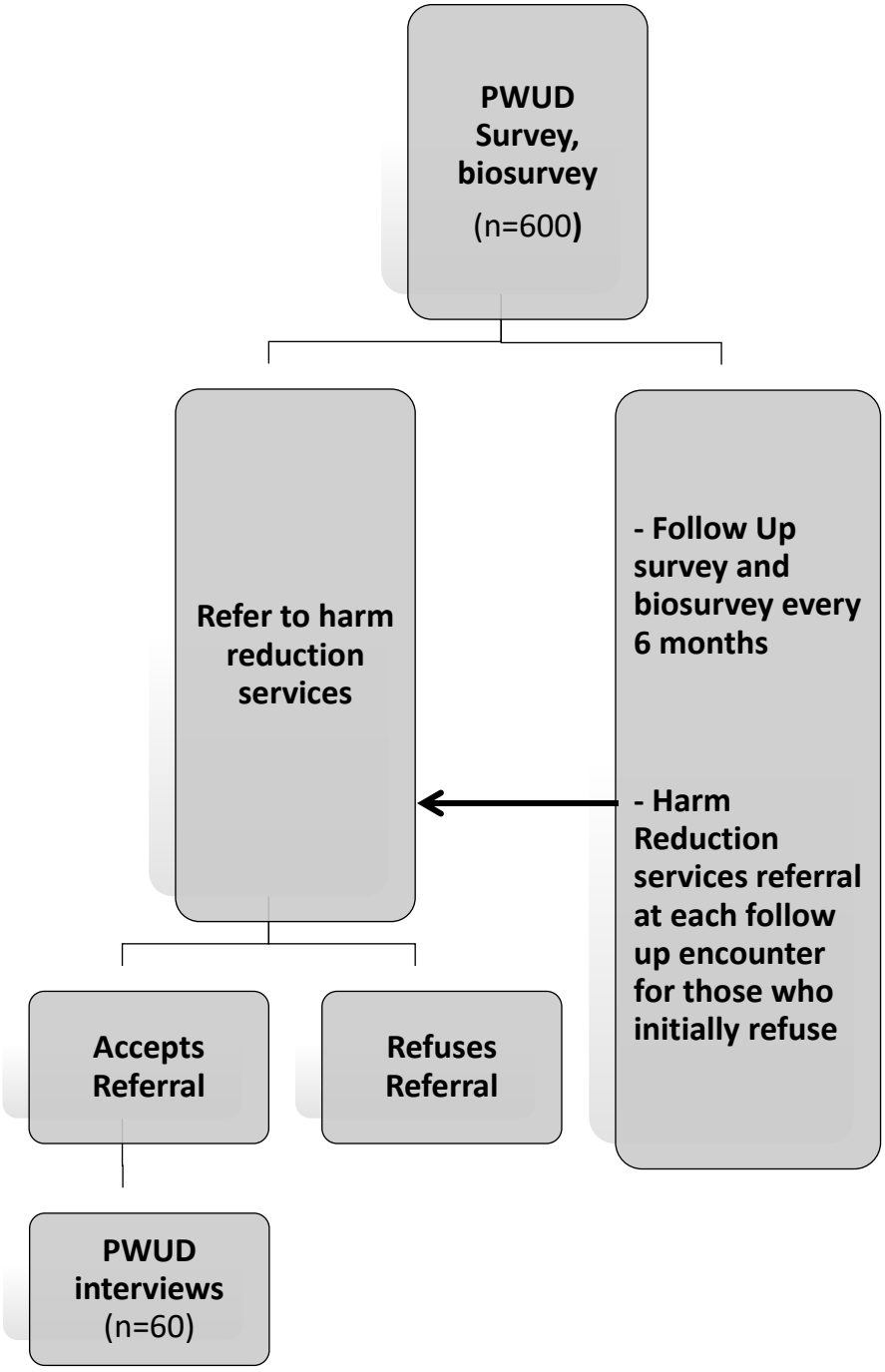


Figure 2. Flowchart for Study participants



4) Eligible participants

a) Type and number of subjects

a. PWUD interviews: 90 study participants will be enrolled (included in total below).

b. PWUD surveys/biosurveys: A minimum of 100 study participants will be enrolled, though we will continue enrolling to a maximum of 800. The exact number will

depend upon recruitment speed, staff availability, and timing of the consolidation of results for UH3 application (approximately spring of 2019). We will seek to capture interest in future research related to this project from consented PWUD subjects. The consent provides permission to the optional future contact for research. Information provided on the locator form will be used for contact in the future for related research projects.

c. Stakeholder Interviews: up to 60 stakeholders working in the Delta region will be enrolled, including:

- Harm reduction organization staff who provide syringe services to PWUD clients
- Law enforcement officers including community corrections
- Public officials and court representatives including judges
- Addiction treatment providers
- Emergency medicine
- Pharmacists
- Local Health Department Administrators

b) Method of subject selection

a. PWUD Interviews: Key informant interviews will be performed for individuals who have used opioids or stimulants by any route, or injected any drugs, to get high in the past 30 days. These key informants will be referred by harm reduction organizations that are partnering organizations in this study (see section 5. Location below).

b. PWUD surveys : Respondent-Driven Sampling (RDS) will be utilized with the harm reduction organization client population. RDS has been widely applied to study hard to reach populations.[13-17] RDS is an efficient method that uses respondents' network connection to generate a sample that approximates a probability sample allowing for valid statistical analysis. RDS uses a small number of initial seeds (generally highly socially connected clients referred by the harm reduction organization), each of who will receive no more than six vouchers to recruit other people who have injected drugs or used opioids or stimulants to get high within the past 30 days. These seeds will be recruited by the harm reduction partners through their existing client base. All efforts will be made to ensure that seeds are diverse from a standpoint of race/ethnicity, gender, and county of residence. New seeds can be added if chains of referral stop. Respondents receive an incentive payment for their participation and an incentive for each voucher that they distribute that produces an additional eligible respondent. The process is then repeated with each new respondent. This system of incentive payments, which is crucial to RDS, also serves to maintain ongoing contact

with respondents and will aid in our retention of respondents. Potential clients who are referred by the harm reduction partners will meet with study staff who will provide eligibility screening, perform the electronic consent process, complete locator form which will be used if a future amendment for this study includes a follow up surveys and/or interviews, and confirmatory test results (SOC), and administer the survey. If consented to by the study participant, results from routine HIV/HCV screening performed for these clients by the harm reduction organization staff will be communicated to the co-PI (Jenkins).

i. In addition to RDS, we will place our study recruitment flyers at spaces available to the public. These spaces will include local health departments, social services organizations, public parks, public transportation, and food pantries. The appropriate permissions will be sought from the venue operators prior to posting the flyers.
ii. Additionally we will hold in person recruitment events when possible where study staff will be available to provide information about the study. These will be held during events open to the public such as health fairs and other service events at local health departments, social service agencies, and other public venues. These recruitment activities may also include cookouts where food (hot dogs, snacks) will be provided free of charge to the public regardless of study eligibility. The appropriate permission will be sought from venue operators, including licensing from the health department when necessary, prior to hosting such events.
iii. Additionally, we will post our digital flyer on Craigslist.org, Grindr.com (and app), and Tinder (and app): Each of these websites is popular for classified ads for research studies, and peer-reviewed research has shown them to be effective spaces for recruitment. Where possible, we will target the ads to audiences in the southern Illinois counties of interest.
iv. Follow-up SMS text message reminder: We will periodically (Appendix 8) follow-up with participants via text, using the cell number (or email) which they provide and authorize us to contact them through, to let the participant know if they have any outstanding coupons to give out (or if they can redeem any coupons which have already been turned in). We will use *Boomerang*, an official Gmail add-on, to do this. Furthermore, each text message reminder will inform the participant that they are protected by our federal Certificate of Confidentiality. Participants will be able to opt-out of the text messages. The complete protocol for sending out the text messages is provided in Appendix 8.

c. **Stakeholder Interviews and demographic survey**: A convenience sample of staff members who provide syringe exchange services to PWUD clients from the three participating harm reduction organizations (Bethany Place, and Community Action Place) will be recruited. Law enforcement officers, including local police / sheriffs, and community corrections, court representatives, as well as treatment providers and local health department administrators will be recruited based on referrals from the Operations Partners Committee as well as the Community Advisory Board. These individuals may also be recruited from the membership of the Southern Illinois Opioid Taskforce (Appendix 7) via referral and via the email distribution list of the membership.. The study PIs (Pho, Jenkins) will contact potential Stakeholder participants directly via email or phone. Interviews will take place over videoconference or by phone.

c) Inclusion/ exclusion criteria

a. **PWUD Interviewees:** Inclusion criteria include age >= 15 yo, who have who have used opioids or stimulants by any route, or injected any drugs, to get high in the past 30 days, English-speaking, and able to provide informed consent at the time of the study visit (i.e. not intoxicated or ill). Exclusion criteria include < 15 yo, non-English speaking, without self-reported drug use of any drug to get high in the past 30 days, and inability to provide informed consent at the time of the study visit.

b. **PWUD surveys and biosurveys:** Inclusion criteria include age >= 15 yo, who have used opioids or stimulants by any route, or injected any drugs, to get high in the past 30 days, English-speaking, and able to provide informed consent at the time of the study visit (i.e. not intoxicated or ill). Exclusion criteria include < 15 yo, non-English speaking, without self-reported drug use of any drug to get high in the past 30 days and inability to provide informed consent at the time of the study visit.

c. **Stakeholder participants:** Inclusion criteria include age >= 18 yo, English speaking, employed in the Delta region in one of the following capacities: law enforcement, court employee, community corrections, treatment provider, or local public health department administrator, and able to provide informed consent at the time of the study visit. Exclusion criteria include < 18 yo, non-English speaking, unable to provide informed consent and not employed as described above.

d) Screening for PWUD Survey / Biosurvey. Eligible clients will undergo four screening procedures: 1) urine toxicology testing using the 10-panel Alere iCup urine toxicology test (point-of-care, with results within 5 minutes), 2) a quiz on different opioid vs non-opioid pills, 3) an injection practices screener and 4) asked to show stigmata of injection use. “Positivity” for 1 or more of the procedures will constitute

eligibility for drug use criteria. Positivity for urine toxicology is constituted by detection of any opioid. Positivity for the opioid pill quiz is constituted by correct identification of at least one opioid on the pictorial pill quiz. Positivity for the injection practices screener is constituted by description of all the components of injection drug preparation and administration. Positivity for stigmata is constituted by identification of skin marks consistent with recent injection. See Appendix 5 for the eligibility screener documents. In the event of state-wide or regional shut down due to COVID-19 urine toxicology testing will not be required.

5) Location where research will be conducted (Setting)

- Southern Illinois University School of Medicine. SIUSOM is located in Carbondale (Jackson County) and Springfield (Sangamon County). SIUSOM will engage in research. Activities will include data collection hub, coordination of the RDS coupon recruitment, subject activities: recruitment, screening, enrollment and electronic consenting. SIUSOM will also perform study activities such as: conducting surveys and interview data, collection of study data, and referrals to CAP. All SIUSOM individuals will be actively involved in participant recruitment, consent, and data collection. Study staff and students are also trained by IDPH as Disease Intervention Specialists and can so perform disease screening as needed.

  The Harm Reduction Organizations who are functioning as our operations partners are listed below. The activities taking place at each organization will vary based on whether they are engaged in research (Community Action Place) or **not** engaged in research (privately contracted laboratory). Below are descriptions of each harm reduction organization, as well as an organizational chart.

  - **Community Action Place, Inc. (CAP):** CAP is a harm reduction organization providing syringe access, support, counseling, naloxone education and dispensing, HIV counseling, testing, and referral, HCV services and STD testing and treatment. CAP is located in Cairo, Il and offers services in West Frankfurt and other mobile outreach sites in southern IL. CAP will be engaged in research. They will recruit from their clients who participate in syringe services as well as HIV/HCV testing services. They will assess eligibility, perform study electronic consent, as well as perform surveys / interviews for consenting, eligible participants. They will perform standard of care screening for HIV, HCV, and STIs (syphilis, gonorrhea and chlamydia). Additional research specimen collection will include urine toxicology testing as well as oropharyngeal and genital swabs for antimicrobial susceptibility testing. They will also work with ETHIC study staff to coordinate recruitment via respondent driven sampling, which will entail coordinating individuals who have been referred by prior study participants through a code system (see protocol) and scheduling them to meet with CAP staff for eligibility screening and study enrollment. CAP staff will be responsible for SOC linkage to care for participants who test positive during routine

screening. Study participants will complete eligibility screening, surveys/interviews, and specimen collection for testing) in a private area within office sites of the harm reduction organizations. All sites will have bathroom facilities available for urine toxicology testing. These private setting will allow sufficient audio and visual privacy to protect the confidentiality of the participants.

- Electronic consent may be obtained remotely either over the phone or video conference, such as Zoom. Potential subjects will be sent a copy of the consent through email or text. The email or text will contain a link to the consent in REDCap. Following the study discussion prior to signing the consent, the subject's identity will be verified with ID (state ID, license, passport, birth certificate, etc). Verification of the subject's identity will be noted in REDCap. Following the signing of the consent by the study team, subjects will be sent a link to a copy of the fully executed consent contained in REDCap.

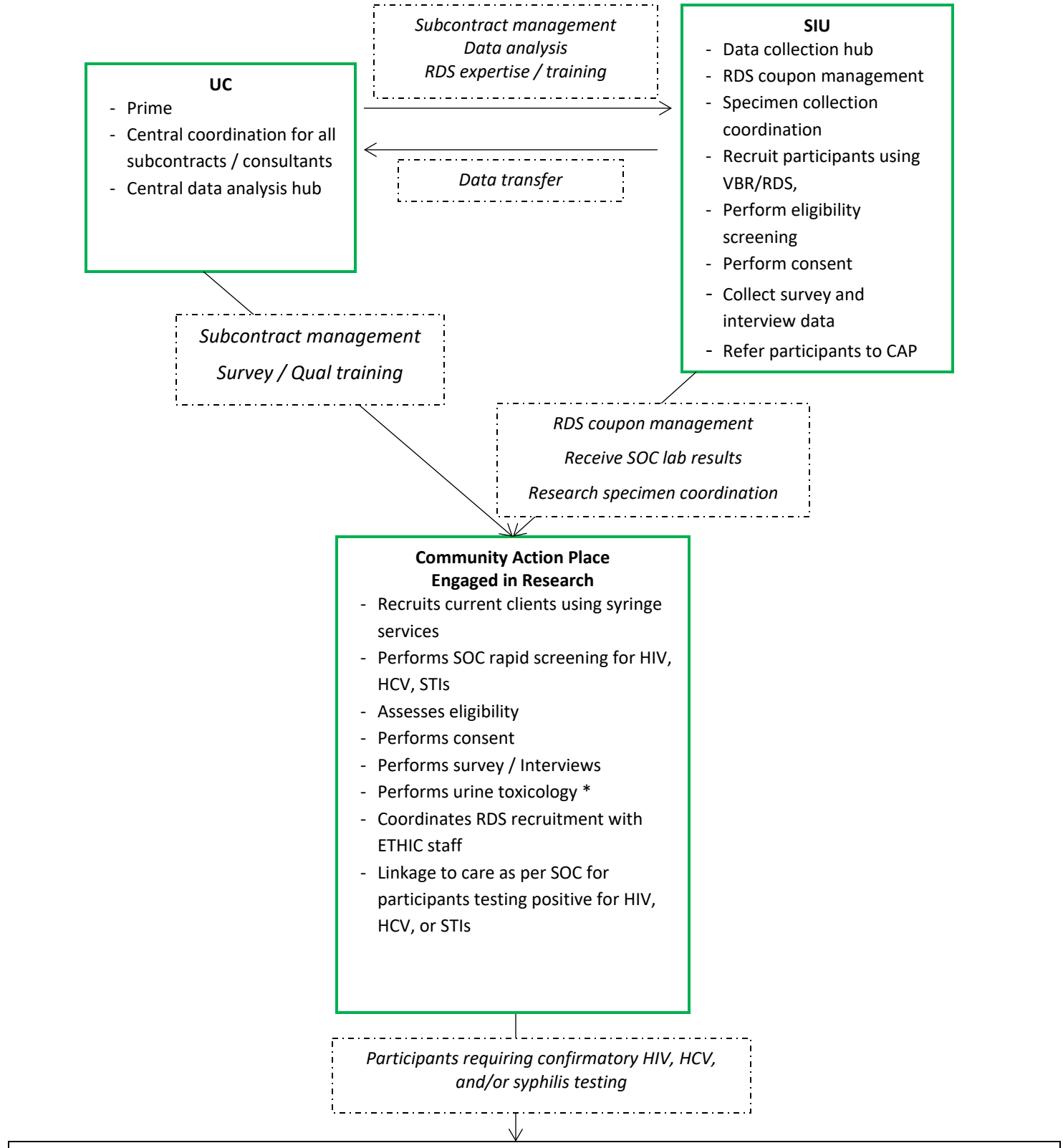


Figure X. Organizational chart for primary data collection. UC: University of Chicago. SIU: Southern Illinois University. SOC: Standard of Care. Green box: Entity engaged in Research.

6) Incentives.

In RDS, which is used for the PWUD survey/biosurvey participant recruitment, participants will receive an incentive payment $40 for their completion of the survey / biosurvey, and will be given no more than 6 RDS vouchers that will be distributed to recruit other people to participate in the study. An incentive ($20) is then given for each voucher that they distribute that produces an additional eligible respondent. Interview participants will receive an incentive payment of $40. Participants will be eligible to receive a minimum of $0 and a maximum of $120 for voucher-based recruitment. To address concerns of possible coercion by recruiting seeds, the incentive payment will be contingent on the eligibility of the referred person, as opposed to consent for enrollment into the study by that person. Participants will have an opportunity to earn an additional $10 for "liking" our page, sending us a Facebook messenger, and then exchanging communication regarding updating contact information, reminders for referrals and scheduling follow ups through Facebook Messenger. Participants will be sent a message from the study team either through text or email to encourage engagement. Survey participants will also be eligible to potentially receive an additional incentive of ($10) for participating in bimonthly Facebook Lotteries to encourage participants to call study staff to update their contact information. Subjects will be entered in the lottery by texting or emailing the study research coordinator with their contact information. Lottery post will be closed for comments to protect against disclosure of study participants. Payment may also be sent electronically through apps, such as CashApp, Venmo or PayPal.

7) Research Partners Engaged in Human Subject Research

The following partners are requesting that U of C function as IRB of record for their work on this study.

Wiley Jenkins, PhD, MPH - Southern Illinois University School of Medicine
Dr. Wiley will oversee field operations in general, and supervise SIUSOM field staff specifically as described above in regards to participant recruitment, informed consent, data and biospecimen collection, disease screening and counseling, and referral to other services such as harm reduction.

- Assistance with the hiring of study staff who will be located at the community organizations to conduct consenting, interviews and survey administration.
- Assistance with study equipment purchasing, such as iPads, in instances where they have access to lower pricing
- Provide space for consenting, interviewing or survey administration if needed.

Lawrence Ouellet, PhD,
Dr. Ouellet will serve as a consultant on this project. Additionally, he will provide training to study staff, and will participate in the interviewing of study subjects.

Community Action Place, Inc. (CAP)

CAP will be engaged in research. They will recruit from their clients who participate in syringe services as well as HIV/HCV testing services.

Sam Friedman, PhD, Director, Institute for Infectious Disease Research – New York University
Dr. Friedman will conduct analysis on identified study data.

Suzan Walters, PhD, Postdoctoral Fellow, – New York University
Dr. Walters will conduct analysis on identified study data.

Jerel Ezell, PhD, MPH, Assistant Professor - Cornell University
Dr. Ezell will support qualitative analysis development, instrument guide development and analysis and will participate in the interviewing of study subjects.

Heather Tillewein, PhD, CHES – Austin Peay State University
Dr. Tillewein will adapt the survey and qualitative instruments and lead in the analysis pertaining to the sexual and gender minority population in ETHIC on de-identified data only. She will lead on conference abstract and manuscript development.

8) Data analysis
Data analysis will be performed by Drs. Pho, Jenkins, Schneider, Friedman, Tillewein and Ouellet as well as Mr. Ezell. Additional statistical analysis will be performed by members of the Biostatistics Laboratory at the University of Chicago.

a) Descriptive statistics, network characteristics and disease burden analyses: Demographic, drug use characteristics, sexual risk behaviors, psychosocial measures and HIV, HCV, HBV and STD status will be analyzed using standard descriptive and comparative statistical analyses. Specifically, t-tests and Chi-square analyses will compare groups for continuous and categorical variables; logistic regression will examine factors associated with disease presence; and repeated measures ANOVA assess factors associated with re-infection/treatment failure. Statistical significance will be assumed with p-values <0.05.

b) Qualitative analysis: Interviews will be analyzed using an inductive thematic approach. At the conclusion of each interview, the interviewer will develop a broad free-text memo detailing any prevailing observations or interpretations from the interview. These interview memos will then be reviewed and discussed with another member of the research team.

   An open coding protocol and thematic analysis will be carried out using ATLAS TI (v. 8.0).[18] This process will be prefaced by the development of a set of *a priori* codes, generated through a close reading of the transcripts, interview memos and relevant peer-reviewed literature, to produce an initial codebook. Each transcript will be coded by one coder; for additional fidelity, a second coder will code a subset of transcripts.

Discrepancies will be resolved through discussion. Emergent themes will be identified the transcripts and memos, following inductive thematic analytic techniques.

c) Epidemiological analysis of public health datasets: We will perform descriptive analysis as described in section as well as use multilevel Poisson regression models to select indicators associated with resident zip codes for patients with emergency department (ED) visits related to heroin and nonmedical prescription drug use in Illinois. This outcome measure is captured by the State syndromic surveillance system. Potential indicators will be selected from a range of datasets including PMP, EMS, treatment and arrest data. ED visits will be modeled against each indicator and in a multilevel Poisson regression model with counties as random effects and total emergency department visits as the offset. We will use backwards stepwise regression to select indicators significantly associated with ED visits.

d) GIS hot spot analysis for resource clustering: We will first produce choropleth maps of all spatial accessibility scores as well as zip code level aggregate data from the Illinois Department of Health and other state entities on infection rates (i.e. HIV, Hepatitis C, chlamydia, gonorrhea), ED visits related to heroin and nonmedical prescription drug use, opioid overdose deaths, criminal justice outcomes. We will perform zip code level hot spot analysis of accessibility scores. Hot spots are areas where the variable of interest (e.g. access to harm reduction, etc.) is significantly higher in magnitude than expected by random chance. We will calculate Local Indicators of Spatial Autocorrelation (LISA) statistics in ARCGIS to determine if the rates of the variables of interest are significantly geographically clustered. If significant clustering is identified, we will use the Getis-Ord tool in ARCGIS to calculate the Gi* statistic, which is used to identify clusters (i.e. census tract) of hot spots. We will also perform bivariate LISA to assess the relationship between accessibility scores and health outcomes (e.g infections, ED visits) to determine if there are areas of low accessibility to services and high levels of PWUD-related outcomes, for example. Both forms of LISA statistics can help determine areas that may be geographic targets for intervention.

e) PWUD Characterization and Exploration of Social Network: This prospective analysis will apply and adapt the extensive expertise of the study team in ethnographic and survey research, network analysis, and non-probability sampling among PWUD (Friedman, Ouellet, Schneider) to an otherwise unstudied population in the IDR. In the first stage, an ethnographic approach will use interviews to inform the development of a survey instrument. Study participants will be recruited using Respondent Driven Sampling (RDS) and a matching will be performed to estimate the social network characteristics of PWUD including injecting and sexual behaviors. Ethnographic and survey data will be used to inform SSP service expansion, outreach, and targeted telehealth programs. Longitudinal analysis will be performed to evaluate acceptability of interventions.

n) Social Network Estimation: An augmented social network will be generated based upon existing matching protocols[19, 20] that generate ties between respondent's self-reported

egocentric networks (both nonsexual social and sexual) and RDS connections. Network structure will be estimated by evaluating main component size, the nodes located in the largest connected component of the network, and average component size. Measures will include the average geodesic distance between participants, network centralization (degree the network centralizes around one or a small group of participants), ranked k-plex measure of cohesion, and transitivity (degree which triadic closure occurs)[21-26] Individual and network factors associated with infectious diseases will be determined.

o) PWUD Population Size Estimation: Multiple estimators for RDS weighting for network factors will be tested for best performance, including the Volz-Heckathorn and the Successive Sampling Estimators.[27, 28] For the Successive Sampling Estimator, we will use mixed-methods triangulation to estimate PWUD population size in the delta regional authority, including survey data, fatalities related to overdose, and drug arrest data.[29]

p) HCV sequencing analysis: analyses of minimum distances, maximum distances, nucleotide diversity, frequency of major haplotypes and calculations for sequence relatedness will be performed on the HVR1 quasispecies using statistical and bioinformatics toolboxes implemented in MATLAB software package version 2011B (The MathWorks, Inc., Natick, MA). The minimum distance between intra-host HCV variants will be calculated, and a minimal hamming distance for the relatedness threshold (3.7%) will be used to identify epidemiologically confirmed outbreaks, as has been previously described.[30] Previous work by key investigators have used this approach in collaboration with the CDC to study HCV outbreaks.[31, 32] Further analytic approaches will be considered in close collaboration with the GHOST laboratory.

q) **Evaluation of Harm Reduction Services Referrals. Evaluation will be performed using the RE-AIM framework (Reach, Evaluation, Adoption, Implementation and Maintenance) using survey, interview and CAP program data.**

1.) Reach Analysis**:** Descriptive analyses will be conducted initially to examine variable distributions and identify outliers, and data will be summarized using frequencies and measures of central tendency. The absolute number and proportion of participants accepting referral to the harm reduction intervention will be calculated at each assessment point (Reach: absolute (%) outcome).

2.) Effectiveness Analysis: Effectiveness measures the impact of harm reduction referral on outcomes of interest as follows;

i. Injection Behavior: Cross sectional analysis will be performed by calculating the injection behavior in individuals engaged and not engaged in the harm reduction intervention.

ii. Overdose: Cross sectional analysis will be performed by calculating the overdose-related behavior outcomes including access to and possession of

naloxone in individuals engaged and not engaged in the harm reduction intervention.

iii. Sexual Behavior: Cross sectional analysis will be performed by calculating the sexual-related behavior outcomes including access to and possession of naloxone in individuals engaged and not engaged in the harm reduction intervention.

iv. MAT / other substance use disorder treatment: Cross sectional analysis will be performed by calculating access to SUD, including MAT in individuals engaged and not engaged in the harm reduction intervention.

v. HIV care and prevention: Cross sectional analysis will be performed by calculating access to HIV care and PrEPin individuals engaged and not engaged in the harm reduction intervention.

vi. HCV care: Cross sectional analysis will be performed by calculating access to HCV care in individuals engaged and not engaged in the harm reduction intervention.

vii. Stigma: Cross sectional analysis will be performed by calculating access to SUD, including MAT in individuals engaged and not engaged in the harm reduction intervention.

viii. Program Data: Cross sectional analysis of client volume, including primary and secondary exchangers, naloxone trainings and kits dispensed, fentanyl strips dispensed, condoms dispensed, HIV/HCV/STI screenings performed, and clients referred to medical care and substance use treatment will be performed.

3.) Adoption Analysis: Adoption of the harm reduction intervention will be defined by i) Utilization and ii) Self -reported access outcomes, stratified by service type:

i. Utilization of any services $\geq$ 2 in the past six months/participants accepting referral (Adoption: absolute (%) outcome),
ii. Self-reported access to services (Adoption: syringe, naloxone, MAT, and condom outcomes)

4.) Implementation Analysis: The fidelity, acceptability, appropriateness, feasibility, and cost of the intervention, and the examination of the RDS-based mechanism as referral into services will be analyzed as follows:

a. Fidelity

i. Field staff observation using the WHO 15 essential element needle exchange program checklist at baseline and every 6 months thereafter will be analyzed based on adherence to each element of service provision, with fidelity as a measure of 100% compliance at 6 months, and maintenance of fidelity defined by 100% compliance at all subsequent observations.

ii. Qualitative analysis: The qualitative instruments will be based on CFIR constructs as described above in the Narrative Study Design section. At the conclusion of each interview, the interviewer will develop a broad free-text memo detailing any prevailing observations or interpretations from the interview. These interview memos will then be reviewed and discussed with another member of the research team. Interviews will be transcribed and will be analyzed using a deductive thematic approach using NVivo. This process will be prefaced by the development of a set of *a priori* codes, generated using the CFIR framework as the basis for the coding scheme. Each transcript will be coded by one coder; for additional fidelity, a second coder will code a subset of transcripts. Discrepancies will be resolved through discussion.

b. Acceptability, Appropriateness, and Feasibility:

i. Acceptability of Intervention (AIM): The baseline score and absolute change on repeated measure every 6 months of this 4-item scale administered to field staff and stakeholders will be calculated,

ii. Intervention Appropriateness (IAM): The baseline score and absolute change on repeated measure every 6 months of this 4-item scale administered to field staff and stakeholders will be calculated.

iii. Feasibility of Intervention (FIM): The baseline score and absolute change on repeated measure every 6 months of this 4-item scale administered to field staff and stakeholders will be calculated.

5.) Maintenance Analysis: Maintenance will be measured The Program Sustainability Assessment Tool (PSAT) responses are rated over each domain, and scores for each domain are averaged for an overall PSAT score. Absolute change in scores will be calculated between the baseline and every six months.

9) Data sharing and use for Multi-Site Rural Opioid Initiative

Fully deidentified data will be securely shared with the University of Washington Data Harmonization Coordinating Center (DCC) as funded by NIDA under 1U24DA048538-01. All PHI

will be removed and the data will be labeled with a study unique number. Datasets across participating sites of the Rural Opioid Initiative will be jointly analyzed. Analyses will include descriptive analyses as well as statistical modeling of the survey data, as well as joint qualitative analyses.

Data from the ETHIC study are expected to be submitted to the DCC as the DCC will be harmonizing data across the 8 ROI FIELD sites in order to create new, combined datasets to be used for analyses across the consortium. Harmonization means the DCC will be combining similar data domains and questions across the ROI 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 ROI grantees will perform data analyses on these data for peer-reviewed publication. The harmonized datasets will be provided to other ROI grantees as required for analysis and will be considered under the umbrella of mandated DCC activities.

Multi-site analyses using data from multiple ROI sites, including ETHIC and other sites' data, will be led by investigators from one or more of the 8 FEILD sites, the DCC, the GHOST laboratory. These investigators are expected to take the lead on hypotheses development and manuscript writing using the harmonized, multi-site datasets. Data analyses for harmonized, multi-site datasets will be conducted by ROI sites and/or the ROI DCC and consultants employed by the ROI (i.e. Abby Rudolph).

Proposals for multi-site analyses using harmonized, multi-site datasets, including ETHIC and other sites' data, will be overseen by the ROI Publications Working Group. The ROI Publications Working Group shall maintain representation from each of the eight ROI sites, including Illinois and the ROI DCC. Any researcher interested in developing manuscripts or other scientific materials using harmonized, multi-site datasets, will be required to submit a proposal narrative to the ROI Publications Working Group. Proposal narratives should be submitted for the approval of all journal articles, research papers, conference abstracts, new grants, or other format of dissemination derived from any The ROI DCC shall not to share the ETHIC dataset with anyone outside the ROI consortium, but may share harmonized, multi-site, project-specific datasets containing ETHIC data with researchers at other ROI consortium sites after approval of a proposal by the ROI Publications Working Group, including an affirmative vote from the ETHIC team representative.

Limited identifiers (zip code and county of residence) will be shared with Ohio State University from 173 subjects that were enrolled between 8/2017 - 7/2019 for analysis. These identifiers will be used to supplement data currently available through DCC.

Before any data transfer, the University of Chicago will encrypt the data both at rest and in transit via a Shared File Transfer protocol (SFTP) to provide a high level of security of sending and receiving file transfers. The encrypted data products will be securely uploaded to a SFTP server using a cyberinfrastructure service such as Globus (https://www.globus.org/) via the Biological Science Division Information Services (BSDIS). Using a STFP will ensure high security

features that meet authentication and authorization standards for sensitive data containing protected health information. Additionally, data management and transferring services for personally identifiable data will be with a High Assurance or HIPAA BAA subscription. If an institution is responsible to provide data (incoming), they will be responsible for encryption.

10) Duration of protocol

Data collection, data analysis and dissemination to partners is expected to take 36 months.

11) Potential risks to study participants

Participants taking the surveys, those interviewed, and third parties, will be subject to minimal risk through their participation. It is possible that the surveys may provide some psychological discomfort, given the sensitive or private information. We will limit this by assuring confidentiality, using well-trained interviewers, clarifying the type of questions that will be asked prior to conducting the surveys, and using sufficiently private interview locations. Participants can always opt to not answer questions. There is a risk of loss of confidentiality. This risk, as well as the protections against this risk as described below, will be described in the consent process.

12) Protection against Risks

Interviewed participants will be informed about their rights as research subjects. They may withdraw at any time during the study without penalty or loss. To further safeguard participants, each will be appointed an independent “Research Advocate”; this individual will be a staff member at Community Action Place and will serve as a supporter and advocate for participants should a participant have concerns or questions that arise during the conduct of the study. In this capacity, the Research Advocate will also serve as an intermediary with study staff.

Data obtained from IDPH as part of this study will be protected in accordance with state and federal statues as dictated by the executed DUA to maintain confidentiality. Furthermore, interviewed participants will be told that unless required by law, only the study investigators, members of the project staff, and representatives of the governing IRBs will have the authority to review study records. In such cases, they too will be required to maintain confidentiality. The data collected will only be accessible to the research team and the Institutional Review Boards. It will be identified via non-identifying subject codes (e.g., sequential identifiers), with the key to other study IDs and names kept in a separate password protected server. Any paper version of such information collected from CAP or BP will be kept in locked cabinets within locked rooms at the University of Chicago. Only study team members who conduct the follow-ups and the data analysts at each site will have the information linking individual subjects to these codes.

a) Protection of Third Party Data

No third party network data will be used for recruitment purposes. This is also explicitly stated in the consent materials.

All network data will be collected and entered through password-protected laptops that will VPN to a second workstation at the University Chicago and within that workstation a secure Department of Medicine server. Partial or whole names of network members, if elicited during study respondent interviews, will be maintained in a separate folder from the respondent-level data and with a non-study ID code (i.e. network ID); therefore attributes of those individuals and their linkage will not be possible without the cross-walk which would be the study-ID and the second network ID. Only the PI (Pho); co-I Schneider and the primary analyst will have access to this cross-walk code which will be kept in a third folder that only these three individuals have access to. After data collection has been completed; matching of names across networks will be performed by the analyst and once matching is completed and all network members receive a unique identifier, the name file and the cross-walk will be destroyed. Therefore, no identifying information collected from the surveys will be linkable to the network.

13) Potential coercion

Eliminating the possibility of coercion by not awarding stipends would make it impossible to conduct many studies, and would shortchange subjects who provide time and energy, and may incur costs such as bus, train or car fares. The resolution to this problem is to ensure that stipends are not inappropriately large, to probe potential subjects to make sure they have not been coerced, and to give persons who may have been coerced the opportunity not to enroll in the study in a manner that will protect them from retribution by the person coercing them.

We believe we meet these conditions with a modest stipend of $40, and $10 for vouchers, and a deliberate consent process that clarify risks and benefits associated with participant.

14) Disclosure of abuse, homicide or suicide risk

A number of procedures will be taken to minimize risk to the participants. The consent procedures will explicitly state that participation in the research is voluntary, and that interviews will include questions regarding sex behavior, HIV status, networks, drug use and mental health. Participants will be informed of the confidentiality of their responses as well as the limits of that confidentiality. They will be informed that sharing any information about the study with others can potentially affect relationships and cause emotional distress to others and self.

Participants will be informed that disclosure of homicide or suicide risk will be referred to appropriate authorities or health care facility for an evaluation by trained mental health experts to determine the best course of action, and that conditions of immediate danger or harm may require reporting or notifying appropriate authorities (i.e. the police or the Department of

Children and Family Services/DCFS). Contact information for such authorities will be provided to study staff as part of the Standard Operating Procedures materials.

Study participants will be informed that voluntary disclosure of sexual activity with others under the age of 17 will be reported to local authorities.

Participants will be informed that disclosure of violence or victimization relating to a person under the age of 18 or to an elderly adult will require reporting to authorities (i.e., the police or the Department of Children and Family Services/DCFS). Though participants will not be asked regarding experiences of assault or abuse while incarcerated, we will inform participants that we are required to inform clinic staff if they do report it.

15) Discomfort or distress during the research

We do not anticipate discomfort or distress during the research study visit; however, we will make every effort to create a secure and trustworthy environment prior to conducting the interview. In addition, the potential benefit of this research outweighs the risks. Participants will be told that they do not have to answer any question they do not wish, and that this in no way will affect the level of health care they are receiving or will receive in the future. Participants experiencing mild distress during the interview will be offered a small break or to reschedule the interview at a later date, if they desire. They also maintain the option to withdraw at any time. Participants will be given the names and office phone numbers of the interviewer and the local PI, and will be provided with a message line that will be checked by the RA daily. Participants who experience significant distress during the survey will be referred to the on-call social worker at the Center for HIV Elimination (CCHE) who is trained in crisis management and distance counseling. Additionally participants expressing intention for self-harm or suicidal ideation will be referred to local emergency services. Information on locale of clinical services will provided to study staff in the Standard Operating Procedures materials.

16) Potential Benefits of the Research to the Subjects and Others

The primary potential benefits of this research will accrue to future cohorts of clinical clients and their potential sexual or needle-sharing partners who may be at reduced risk of infection because of the interventions that eventually result from this research. For individual participants benefits include infectious disease screening and linkage to care if appropriate, naloxone training, and access to clean needles.

17) Federal Certificate of Confidentiality

According to new guidance from the NIH, “Section 2012 of the 21st Century Cures Act, enacted December 13, 2016, enacts new provisions governing the authority of the Secretary of Health and Human Services (Secretary) to protect the privacy of individuals who are the subjects of research, including significant amendments to the previous statutory authority for such protections, under subsection 301(d) of the Public Health Service Act. Specifically, the

amended authority requires the Secretary to issue to investigators or institutions engaged in biomedical, behavioral, clinical, or other research in which identifiable, sensitive information is collected ("Covered Information"), a Certificate to protect the privacy of individuals who are subjects of such research, if the research is funded wholly or in part by the Federal Government. The authority also specifies the prohibitions on disclosure of the names of research participants or any information, documents, or biospecimens that contain identifiable, sensitive information collected or used in research by an investigator or institution with a Certificate… Effective October 1, 2017, all research that was commenced or ongoing on or after December 13, 2016 and is within the scope of this Policy is deemed to be issued a Certificate through this Policy and is therefore required to protect the privacy of individuals who are subjects of such research in accordance with subsection 301(d) of the Public Health Service Act. This Policy will be included in the NIH Grants Policy statement as a standard term and condition of award effective October 1, 2017 for new and non-competing awards. Institutions and their investigators are responsible for determining whether research they conduct is subject to this Policy and therefore issued a Certificate. Certificates issued in this manner will not be issued as a separate document."

We will abide the requirements of the Certificate by informing study participants of these protections in the informed consents (See Appendix 1). We will inform participants that criminal behavior (i.e. drug use) is not reported to authorities and that the security of this information is protected by the Federal Certificate of Confidentiality. These procedures will be reviewed in writing and in person by the study staff as part of the informed consent process to help youth assess whether they wish to participate in the research, and to minimize the inadvertent disclosure of information. Regardless of age, if a participant discloses suicidal ideation or intent of themselves or the other study participant in their network, or any type of abuse, or homicidal intent, the participant will be referred immediately to care (e.g. send to the emergency room, notify police, etc.). We will clarify that information like child abuse and threats of homicide or suicide will be reported to authorities.

18) Controls/placebos

None.

19) Safety and monitoring

The research is not a clinical trial. There will not be a formal data and safety monitoring committee. We will report any confidentiality issues to the Institutional Review Board as mandated.

20) Informed consent

Written consent will be obtained by a trained study staff prior to the clients' participation in the study. The consent forms will be approved by the designated institutional review boards. The consent discussion will involve a 2-step process. First, the study staff determines if the person

understands the study goals by asking “Can you tell me what this study is about?” In step 2, potential subjects will be asked questions designed to assess their capacity to understand, appreciate, reason with, and express a choice about participation in our specific protocol. We will base this off the widely used Evaluation to Sign Consent Form: Subjects are asked to: (1) name things they will be expected to do during the study, (2) explain what they would do if they no longer wished to participate in the study, (3) explain what they would do if they experienced distress during the study and (4) identify potential risks for participating in the study. Subjects will be enrolled only if they are able to provide clear and correct answers to each of these items, without prompting or correction.

For youth under the age of 18, study staff will ensure that the participant understands the risks associated with the study. The interviewing staff reviews the consent to make a formal assessment of the participant’s decisional capacity to consent prior to signing, using a 2-step process. First, the interviewing staff determines if the person understands the study goals by asking “Can you tell me what this study is about?” In step 2, potential subjects will be asked questions designed to assess their capacity to understand, appreciate, reason with, and express a choice about participation in our specific protocol. Subjects are asked to: (1) name things they will be expected to do during the study, (2) explain what they would do if they no longer wished to participate in the study, (3) explain what they would do if they experienced distress during the study and (4) identify potential risks for participating in the study. Respondents will be enrolled only if they are able to provide clear and correct answers to each of these items. For youth under the age of 18, study staff will ensure that the participant understands the risks associated with the study. If study staff feel there is a question about the need for a more formal assessment of the decisional capacity of a potential participant s/he will contact the PIs or other senior staff. Additionally, study staff will inform the person that the research study is voluntary and their decision whether to participate will not impact their relationship with the research sites. If volunteers agree to participate, they will be immediately enrolled in the study.

We request a waiver of parental consent for minors enrolled in this study in all phases. Parental consent may decrease participation rates because some youth will fear that they may be “outed” as a result of participation. Disclosure of sexual orientation may place participating youth at risk for parental harassment and/or abuse or expulsion from the home. The nature and scope of the proposed research do not pose more than “minimal risk” to participants. Study measures are standard in this population, as are waivers of parental permission for survey and interview studies. HIV/STI testing is also common (and encouraged) in this group, and does not require parental permission or notification. To compensate for waiver of parental consent participants receive a formal individual assessment of capacity to consent (above) to ensure their understanding of study goals, procedures, and risks from disclosure of sensitive information.

Stakeholder subjects will be taken through a consent discussion in a private office with a staff member. The discussion will offer the stakeholder subjects opportunities to have all questions answered. The oral consent will be obtained prior to the start of any study interview and audio recording.

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ETHIC Addendum: ECHO Protocol

Background:

The prevention opioid overdose and transmission of infectious diseases related to injection drug use will depend upon increased access to opioid use disorder treatment such as medication assisted therapy (MAT), hepatitis C treatment as well as testing, screening and linkage to these services. As of the submission of this protocol there are only 26 DATA 2000 waivered buprenorphine prescribers in the study region and no methadone clinics. Eight of the 16 counties are designated "MAT Deserts", i.e. no MAT provider available per the Illinois Department of Human Services. This lack of access was reflected in survey data where only 13% of respondents had received any substance use disorder support in the past 30 days and 70% were unsure or felt that it would be difficult to access buprenorphine for treatment if they wanted it. In regards to Hepatitis C, the prevalence of HCV+ Ab in our study was high (47.8%) and access to treatment was low (10.4%). As of the submission of this protocol there were only 3 infectious diseases specialists and 4 gastroenterologists with active licenses in the study region according to the Illinois Department of Professional Regulation.

Survey respondents reported low access / utilization of general medical care (24% had not received care in in past 6 months) citing barriers including transportation (40.9%), and fear of being disrespected (41.6%) in the healthcare environment. The largest percentage of those receiving healthcare (35%) reported obtaining it in emergency departments (EDs). Our qualitative data revealed many problematic encounters in that setting, citing breaches of trust by ED providers, such as disclosures of protected health information to law enforcement and child protective services, as well as stigmatizing and humiliating provider-patient interactions. These experiences and perspectives were substantiated by commentary from healthcare providers whom we interviewed.

To promote HCV, MAT, and PWUD health trained ED workforce development we will utilize the Extension for Community Healthcare Outcomes (ECHO) model. ECHO was developed in 2003 at the University of New Mexico (UNM) by Dr. Sanjeev Arora, a hepatologist, as a way to provide hepatitis C patients with timely care. Using videoconferencing technology, the ECHO

model brings community-based PCPs together with subspecialist teams from academic medical centers for “telementoring” and collaborative, curriculum-driven, case-based training. Unlike a webinar, participants and facilitators alike can see, hear, and learn from each other, fostering a more engaging and interactive learning experience. Modeled after medical “rounds,” PCPs present challenging patient cases, sharing how they have implemented suggested practices and identifying issues with which they continue to struggle. Many of these discussions focus on issues such as how to approach difficult conversations with patients, how to work with patients to scale goals to be more practical and achievable, and building trust.

Since 2008, the Project ECHO model has been leveraged to train thousands of clinicians in many different specialty areas around the country. To date there are a total of 287 partners in more than 35 countries replicating the ECHO model on 70 different categories. The highly successful ECHO model can be leveraged and applied to train clinicians in a manner that is very scalable, in order to meet the ever increasing medical care needs.

The literature to date supports the effectiveness of the ECHO model in improving PCP outcomes, including growing knowledge, enhancing self-efficacy, improving job satisfaction, and increasing empowerment to treat complex, chronic conditions including hepatitis C and opioid use disorder.1-10 While the literature on the broader impact of ECHO continues to grow, early studies point to the model being able to successfully improve chronic disease management, boost disease management in primary care to be on par with subspecialists, and achieve cost savings. 6,11-14

Mapping of current primary care, psychiatry, and emergency medicine sites in the Delta region was performed to identify potential ECHO sites. Data sources included a survey performed by the Southern Illinois School of Medicine (SIUSOM) Office of Continuing Professional Development (CPE) of primary care providers, active license listings from the Illinois Department of Financial and Professional Regulation and the Illinois Department of Human Services. At the time of this protocol development there were 181 general practitioners (family medicine, internal medicine, etc.) and 16 psychiatrists with active licenses in the study area.

There were a total of 96 clinical sites, including 26 family medicine practices, 23 rural health clinics and 24 FQHCs

Aim:

Build capacity for HCV management, substance use screening, referral, and medication-assisted treatment through the Extension of Community Healthcare Outcomes (ECHO) model targeted at PWUD-preferred service settings.

Sub aim:

We will develop and implement an innovative ECHO curriculum targeted to emergency medicine providers on PWUD healthcare (ECHO-ED)

Sites conducting research:

University of Chicago

Southern Illinois University (SIUSOM)

Methods:

ECHO-ED curriculum development:

We will adapt existing CME materials to develop an ECHO-ED curriculum covering the following topical areas: prescription monitoring, opioid prescribing recommendations, non-opioid pain control in the ED and after leaving the ED, an introduction to MAT and warm handoff to resources, take home naloxone, skin and soft tissue infection, screening for infectious diseases, communicating with patients that have OUD and legal implications. Additional topical areas identified in the Pre-ECHO Key informant interviews will also be addressed. Key informant interviews will also serve to identify potential barriers to providing the ECHO intervention, including appropriateness of the ECHO format such as scheduling around ED shifts that can inform the delivery of the intervention. The curriculum will be reviewed by representatives from the Illinois Poison Center and the Illinois College of Emergency Physicians for accuracy and appropriateness.

ECHO Implementation :

ECHO-Chicago will implement an evidence-based ECHO-HCV curriculum and the ECHO-ED series twice annually. Evidence based ECHO-MAT curriculum will be provided by the Southern Illinois University Department of Psychiatry twice annually. Participant will join hour-long weekly sessions via the Zoom video-conferencing platform. Sessions will be facilitated by a multidisciplinary expert team.

Study Activities

Interviews/Focus Groups:

All interviews will be conducted either face to face in a private office/space, over the telephone or Zoom. Focus groups will be conducted over Zoom. All interviews and focus groups will be audibly recorded without the collection of any identifiers and then transcribed. The audio recordings will be stored for 5 years and then destroyed. We will not collect any PHI during the interviews described below. Following the interviews, all subjects will be asked to complete a brief demographic survey. The information captured through this survey will be used to help us contextualize the background and general traits of these participants.

Pre ECHO-ED

Up to 10 clinical providers will be asked to take part in an interview prior to the ECHO-ED development. These providers will include emergency medicine physicians, nurses, pharmacists, and primary care providers who will serve as key informants to the development of the ECHO-ED curriculum. The interview will take approximately 30 minutes to complete.

Recruitment: A study flyer with contact information will be distributed to clinical sites in southern Illinois by ETHIC Operations Partners Committee, namely Southern Illinois Healthcare and the Center for Rural Health and Social Services Development, as well as the Illinois Hospital Association and the Illinois College of Emergency Physicians.

Post-ECHO Trainee

Up to 15 providers who have participated in the ECHO curriculum (4-5 for each curriculum) will be interviewed as a component of implementation evaluation for the ECHO intervention (i.e. ECHO as a delivery mechanism for clinical training). The interview will be help to elicit barriers

and facilitators from the trainee perspective. The interview will take approximately 60 minutes to complete.

Recruitment: A slide with study information will be posted by the ECHO administration group during each of the curriculum presentations to seek interested providers. The slide will contain study contact information.

Post-ECHO Expert Trainer

Up to 9 ECHO expert trainers (ie gastroenterologist, addiction specialist, emergency medicine physician) at the ECHO hubs (University of Chicago and SIUSOM) covering each curriculum will be invited to participate in a focus group as a component of implementation evaluation for the ECHO intervention (i.e. ECHO as a delivery mechanism for clinical training). The focus group guide will be developed to elicit barriers and facilitators from the trainer perspective. The focus group will take approximately 40 minutes to complete.

Recruitment: Participants will be recruited from the team of expert trainers leading the ECHO curriculum supported by the University of Chicago and SIUSOM ECHO programs. They will be directed contacted via email by the study PIs.

Program Sustainability Assessment Tool (PSAT)

Up to 10 clinical directors / supervisors at ECHO trainee sites will be invited to complete the PSAT, which is a 40 question self-assessment. The PSAT evaluates the sustainability capacity of ECHO based training in the setting (i.e. maintenance).16 The PSAT covers eight sustainability domains (environmental support, funding sustainability, communications, strategic planning, partnerships, strategic planning, organizational capacity and program evaluation) and takes approximately 10-15 minutes to complete. The PSAT will be administered at baseline and after completion of at least 1 ECHO curriculum at their clinical site via a RedCap survey link.

Recruitment: Clinical directors will be informed of the opportunity to participate via notification through the ECHO programs. Clinical directors will receive an email which will be sent through the ECHO programs.

Additional Data Elements

In addition to the data collected above, we will also receive anonymous responses provided in

the surveys (150 surveys total as approximately 30-50 surveys are expected per year) which are administered to all trainees before and after ECHO training. As standard of care in ECHO, these surveys measure effectiveness of the training by asking questions which will measure knowledge of the subject matter, self-efficacy, and acceptability of the intervention, intervention appropriateness, and feasibility of the intervention. As part of the study data from ECHO-Chicago will we will receive anonymous survey data from the program which will include program data regarding attendance of ECHO sessions and the zip code of the place of practice. No individual identifiers will be received from ECHO-Chicago

Subjects:

Inclusion criteria:

Males and females age >= 18 years old, English speaking, employed in the study region (southern 16 counties: Alexander, Franklin, Gallatin, Hamilton, Hardin, Jackson, Johnson, Massac, Perry, Pope, Pulaski, Randolph, Saline, Union, White, and Williamson) as well one of the clinical provider types listed above (family medicine, primary care, internal medicine, psychiatry, emergency medicine, social work, case manager, physician, mid-level).

Exclusion criteria:

Males and females < 18 years old, non-English speaking, unable to provide informed consent and not employed as described above.

Incentives

Interviewees and PSAT survey completers will be offered a $40 gift card for their participation.

Informed consent:

Oral consent will be obtained from those who take part in the study interviews.
Electronic consent will be obtained from those who complete the PSAT.
A waiver of consent will be requested for the anonymous survey data

Potential risks and benefits to subjects:

A minimal risk of loss of confidentiality exists for this study. PHI will not be linked to any of the responses given in surveys/interviews. Limited PHI will be collected to allow for communication during interviews, surveys and to allow for payment. PHI will be destroyed after the study is complete.

Data Analysis:

a. Reach: Reach will be defined by the absolute number of ECHO trainees participating in the first session of each ECHO curriculum. The proportion of providers reached will be calculated using the number of ECHO trainees participating divided by the number of eligible providers for the respective topic areas as estimated in section 1.g) above.

b. Effectiveness Analysis: Effectiveness of each ECHO curriculum type will be based upon change in knowledge, self-efficacy, stigma, and adoption of practice change based on aggregate data received from the program from the Pre-and Post-ECHO Provider Survey. Paired t-tests with an alpha of .05 will be conducted to assess absolute change in knowledge, self-efficacy, stigma, and practice change.

c1. Adoption of Practice Change: The degree of acceptability, appropriateness, and feasibility of adopting practice change for MAT, HCV and ED as promoted by the ECHO curriculum will be calculated from the trainees surveys.

c2. Adoption of the ECHO Intervention: In contrast to adoption of training into clinical practice as discussed in the evaluation of effectiveness of the ECHO intervention, the adoption of the ECHO intervention as a mechanism for workforce capacity development will be measured by the proportion of ECHO trainees that attend 75% of live sessions, or in the case of ECHO-ED 75% of all session including recorded sessions.

d. Implementation: The assessment of implementation fidelity for each ECHO delivery for each topical area will be performed using qualitative measures collected in the Post-ECHO Trainee interviews and Post-ECHO Expert Trainer focus group, as well as through direct session

observation using a predetermined ECHO checklist. Interviews will be transcribed and will be analyzed using a deductive thematic approach using NViVO. Each transcript will be coded by one coder; for additional fidelity, a second coder will code a subset of transcripts. Discrepancies will be resolved through discussion.

e Maintenance: The extent to which the ECHO intervention is valued and promoted subsequent to the study by clinical care leadership will be assessed by the PSAT tool as administered to clinical supervisors at participating ECHO sites. The PSAT is a Likert-scare based 40 item survey that is scored based on average rating across eight domains.

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