

A Descriptive Cross-Sectional Analysis Of Potential Factors, Motivations, And Barriers Influencing Research Participation And Retention Among People Who Use Drugs In The Rural United States

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Abstract

Background: Despite high morbidity and mortality among people who use drugs (PWUD) in rural America, most research is conducted within urban areas. We describe influencing factors, motivations, and barriers to research participation and retention among rural PWUD.

Methods: We recruited 255 eligible participants from community outreach and community-based, epidemiologic research cohorts from April-July 2019 to participate in a descriptive cross-sectional study. Eligible participants reported opioid or injection drug use to get high within 30 days and resided in high-needs rural counties in Oregon, Kentucky, and Ohio. We aggregated response rankings to identify salient influences, motivations, and barriers. We estimated prevalence ratios to assess for gender, preferred drug use, and geographic differences using log-binomial models.

Results: Most participants were male (55%) and recently injected methamphetamine (61%) and/or heroin (57%). The primary influential factors for research participation are confidentiality, amount of financial compensation, and time required. Primary motivations for participation include financial compensation, free HIV/HCV testing, and linkage with resources. Changed or false participant contact information and transportation are principal barriers to retention. Respondents who prefer methamphetamines over heroin are more influenced by why their information is collected and how it is used (PR=1.12; 95%CI:1.00, 1.26). Knowing and wanting to help the research team are motivations for participation among Oregon participants (PR=2.12; 95%CI:1.51, 2.99) and females (PR=1.57; 95%CI:1.09, 2.26).

Conclusions: Beyond financial compensation, researchers should emphasize confidentiality, offer testing and linkage with care, use several contact methods, aid transportation, and accommodate demographic differences to improve research participation and retention among rural PWUD.

Introduction

The rural United States (U.S.) is in the midst of an ongoing substance use disorder epidemic. In 2019, one in five Americans used an illicit drug and 70,630 drug overdose deaths occurred in the U.S, of which 71% were opioid-related [1, 2]. Further exacerbating the substance use epidemic is the prediction of the opioid epidemic's '4th wave', or the rise in methamphetamine use among people with opioid use disorders [3–6]. People who use drugs (PWUD) such as opioids and methamphetamines face rising rates of HCV, HIV, and other chronic health conditions [7–9]. When rural PWUD attempt to access treatment for these health conditions, they face transportation barriers, stigma from healthcare providers, and a shortage of providers who offer care for addiction and its associated harms (e.g. HCV and HIV)[8, 10–12].

Despite high morbidity and mortality among PWUD in rural America, most clinical research is conducted among urban residents [13]. Results from clinical studies may not always translate to rural communities because of the various demographic, sociocultural, and infrastructural differences [14–17]. PWUD in rural communities may benefit from participation in research through otherwise unavailable access to substance use disorder (SUD) knowledge, specialists, and medical facilities, the receipt of new and

effective treatments and medical care, and supported linkage to community SUD resources and programs [18, 19]. Although clinical trials may provide valuable care and treatment to rural PWUD, retention and recruitment remains challenging [15, 20, 21]. Those in rural communities note mistrust and fear as contributors to low recruitment, and rural residents have a lower likelihood of awareness of opportunities to participate in research compared to their urban counterparts [21, 22].

Factors affecting clinical trial adherence can be categorized using the Ickovics and Mieslers multifactorial framework: the individual, treatment regimen, patient-provider relationship, clinical setting, and the disease [23]. Individual level differences between genders in research recruitment and participation among rural PWUD have been mixed. The National Institute on Drug Abuse (NIDA) Treatment Clinical Trials Network (CTN) did not identify gender differences in research recruitment and retention among PWUD, and willingness to participate in an HCV vaccine trial among PWUD did not differ by gender [24, 25]. However, women are still underrepresented in HCV and HIV clinical research [26], and gender differences in utilization of harm reduction services exist among rural PWUD [27]. An individual's drug preference for methamphetamine over heroin may also impact trust in research due to adverse effects such as elevated paranoia and suspiciousness associated with methamphetamine use [28]. Patient-provider relationship factors such as stigmatizing attitudes unique to certain drugs [29–31] could result in variations in the perceived judgement by staff as a factor affecting participation.

Our study's primary objective is to describe the influencing factors, motivations, and barriers of rural PWUD in participation and retention in research studies. The study's secondary objective is to examine variation in influencing factors, motivations, and barriers across geographic regions, gender, and substance use to inform retention and recruitment strategies.

Methods

Study Setting

We recruited participants in rural areas of Kentucky, Ohio, and Oregon, where each state has an established research infrastructure through the National Rural Opioid Initiative [32]. Rural study sites in Eastern Kentucky and Southeastern Ohio are located in Appalachia, a cultural and geographical region that spans 13 states from New York to Mississippi [33]. The Oregon rural study sites in the Pacific Northwest include both coastal and interior communities in large, sparsely populated counties. The populations in these areas of Appalachia and Oregon are predominantly White, and on average 14–25% of the population lives below the poverty line [34]. These rural communities are at increased vulnerability for HIV and HCV transmission due to high injection drug use rates and inadequate healthcare infrastructures [35–37].

Study Design

We conducted a cross-sectional, multi-state survey from April-July 2019. The survey was part of the formative phase of the Peer-based Retention of People who Use Drugs in Rural Research (PROUD-R²)

study that tests rural peers' ability to improve study retention (ClinicalTrials.gov identifier: NCT03885024) [38]. We derived a sample size of 225 participants to complete the cross-sectional survey and inform the central phase of PROUD-R².

Eligible participants were at least 18 years of age, injected any drug or used opioids to get high within the past 30 days, and lived within rural counties associated with each study site. We recruited participants using convenience sampling at syringe service programs, local health departments, community-based settings, and through concurrent epidemiologic studies. We obtained informed consent from all participants and provided each participant with \$20 cash or a gift card as reimbursement for survey participation. The survey was interviewer-administered in Kentucky and Oregon and self-administered in Ohio. In Kentucky and Ohio, we collected data using Qualtrics software, Version June 2019 (Qualtrics, Provo, UT). In Oregon, study data were collected using REDCap electronic data capture tools hosted at Oregon Health & Science University [Grant#: UL1TR002369][39].

Data Collection

We adapted survey questions from a study that assessed willingness to participate in an HCV vaccine clinical trial among rural PWUD in Appalachia [24]. The Community Advisory Board of the Kentucky CARE2HOPE study and peer recovery support specialists of the Oregon OR-HOPE study reviewed and approved the survey's final version to confirm the appropriateness of the survey.

Participants provided the following demographic information: age, gender, education, race, and ethnicity. We assessed participant's gender using the construct, "What is your gender?" in alignment with recommendations to use gender as opposed to sex when reporting psychosocial or cultural factors [40]. We also asked participants about recent drug use, "Have you ever injected drugs to get high?," "Which drugs have you injected in the past 30 days to get high?," and "Which is your drug of choice for getting high?."

We collected data on (1) influencing factors for research participation, (2) motivations for participating in research, and (3) barriers to attend follow-up research appointments through a series of nominal response option questions in which the participant could "select all that apply." To elicit factors that influenced participants' decision to participate in a research study, we asked, "What are some of the things that people who use drugs in this community may consider when deciding to participate in a research study?" [15 response options]. We inquired, "What are some of the reasons that people who use drugs in this community may decide to participate in a research study?" [10 response options] to obtain their motivations for participation in research. To assess barriers to retention in attending follow-up research appointments, we asked, "What do you think are some of the challenges to getting people to come back for follow-up appointments?" [11 response options]. Complete response options for all three questions are listed in Tables 3–5. If a participant selected more than three responses to the above questions, a second question prompted the participant to rank their first, second, and third options from their previously selected responses, hereafter referred to as primary, secondary, and tertiary responses.

Statistical Analyses

Participant sociodemographics and drug use characteristics were summarized using descriptive statistics. We excluded participants from the analysis if they did not provide a response for any eligibility criterion. To visually represent and compare the ranking of participant responses, we used diverging stacked bar charts [41]. We displayed survey items with the highest to lowest frequency of primary, secondary, and tertiary responses. We also included counts of selected, but unranked, responses for each survey item.

We aggregated the survey responses into 36 binary dependent variables to analyze the differences of influencing factors, motivations for participation, and barriers to retention in research among subgroups of the study population. Due to small cell sizes, we condensed the rankings of each response into dichotomous variables ('selected', 'not selected') that represented a participant's response to selecting items as essential influencing factors, motivations, or barriers.

We assessed differences in the dependent variable by the independent variables of gender (male, female), region (Appalachia, Oregon), and preferred drug of choice (heroin, methamphetamine). We combined Kentucky and Ohio into a single 'Appalachia' group for several conceptual and statistical reasons: the stratified prevalence ratios of Kentucky and Ohio were similar when compared to Oregon, the Kentucky and Ohio research sites are geographically close, and both are in the Appalachian region. To ensure that "preferred drug of choice" reflected actual use, we verified that most participants had access to their preferred drug of choice by generating cross tabulations with their preferred drug of choice and reported substance use in the past 30 days.

We performed log-binomial regression to assess differences in site, gender, and preferred drug use for each of the 36 selected responses. Prevalence ratios (PR) and corresponding 95% confidence intervals (CI) were estimated for each bivariable model. To reduce bias and improve model precision, only survey items with at least ten responses at each level of the binary dependent variable were modeled [42–44].

We aggregated and analyzed data using SAS software version 9.4 (SAS Institute Inc., Cary, NC) at Oregon Health and Science University and the Ohio State University. Plots were developed with the "HH" package in R version 4.0.2 (R Core Team, Vienna, Austria)[45, 46]. The Ohio State University Institutional Review Board, University of Kentucky Institutional Review Board, and Oregon Health and Science University Institutional Review Board approved this study.

Results

Participant Characteristics

A total of 290 participants completed the survey. In Oregon and Kentucky, a total of 218 participants were screened, and 34 participants were ineligible due to not meeting drug use eligibility criteria (n = 28), living outside of the study location (n = 4), or missing information for all eligibility criteria (n = 2). In Ohio, participant eligibility was assessed verbally, and the number of ineligible participants and reasons for

ineligibility were not obtained. We excluded one Ohio participant from analyses due to missing age. The final analytic sample contained 255 participants and included a complete set of responses for all independent and dependent variables.

The characteristics of the 255 participants included in our study are shown in Table 1. Most participants were from Kentucky (n = 105), then Oregon (n = 79), followed by Ohio (n = 71) and the mean age was 38 years (SD = 9.7). Most participants identified as male (55%), white (88%), and had at least a high school diploma/General Educational Development (GED) (73%).

Table 1. Demographics of a cross-sectional survey of PWUD in rural Oregon, Ohio, and Kentucky, April-July 2019

	Total Study Population		Oregon		Kentucky		Ohio	
	(n=255)		(n=79)		(n=105)		(n=71)	
	<i>n</i>	<i>%</i>	<i>n</i>	<i>%</i>	<i>n</i>	<i>%</i>	<i>n</i>	<i>%</i>
Age								
Mean (SD)	37.9	10	36.1	10	38.2	10	39.3	9
Gender								
Female	116	45	36	46	51	49	29	41
Male	137	55	43	54	54	51	40	56
Transgender	1	0	0	0	0	0	1	1
Unknown/unsure	1	0	0	0	0	0	1	1
Race								
White	225	88	60	76	104	99	61	86
Black/African American	5	2	2	3	0	0	3	4
American Indian/Alaskan Native	6	2	5	6	0	0	1	1
Mixed Race	13	5	10	13	1	1	2	3
Other	6	2	2	3	0	0	4	6
Ethnicity								
Hispanic	14	5	11	14	1	1	2	3
Non-Hispanic	241	95	68	86	104	99	69	97
Education								
Less than high school	69	27	10	13	41	39	18	25
High school diploma or GED	106	42	36	46	40	38	30	42
Some college	59	23	29	37	19	18	11	16
Associate's degree, trade, or technical college	16	6	3	4	4	4	9	13
Bachelor's degree or higher	3	1	1	1	1	1	1	1
Missing	0	0	0	0	0	0	2	3
Highest level of education								

High school diploma or GED	184	73	69	87	64	61	51	74
below high school diploma or GED	69	27	10	13	41	39	18	25

Nearly all participants had injected some type of drug in the past 30 days to get high (93%) (Table 2). Most participants preferred either heroin or methamphetamine; both groups reported recent use (92% for heroin, 95% for methamphetamine), and both were the most commonly injected drugs in the past 30 days (57% and 61%, respectively). Other recently injected drugs included fentanyl (18%), buprenorphine (18%), painkillers (15%), cocaine/crack (8%), methadone (3%), and prescription anxiety drugs (3%).

Table 2. Drug use history among rural PWUD in Kentucky, Ohio, and Oregon, April 2019-July 2019

	Total Study Population (n=255)		Oregon (n=79)		Kentucky (n=105)		Ohio (n=71)	
	<i>n</i>	%	<i>n</i>	%	<i>n</i>	%	<i>n</i>	%
Ever injected drugs to get high	237	93	75	95	95	91	67	94
Drugs injected to get high in past 30 days								
Methamphetamines	155	61	61	77	70	67	24	34
Heroin	144	57	42	53	48	46	54	76
Buprenorphine	47	18	5	6	33	31	9	13
Fentanyl	47	18	14	18	10	10	23	32
Painkillers	38	15	21	27	12	11	5	7
Cocaine/crack	21	8	11	14	6	6	4	6
Other	11	4	10	13	0	0	1	1
Methadone	8	3	5	6	2	2	1	1
Prescription anxiety drugs	8	3	6	8	1	1	1	1
Gabapentin	1	1	1	1	0	0	0	0
Kratom ^a	1	1	1	1	0	0	-	-
Clonidine	0	0	0	0	0	0	0	0
Synthetics	0	0	0	0	0	0	0	0
Drug of choice to get high								
Methamphetamines	91	36	37	47	45	43	9	13
Heroin	90	35	33	42	24	23	33	47
Buprenorphine	14	6	0	0	12	11	2	3
Painkillers	13	5	2	3	11	11	0	0
Fentanyl	5	2	0	0	0	0	5	7
Other	3	1	3	4	0	0	0	0
Gabapentin	2	1	0	0	0	0	2	3
Methadone	1	1	0	0	1	1	0	0
Cocaine/crack	1	1	0	0	1	1	0	0

a. Kratom was not listed as a response option in the Ohio survey

Patterns of Influencing Factors in Decision to Participate in Research Studies

The primary influencing factor for research participation was the amount of financial compensation received in exchange for participation (Fig. 1), followed by confidentiality of information. Other essential influencing factors among rural PWUD were the time required to participate in the research study and privacy of the research office. The influencing factor with the least number of ranked responses was whether the research institution or university was well-respected.

In considering participation in research, Oregon respondents had a higher prevalence of selecting all influencing factors listed compared to Appalachian respondents. When compared to Appalachian respondents, Oregon respondents were more influenced by how much time is required for participation (PR = 1.42; 95% CI:1.21, 1.67) and the frequency of research appointments (PR = 2.14; 95% CI:1.75, 2.60). Oregon respondents also had a higher prevalence of noting schedule conflicts, such as whether they have childcare available to attend research appointments (PR = 1.54; 95% CI:1.21, 1.95), and if their appointment times will interfere with their work schedule (PR = 1.63; 95% CI:1.24, 2.14). Privacy of the research office (PR = 1.32; 95% CI:1.13, 1.53) and knowledge of why their information is being collected and what it will be used for (PR = 1.46; 95% CI:1.24, 1.73) were increased concerns among Oregon compared to Appalachian respondents (Table 3).

Table 3. Influencing factors and motivators to research participation and barriers to retention: Oregon versus Appalachia PWUD

Survey Item	PR ^{a,b}	95% CI
<i>Influencing Factors</i>		
What the research study involves (e.g., survey, drug testing for research) ^c	-	-
How much time is required	1.42*	(1.21, 1.67)
How often they have to come in for visits	2.14*	(1.75, 2.60)
How far they have to travel to participate (i.e., nearby vs. out of town) ^c	-	-
Privacy of the research office	1.32*	(1.13, 1.53)
Why their information is being collected and what it will be used for	1.46*	(1.24, 1.73)
Whether their information will be kept confidential ^c	-	-
Whether the staff doing the research is friendly and trustworthy ^c	-	-
Whether the research institution or university is respected	1.26	(0.97, 1.63)
Whether they can skip questions of parts of the study that make them uncomfortable	1.52*	(1.25, 1.84)
How much money they will receive ^c	-	-
How much the project will benefit them overall ^c	-	-
Whether their appointment times will interfere with their work schedule	1.63*	(1.24, 2.14)
Whether they have childcare so that they can attend their appointments	1.54*	(1.21, 1.95)
How their friends, family, or partner feels about them participating	1.71*	(1.31, 2.21)
<i>Motivations</i>		
Financial incentive (i.e., money or gift card given for participation) ^c	-	-
They believe in the mission of the research and want to contribute	1.42*	(1.18, 1.70)
Their friends, family, or partner participates	1.49*	(1.26, 1.77)
They want to tell their story	1.37*	(1.11, 1.70)

They know someone on the research team and want to help them out	2.12*	(1.51, 2.99)
They want to learn about the topic	1.44*	(1.14, 1.81)
They would want to get free testing (for example, rapid tests for HIV & Hepatitis C) if it was offered as part of the study ^c	-	-
They would want to be linked with resources and/or follow-up testing if it was offered as part of the study	1.49*	(1.28, 1.73)
They would want to try a new treatment if it was offered as part of the study	1.44*	(1.24, 1.68)
Their friends, family, or partner pressures them to participate so that they can share the financial incentive	2.18*	(1.56, 3.03)
<i>Barriers</i>		
Not being able to get in touch with participants because their contact information changed ^c	-	-
Not being able to get in touch with participants because they gave false contact information when they started the study	1.02	(0.82, 1.29)
They may have trouble getting transportation for their appointments	1.15	(0.99, 1.33)
They may have trouble being able to show up at a specific appointment time ^c	-	-
They may have trouble getting to their appointment because of their work schedule	1.60*	(1.26, 2.04)
They may have trouble finding childcare so that they can go to their appointment	1.60*	(1.26, 2.01)
They may have concerns about confidentiality and privacy	1.52*	(1.22, 1.90)
They may be afraid that the staff would judge them if they are still using drugs	1.20	(0.92, 1.58)
They may have stopped using drugs and no longer think the study is relevant to them	1.42*	(1.10, 1.82)
They are in a drug treatment or recovery facility and are unable to be contacted by research staff	1.33*	(1.09, 1.63)
Their friends, family, or partner may want them to stop participating	1.27	(0.87, 1.86)

a. Kentucky and Ohio sites were combined to represent the referent group of 'Appalachia'

b. The level of response for each survey item was dichotomized into 'selected' or 'not selected' to generate prevalence ratios

c. Oregon cell sizes <10; analysis not performed

** Significant at $\alpha = 0.05$ level*

Compared to males (n = 137), female participants (n = 116) were more influenced to participate if they could skip uncomfortable questions of parts of the study (PR = 1.34; 95% CI:1.09, 1.65) and if their information would be kept confidential (PR = 1.15; 95% CI:0.99, 1.32) (Table 4).

Table 4

Influencing factors and motivators to research participation and barriers to retention among PWUD:
Gender Differences

Survey Item	PR ^{a,b}	95% CI
<i>Influencing Factors</i>		
What the research study involves (e.g., survey, drug testing for research)	0.98	(0.84, 1.15)
How much time is required	1.02	(0.85, 1.23)
How often they have to come in for visits	0.98	(0.78, 1.22)
How far they have to travel to participate (i.e., nearby vs. out of town)	1.09	(0.90, 1.31)
Privacy of the research office	1.18	(0.70, 2.01)
Why their information is being collected and what it will be used for	1.09	(0.91, 1.31)
Whether their information will be kept confidential	1.15	(0.99, 1.32)
Whether the staff doing the research is friendly and trustworthy	1.03	(0.89, 1.19)
Whether the research institution or university is respected	1.05	(0.81, 1.36)
Whether they can skip questions of parts of the study that make them uncomfortable	1.34*	(1.09, 1.65)
How much money they will receive	1.01	(0.87, 1.18)
How much the project will benefit them overall	1.14	(0.94, 1.38)
Whether their appointment times will interfere with their work schedule	0.84	(0.63, 1.13)
Whether they have childcare so that they can attend their appointments	1.07	(0.83, 1.38)
How their friends, family, or partner feels about them participating	0.79	(0.60, 1.05)
<i>Motivations</i>		
Financial incentive (i.e., money or gift card given for participation)	1.10	(0.99, 1.23)

Survey Item	PR ^{a,b}	95% CI
They believe in the mission of the research and want to contribute	0.99	(0.81, 1.20)
Their friends, family, or partner participates	0.98	(0.82, 1.19)
They want to tell their story	0.96	(0.77, 1.21)
They know someone on the research team and want to help them out	1.57*	(1.09, 2.26)
They want to learn about the topic	0.94	(0.74, 1.20)
They would want to get free testing (for example, rapid tests for HIV & Hepatitis C) if it was offered as part of the study	1.03	(0.87, 1.22)
They would want to be linked with resources and/or follow-up testing if it was offered as part of the study	1.02	(0.86, 1.21)
They would want to try a new treatment if it was offered as part of the study	1.03	(0.87, 1.22)
Their friends, family, or partner pressures them to participate so that they can share the financial incentive	0.84	(0.59, 1.20)
<i>Barriers</i>		
Not being able to get in touch with participants because their contact information changed	1.03	(0.91, 1.16)
Not being able to get in touch with participants because they gave false contact information when they started the study	1.11	(0.90, 1.37)
They may have trouble getting transportation for their appointments	1.12	(0.96, 1.30)
They may have trouble being able to show up at a specific appointment time	1.09	(0.93, 1.28)
They may have trouble getting to their appointment because of their work schedule	1.03	(0.79, 1.33)
They may have trouble finding childcare so that they can go to their appointment	1.26	(0.98, 1.61)
They may have concerns about confidentiality and privacy	1.08	(0.86, 1.37)
They may be afraid that the staff would judge them if they are still using drugs	1.15	(0.88, 1.50)
They may have stopped using drugs and no longer think the study is relevant to them	1.11	(0.86, 1.44)

Survey Item	PR ^{a,b}	95% CI
They are in a drug treatment or recovery facility and are unable to be contacted by research staff	0.98	(0.79, 1.21)
Their friends, family, or partner may want them to stop participating	1.23	(0.85, 1.79)
<i>a. Male is the referent group</i>		
<i>b. The level of response for each survey item was dichotomized into 'selected' or 'not selected' to generate prevalence ratios</i>		
<i>* Significant at $\alpha = 0.05$ level</i>		

Compared to those who selected heroin (n = 90) as their preferred drug of choice, respondents who selected methamphetamine (n = 91) were more influenced by the privacy of the research office (PR = 1.10; 95% CI:0.99, 1.20), knowing why their information is collected and what it will be used for (PR = 1.12; 95% CI:1.00, 1.26), and the confidentiality of their information (PR = 1.07; 95% CI:0.99, 1.16) (Table 5).

Table 5. Influencing factors and motivators to research participation and barriers to retention: Drug of Choice Differences

Survey Item	PR ^{a,b}	95% CI
<i>Influencing Factors</i>		
What the research study involves (e.g., survey, drug testing for research)	0.96	(0.86, 1.06)
How much time is required	0.91	(0.79, 1.03)
How often they have to come in for visits	0.90	(0.78, 1.05)
How far they have to travel to participate (i.e., nearby vs. out of town)	1.01	(0.90, 1.13)
Privacy of the research office	1.10	(0.99, 1.20)
Why their information is being collected and what it will be used for	1.12*	(1.00, 1.26)
Whether their information will be kept confidential	1.07	(0.99, 1.16)
Whether the staff doing the research is friendly and trustworthy ^c	-	-
Whether the research institution or university is respected	1.25*	(1.08, 1.43)
Whether they can skip questions of parts of the study that make them uncomfortable	1.04	(0.91, 1.19)
How much money they will receive	1.01	(0.92, 1.11)
How much the project will benefit them overall	0.93	(0.82, 1.05)
Whether their appointment times will interfere with their work schedule	1.07	(0.88, 1.30)
Whether they have childcare so that they can attend their appointments	1.08	(0.91, 1.28)
How their friends, family, or partner feels about them participating	1.09	(0.90, 1.31)
<i>Motivations</i>		
Financial incentive (i.e., money or gift card given for participation)	0.97	(0.91, 1.04)
They believe in the mission of the research and want to contribute	0.93	(0.82, 1.06)
Their friends, family, or partner participates	0.93	(0.82,

		1.04)
They want to tell their story	1.03	(0.88, 1.20)
They know someone on the research team and want to help them out	1.00	(0.79, 1.28)
They want to learn about the topic	1.05	(0.90, 1.23)
They would want to get free testing (for example, rapid tests for HIV & Hepatitis C) if it was offered as part of the study	1.08	(0.99, 1.18)
They would want to be linked with resources and/or follow-up testing if it was offered as part of the study	1.09	(0.99, 1.21)
They would want to try a new treatment if it was offered as part of the study	1.03	(0.93, 1.13)
Their friends, family, or partner pressures them to participate so that they can share the financial incentive	0.88	(0.69, 1.13)
<i>Barriers</i>		
Not being able to get in touch with participants because their contact information changed	1.00	(0.93, 1.08)
Not being able to get in touch with participants because they gave false contact information when they started the study	0.99	(0.87, 1.14)
They may have trouble getting transportation for their appointments	0.99	(0.89, 1.09)
They may have trouble being able to show up at a specific appointment time	1.05	(0.95, 1.16)
They may have trouble getting to their appointment because of their work schedule	1.04	(0.89, 1.21)
They may have trouble finding childcare so that they can go to their appointment	0.94	(0.79, 1.12)
They may have concerns about confidentiality and privacy	1.09	(0.95, 1.26)
They may be afraid that the staff would judge them if they are still using drugs	1.09	(0.91, 1.31)
They may have stopped using drugs and no longer think the study is relevant to them	1.01	(0.86, 1.19)
They are in a drug treatment or recovery facility and are unable to be contacted by research staff	1.09	(0.96, 1.25)
Their friends, family, or partner may want them to stop participating	0.94	(0.71, 1.24)

a. Heroin as the preferred drug of choice is the referent group

b. The level of response for each survey item was dichotomized into 'selected' or 'not selected' to generate prevalence ratios

c. Cell sizes <10; analysis not performed

** Significant at $\alpha = 0.05$ level*

Patterns of Motivations for Research Participation

Financial compensation was the primary motivator for participation, followed by free diagnostic testing for infectious diseases such as HCV and HIV, linkage to resources, and follow-up testing (Fig. 2). Knowing a person on the research team was the least selected motivator for participation.

Compared to Appalachia respondents, Oregon respondents had a higher prevalence of motivation to enroll in research if they believe in the mission of the research and want to contribute (PR = 1.42; 95% CI:1.18, 1.70) and to tell their story (PR = 1.37; 95% CI:1.11, 1.70). The prevalence of noting feeling pressured to participate by peers to share the financial incentive (PR = 2.18; 95% CI:1.56, 3.03) and knowing someone on the research team and wanting to help them out (PR = 2.12; 95% CI:1.51, 2.99) was over two times greater among Oregon respondents compared to Appalachian respondents (Table 3).

Female participants were nearly twice as likely to report being motivated to participate in a research study if they knew someone on the research team (PR = 1.81; 95% CI:1.09, 2.26), and were marginally more motivated to participate if a financial incentive was offered (PR = 1.10; 95% CI:0.99, 1.23) (Table 4).

Respondents whose preferred drug of choice was methamphetamine had a higher prevalence of being motivated to participate in research if they would receive free diagnostic testing (PR = 1.08; 95% CI:0.99, 1.18) and linkage to resources and follow-up testing as part of the study (PR = 1.09; 95% CI:0.99, 1.21), compared to respondents whose preferred drug of choice was heroin (Table 5).

Patterns of Anticipated Barriers for Retention in Follow-up Research Appointments

Losing contact with participants due to changed contact information had the highest frequency of primary responses among barriers to returning to follow-up research appointments, followed by trouble obtaining transportation and sharing false contact information at their initial appointment (Fig. 3). The barrier with the lowest number of ranked responses among respondents was that they may have stopped using drugs and no longer believe that the study is relevant to them.

Reporting conflicts in returning to follow-up appointments due to work, finding childcare, and transportation were greatest among Oregon participants compared to Appalachian participants (PR = 1.60; 95% CI:1.26, 2.04), (PR = 1.60; 95% CI:1.26, 2.01), and (PR = 1.15; 95% CI:0.99, 1.33), respectively. Oregon participants also had a higher prevalence of reporting privacy and confidentiality concerns (PR = 1.52; 95% CI:1.22, 1.90) and becoming unreachable due to participation in a drug treatment program (PR = 1.33; 95% CI:1.09, 1.63). Barriers that did not differ between Appalachian and Oregon participants included not being able to get in touch with participants because they provided false contact information and they may be afraid that the staff would judge them if they are still using drugs (Table 3).

Female participants were more likely to identify trouble finding transportation (PR = 1.12; 95% CI:0.96, 1.30) and childcare (PR = 1.26; 95% CI:0.98, 1.61) as challenges to returning to follow-up research appointments (Table 4).

Participant-prioritized barriers did not differ by drug of choice (Table 5).

Discussion

We identified several themes of rural PWUD considerations in deciding to participate and remain in research studies. The primary influencing factor and motivator for rural PWUD to participate in research is the amount and presence of financial compensation. Economic and social factors of the risk environment framework are determinants of substance use [47] and promote a disproportionate burden of substance use among people living below the federal poverty threshold [1]. A lack of assistance programs in areas where rural PWUD reside further exacerbate the economic needs of this population [48, 49]. The weight of financial compensation in our findings is consistent with studies of rural Kentucky PWUD populations and others that note receipt of financial compensation as positively associated with research participation and retention [24, 50, 51]. Lower economic status is also associated with poorer study retention; once enrolled in a longitudinal research study, PWUD who live below the federal poverty line are more likely to be lost to follow-up [52].

Financial need is an undercurrent relevant to other highly noted factors. Transportation was a major perceived barrier to retention among all participants irrespective of participant region, gender, or preferred drug use. Our findings align with previous studies that note transportation, or distance, as a primary barrier to retention among rural community members [20]. Western Oregon's remote setting may increase transportation challenges. Oregon participants were more likely to consider the frequency of visits and if their friend, family, or partner participates, which can both influence transportation concerns. Strategies to alleviate transportation challenges might include travel reimbursement, financial incentive amounts that account for transportation cost, or use of mobile or outreach models that bring the research to the participant.

Although financial incentive is the primary motivation for research participation among rural PWUD, our study supports other findings that motivations are multi-dimensional beyond monetary gains such as believing in the mission of the research and seeking linkage to care and other resources [50]. A lack of income paired with scarce medical care in rural locations may also explain the motivations noted by most rural PWUD to participate if linkage with resources and free testing are offered as part of the study. Due to a lack of healthcare assistance programs, rural PWUD may utilize access to the minimal healthcare offered by clinical trials [48].

Privacy, confidentiality, and interaction quality with research staff are crucial influencing factors for PWUD in deciding to participate in research, likely due to stigma and the legal, employment, and interpersonal relationship consequences of substance use. Oregon respondents were more likely to be motivated to participate in research if they knew someone on the research staff. This finding may be

related to the design of Oregon's concurrent study (i.e., the Oregon HIV/HCV and Opioid Prevention and Engagement, or OR-HOPE) which employs peer recovery support specialists as study staff members. While we found that most factors among rural PWUD did not differ between males and females, aligning with the findings of an analysis of 24 NIDA CTN trials [53], we found a notable difference in the importance of privacy between genders. Females reported an increased likelihood of indicating if their information would be kept confidential and whether they can skip questions that make them uncomfortable as important for participation. Female PWUD participants might be more concerned with privacy due to concerns of losing custody of their children if their drug use became publicly known [48] or due to anticipated distress around certain topics related to past trauma. Studies that recruit primarily rural, female PWUD populations should highlight the ability to skip questions and confidentiality protections when obtaining informed consent, and in surveys, questionnaires, and other data collection items to encourage participation.

Changing of participants' contact information was a primary perceived barrier to returning to follow-up appointments, and did not differ between participant region, gender, or preferred drug use. Our findings align with previous studies that note successfully contacting participants as a barrier to retention among rural community members and PWUD [54]. Obtaining information from participants about contact information of others (family, friends, etc.) who know how to reach them in case they cannot be contacted may improve retention [20]. The challenge of losing contact with participants may be alleviated by providing phone cards or other forms of contact reimbursement.

Participants who reported methamphetamine as their drug of choice to get high, as compared to those who selected heroin, had a higher prevalence of considering factors central to privacy and confidentiality. While not all of these factors met the threshold for statistical significance, the positive measure of association speaks to a theme of distrust and privacy concerns present among those who prefer methamphetamine use. These findings align with a community-based study in Vancouver, Canada, that found those who use methamphetamine reported greater suspiciousness and paranoia compared to those who use opioids [28]. Methamphetamine-associated paranoia may magnify the general distrust of healthcare systems where PWUD frequently experience stigma [55, 56] and may exacerbate skepticism about the transparency of research which is already elevated among rural residents [57]. Research enrolling people who use methamphetamines in rural communities should tailor recruitment and retention strategies to emphasize confidentiality and privacy.

Our findings should be interpreted in light of several potential limitations. First, though our sample was drawn from U.S. rural communities in three states, findings may not be generalizable to rural communities outside of Appalachia and southwestern Oregon and may not be representative of all PWUD in the study communities due to our use of convenience sampling for data collection. Second, the numerous response options provide crucial descriptive information on improving clinical trial recruitment and retention in rural areas but are likely correlated. Future work with large population-based samples will be needed for testing multiple hypotheses of multilevel factors. Still, our study found differences in factors for participation and retention between geographic locations and types of preferred drug use. The

cross-sectional design of our study is a limitation in regard to capturing the challenges of enrollment and retention over time. We recommend that future longitudinal clinical research studies explore enrolled participants' influencing factors and motivations for participation. Study staff should collect data on the reasons rural PWUD participants miss follow-up appointments among participants who are not lost to follow-up. Finally, participants were recruited in locations where epidemiological studies had already been recruiting rural PWUD; nearly two-thirds of participants (64% overall, ranging from 42% in Ohio to 75% in Kentucky) reported previously participating in a research study. Therefore, our results may not adequately capture the perspectives of rural PWUD less familiar with or interested in research, which may differ. However, because our participants are more familiar with research, the reported factors may have been less hypothetical than with research naïve or adverse PWUD.

Conclusions

Our findings contribute to the CTN's focus on reaching underserved populations, such as rural PWUD, by identifying services such as testing, linkage to care, transportation, and factors such as privacy of clinic location and confidentiality of participant information that may enhance research participation and retention among this population. Research staff can address barriers to returning to follow-up appointments for rural PWUD by providing financial compensation, collecting detailed contact information from participants, and providing resources for transportation or by bringing the research to the participants through mobile or street outreach. Future longitudinal clinical research can leverage prominent influencing factors, motivations, and barriers to enhance participation and retention among rural PWUD.

Abbreviations

PWUD: People Who Use Drugs

Declarations

Ethics Approval and Consent to Participate

The Ohio State University Institutional Review Board, University of Kentucky Institutional Review Board, and Oregon Health and Science University Institutional Review Board reviewed and approved the study protocol before research activities were initiated. All participants provided informed consent prior to enrollment.

Consent for Publication

Not applicable.

Availability of Data and Materials

The data that support the findings of this study are not openly available due to the sensitive nature of the data and are available from the corresponding author upon reasonable request.

Competing Interests

The authors declare that they have no competing interests.

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Author's Contributions

All authors listed (ATH, AMY, MRE, SB, RLA, MB, ENW, PTK, KEL) have made a substantial, direct, and intellectual contribution to the work, and approved it for publication.

Additional Files

The authors stratified the graphs in Figures 1-3 by site and included them in 'Additional File 1' as a supplementary resource for readers.

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Figures

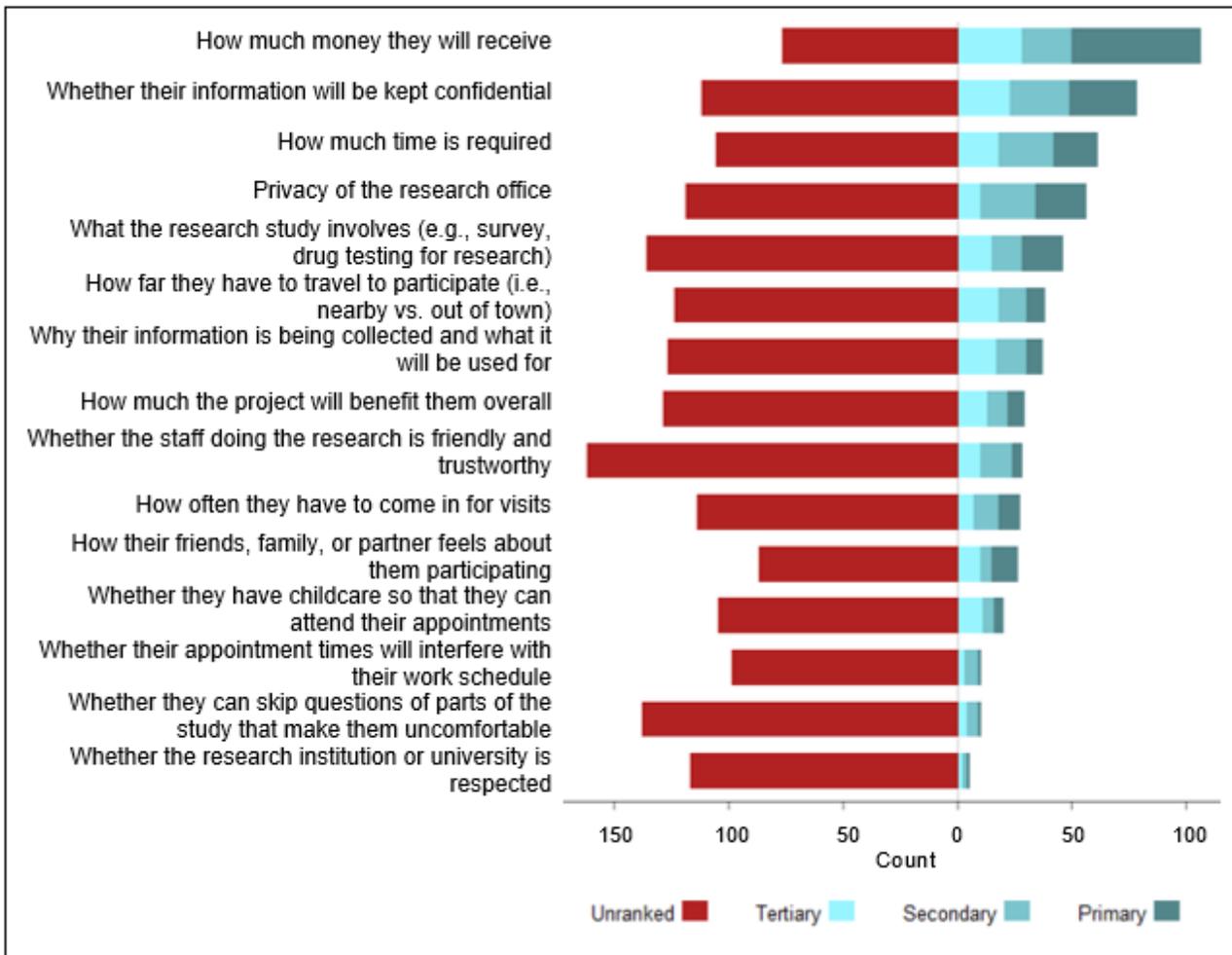


Figure 1

Ranked influencing factors for participating in research among PWUD in rural communities, April 2019- July 2019

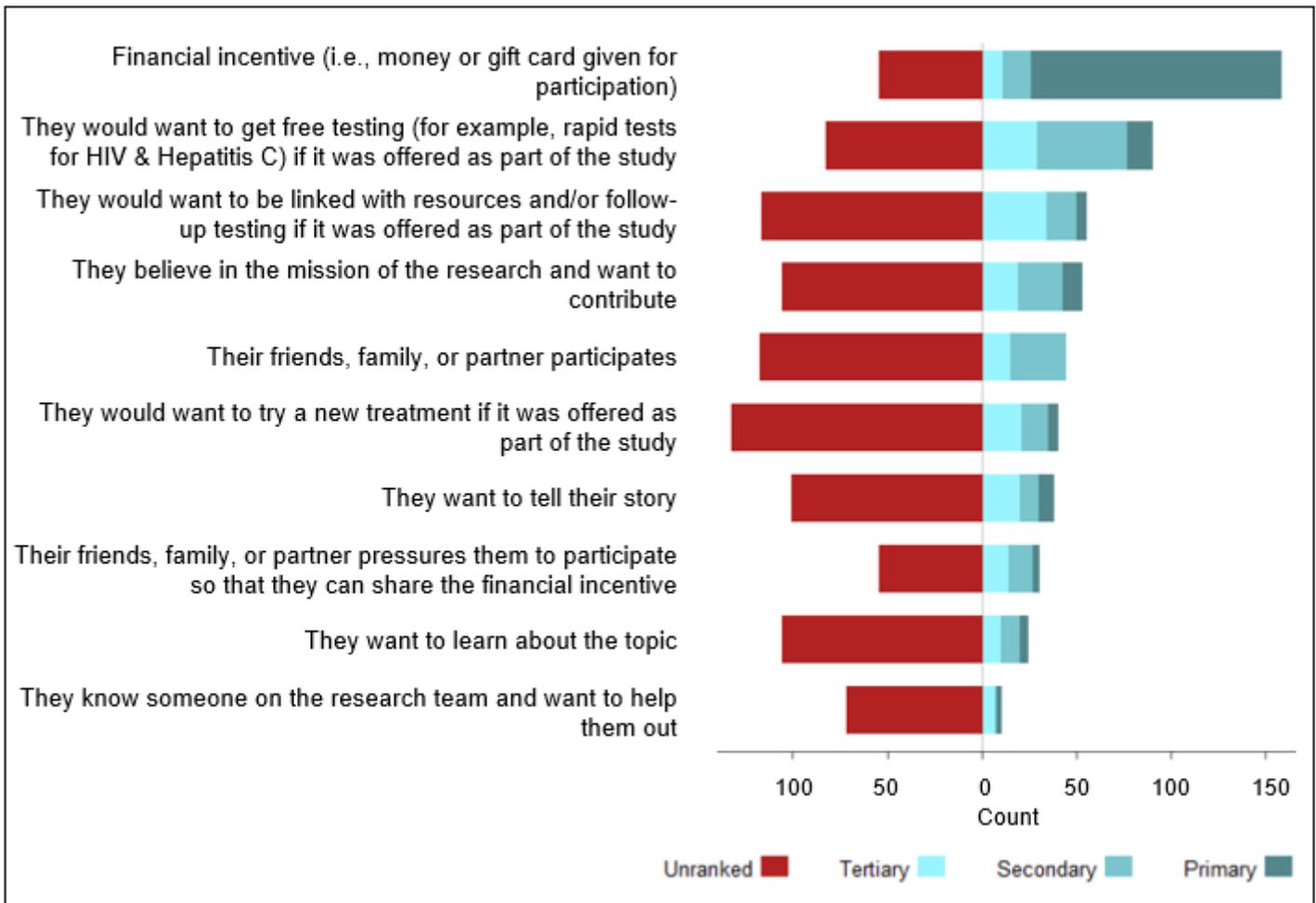


Figure 2

Ranked motivators for joining a research study among PWUD in rural communities, April 2019-July 2019

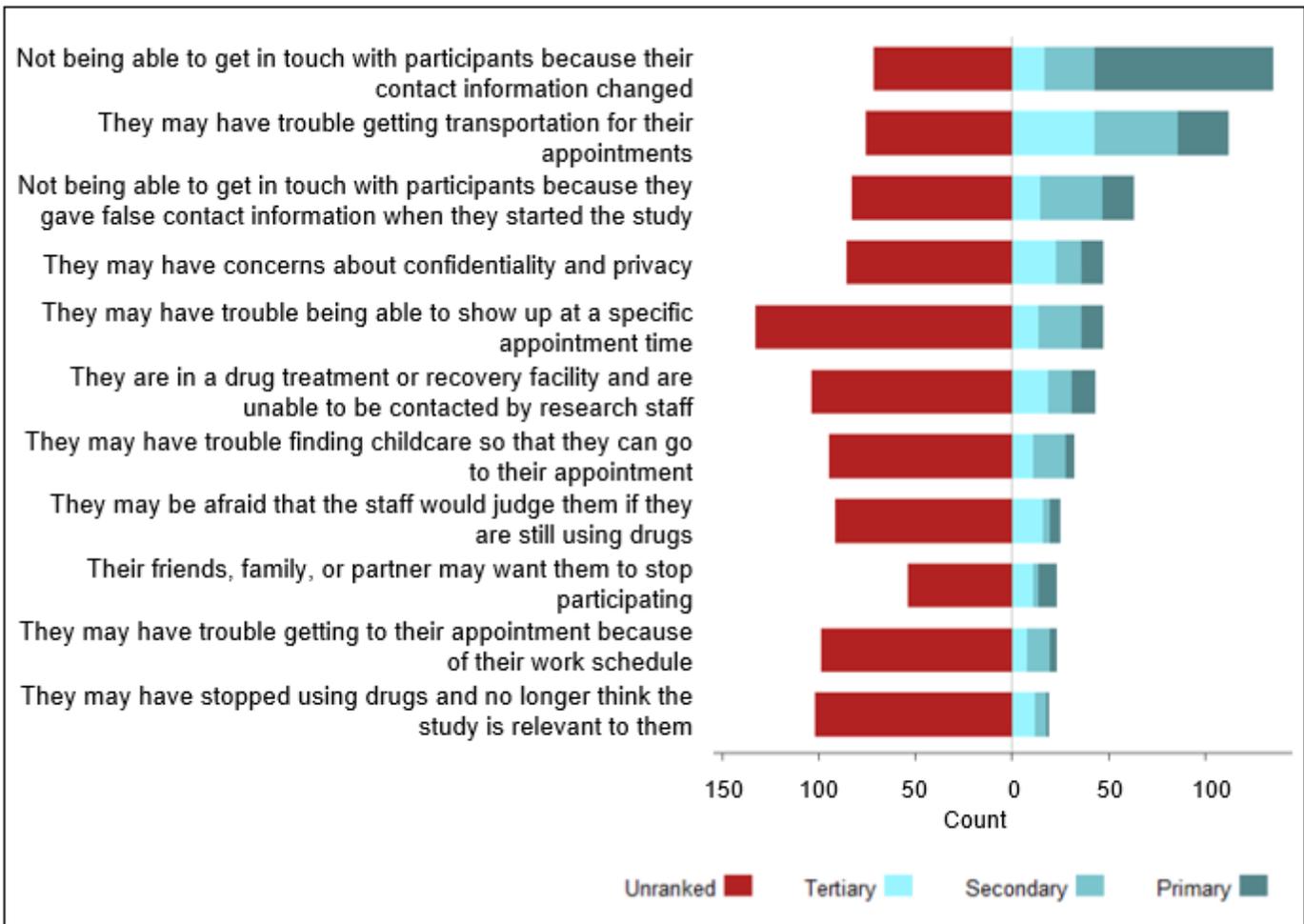


Figure 3

Ranked barriers to returning to follow-up appointments among PWUD in rural communities, April 2019-July 2019

Supplementary Files

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