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Benefits Related to Participating in an International HIV Prevention Trial (HPTN 074) Involving People Who Inject Drugs

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Abstract

Background: Given ethical concerns about research involving people who inject drugs (PWID) and those affected by HIV, identifying potential participation benefits is important. We evaluated participant reported benefits in a trial assessing an intervention combining psychosocial counseling and referral for antiretroviral therapy and substance use treatment for HIV-infected PWID in Vietnam, Ukraine and Indonesia.

Methods: Benefits were assessed at each study visit. Reported benefits were aggregated into 3 groups: clinical (ART, cravings, drug use, lab testing, medical referral, mental health, physical health); social (employment, financial, relationships, stigma); and general (gained knowledge, life-improvement).

Results: Overall, 438 (90.5%) index participants and 642 (83.1%) partners reported at least one benefit. Significantly more intervention index participants reported at least one benefit versus standard of care participants.

Conclusions: Most participants reported benefits of participation. Clinical trial participation can provide broad direct and indirect benefits for stigmatized populations, which has implications for assessing its ethical appropriateness.

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Keywords

People who inject drugs; HIV prevention; clinical trials

INTRODUCTION

Given concerns about the social risks and ethics of conducting research with people who inject drugs (PWID) who may be affected by HIV it is important to identify not only research-related risks, but also the benefits that may be realized by research participation. These can include direct benefits due to the study intervention and indirect benefits related to participation.

In a previous Phase III randomized controlled prevention trial in China and Thailand, 77% of PWID who were enrolled and received long-term versus short-term medication assisted treatment and counseling reported positive social impacts related to trial participation.[1] This stood in stark contrast to scant reports of negative social impacts (n=4). All of these negative social impacts were considered minor; three related to problems with friends or family and one to troubles with schedule conflicts.[2] Capturing these data helped to elucidate participants' experiences in the trial, suggesting that research participation may provide tangible benefits where drug use and HIV are stigmatized. In addition, the possibility of these benefits should arguably be considered in evaluating the ethical acceptability of research in such settings. However, it is unclear whether such benefits are realized in the context of related research in different settings and with different interventions.

HPTN 074, "Integrated Treatment and Prevention for People Who Inject Drugs: A Vanguard Study for a Network-based Randomized HIV Prevention Trial Comparing an Integrated Intervention Including Supported Antiretroviral Therapy to the Standard of Care" [NCT02935296], is a trial that assessed the feasibility of an integrated intervention combining psychosocial counseling and supported referral for antiretroviral therapy (ART) and substance use treatment for HIV-infected PWID in Vietnam, Ukraine and Indonesia in preventing transmission of HIV to their identified injection partners. One to five HIV-negative injecting partners could be enrolled for each index participant. Index participants were randomly assigned in a 3:1 ratio to the standard of care (SOC) or the intervention (INT). Details about HPTN 074 and initial results are reported elsewhere.[3] However, very briefly, SOC consisted of referrals to HIV and medication assisted drug treatment clinics as well as a country-specific harm reduction package that included counseling and referrals related to HIV, sexually transmitted infections, drug use, risk reduction counseling and provision of condoms. INT included SOC plus system navigation designed to enhance use of these services, psychosocial counseling, and immediate initiation of antiretroviral therapy for HIV. Injection partners in both arms received a country-specific standard harm reduction package. Small financial incentives were given to index participants upon enrollment of injection partners and all participants at each study visit*.The amounts varied based on site

*The local rates for each country are specified in local currency along with a conversion to United States Dollars (USD) as of 16 February 2019. Indonesia: 50,000 IDR (3.54 USD) for partner recruitment; 100,000 IDR (7.07 USD) for each visit. Vietnam: 20, 000 VND (0.86 USD) for partner recruitment; 100, 000 (4.30 USD) for each visit. Ukraine: 100 UAH (3.64 USD) for partner recruitment;

custom and practice and were approved by local Institutional Review Boards. Given the vulnerable nature of the study population, multiple steps to minimize potential social harms were implemented, which proved to be effective.[4] In this paper, we evaluate participant reported benefits related to trial participation.

METHODS

Based on the benefits reported in a prior international collaborative HIV prevention trial involving PWID,[5] benefits related to trial participation were assessed at each of seven to eleven study visits, depending upon when participants enrolled in the study (those who enrolled earlier had a longer follow-up period). Specifically, the scheduled visits were for screening, enrollment, four weeks following enrollment and then every subsequent three months. At each visit following screening participants were asked: “Because of your participation in this study, have you experienced: Employment improvement? Financial improvement? Reductions in drug use? Reductions in cravings/withdrawal? Gained knowledge? Life improvement? Physical health improvement? Improved relationships? Reduced stigma? Improved mental health? Other, specify?”. None of these terms were defined explicitly for participants. Due to the high frequency of particular themes inductively observed among responses to the “Other” query, post-hoc codes were applied to responses consistent with these themes: related to initiation of ART; referral for lab testing; other medical referral; and other. To do so, reports of “Other” benefits were reviewed and coded with consensus among two authors (JS, IMT).

Reported benefits were aggregated for analysis into three groups: clinical (initiation of ART, cravings/withdrawal, drug use, lab testing, medical referral, mental health, physical health); social (employment, financial, relationships, stigma); and general (gained knowledge, life-improvement). The binary outcome of whether participants reported experiencing a benefit at least once after the baseline visit was investigated. Data were analyzed using standard descriptive statistics. Bivariate differences between study arms were assessed using Chi-square tests. Poisson regression modeling with robust error variances was employed to assess associations between covariates of interest (demographic characteristics, study arm, site, drug use intensity, and prior incarcerations) and reports of benefits.

Ethics approval was obtained at all research sites and at the University of North Carolina, Chapel Hill.

RESULTS

The study enrolled 502 index participants with reported benefit data available for 484 participants; of these, 122 were assigned to INT and 362 to SOC. The study also enrolled 806 injection partners with reported benefit data available for 774 of them; of these, 177 were assigned to the INT and 597 to SOC. Table 1 includes demographic characteristics of all participants for whom benefit data are available. While reported benefit data are missing for only a small proportion of study participants (3.6% indexes, 4.0% partners), those who

200 UAH (7.28 USD) for enrollment and screening visits with 20 UAH (0.73 USD) added for every visit for a maximum of 400 UAH (14.56 USD).

did not provide these data were more likely to be men, less educated, single, and have a history of unemployment, as compared to the overall study population (data not shown).

A substantial majority of trial participants reported at least one benefit from study participation. This included 438 (90.5%) index participants and 642 (83.1%) partner participants. Figure 1 depicts the types of benefits and proportions of participants that experienced those benefits at any time following baseline assessments in the trial. Particularly, social benefits included improvement in: employment (13.6% of indexes, 14.2% of partners); financial (33.7% of indexes, 26.9% of partners); relationships (57.6% of indexes, 48.2% or partners); and reduced stigma (50.6% of indexes, 35.1% of partners).

Overall, significantly more INT index participants reported benefits than SOC index participants (97.5% versus 88.1%, p=0.002 respectively). Specifically, INT and SOC index participants respectively reported: 93.4% vs 78.2% clinical benefits (p <0.001); 83.6% vs 68.2% social benefits (p=0.001); and 97.5% vs 87.6% general benefits (p=0.001). In contrast, reported benefits among partner participants did not differ substantially by study arm (81.4% INT partners and 83.4% SOC partners, p=0.522).

Finally, multivariate Poisson regression modeling (age in 10 year increments, study arm, education, employment status, homelessness, injection frequency, prior incarceration, relationship status and site) with robust error variances was used to estimate the association between socio-demographic factors and self-reported benefits. Complete results are included in the Appendix. However, drug-use intensity was found to be related to benefit reporting in index participants (for the lowest vs. highest injection frequency groups: clinical RR 1.11, p=0.015; social RR 0.97; p=0.693; and general RR 1.06, p=0.035). Figure 2 shows the percentage of index participants reporting any benefit by prior injection frequency, with those who engage in the least intensive drug use reporting more benefits (Chi-Square test p-value=0.012) than those who engage more frequently. Among partners, older participants were significantly more likely to report all types of benefits (clinical RR 1.10, p<0.001; social RR 1.16, p<0.001; and general RR 1.07, p=0.001). Further, there is variability among sites in the types of benefits reported (Chi-Square test clinical p-value < 0.0001; social p-value = 0.013; and general p-value<0.001). Of note, participants in Vietnam reported the most clinical and social benefits, and those in Indonesia reported the most general benefits (See Figure 3).

DISCUSSION

In this trial, most participants in both study arms reported benefits, likely reflecting direct and indirect benefits of participation. Given that the trial involved an intervention to enhance linkage to care, including treatment of HIV infection, medication assisted treatment of drug use and harm reduction services, the high proportion of clinical benefits is not surprising. This finding is consistent with the primary study outcomes as well as how potential benefits were communicated to participants at enrollment. For example, the benefit section of the informed consent form used at enrollment for index participants indicated: “There may be no direct benefit to you from this study.” However, the consent forms for both index participants and injection partners did describe indirect or collateral benefits such as clinic

referrals, notification about test results, the ability to talk with counselors and the provision of condoms. These documents also included aspirational benefits related to the knowledge that will be gained in the study. Nonetheless, consonant with widespread efforts in clinical trials and clinical practice to assess patient reported outcomes,[6] these findings suggest that the clinical outcome measures of the primary study (e.g., use of ART, decreased drug use) were also of relevance to study participants.

Participants in both study arms also realized substantial social and general benefits related to trial participation. The large proportion of social benefits included improvements related to employment, finances, relationships, and stigma. This is remarkable given that other than providing knowledge-based interventions about care and prevention options, no study interventions were designed specifically to promote such salutary social effects that are especially complex given the research context. While the relationship to study participation and these reported benefits is unclear, a variety of factors may have played a role. These include social benefits that may result from linkage to care for HIV infection and drug use as well as being part a trial in which participants are treated with respect while engaged in an endeavor that is of important scientific and social value.

In the trial, ART uptake was highest in Vietnam so it's not surprising that the reported clinical benefits were highest there compared to other sites as well. However, it is unclear why the proportion of particular benefits differ somewhat by site. While these are likely due to local context (for instance the Vietnam site was rural while the Indonesian and Ukraine sites were not), further qualitative work is needed to assess these findings.

Although our findings are largely consistent with our earlier work in another study involving PWID in China and Thailand mentioned earlier[1] they should be interpreted with some limitations in mind. It is conceivable that the high proportion of reporting of benefits could be due at least in part to a social response bias when being asked questions about benefits by study staff. To assess this possibility, future studies could inquire about benefits with computer assisted technologies. Further, since benefit information in this study was obtained by endorsement of particular categories of benefits, it is not possible to comprehensively understand the nature of these benefits. For example, indicating financial improvement could have been due to a more stable economic situation, the incentives provided during the study and/or something else. Accordingly, future work could be directed at exploring reported benefits more thoroughly using qualitative research methods. Alternatively, additional quantitative items seeking more granular information could be developed to use in such studies in the future. Finally, while the findings here represent the experiences of a large number of participants in three countries, they were all enrolled in a single trial. Accordingly, it is unclear whether the results here are generalizable to other trials, other countries and different populations. Therefore, additional systematic collection of benefits related to research participation should be done in other clinical trials.

Regardless of these limitations, our findings are useful in informing debates about the ethical appropriateness of research involving PWID who are affected by HIV in particular and other research that involves key research populations who may be considered vulnerable due to social circumstances and behaviors that may be stigmatized. While a critical

consideration in determining the ethical appropriateness of research involves close attention to identifying and minimizing risks, various types of benefits also must be considered. These include direct benefits that arise from the study intervention, indirect or collateral benefits due to enrollment in research, and aspirational benefits related to helping answer an important scientific or clinical question[7]. However, with few exceptions,[8] the standard approach to weighing risks and benefits in research privileges clinical risks and benefits.[9] Nonetheless, while incommensurable with clinical benefits, the potentially profound social benefits reported here may for some participants have enormous value. Accordingly, future conceptual work should be directed at determining if and when such benefits should rightly be considered in determining the ethical appropriateness of particular proposed research trials.

In conclusion, clinical trial participation can provide broad benefits to stigmatized populations such as PWID who may be affected by HIV, well beyond specific intervention targets. Going forward, such benefits should be measured systematically as efforts are also taken to minimize risks related to participation.

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APPENDIX

Appendix Tables A1–A6: Estimated Relative Risks and P-values for Predictors of Benefits from Poisson regression models with robust error variances. The binary outcome of a beneficial impact occurring at any time post-baseline was modeled.

Table A1:

Clinical Benefits – Indexes

Predictor	Relative Risk (95% CI)	P-value
Age (10 year increments)	1.03 (0.95, 1.10)	0.505
Arm (Intervention vs. SOC)	1.21 (1.12, 1.29)	<0.001
Education (Completed Secondary School or Beyond vs. Did Not Complete Secondary School)	0.91 (0.83, 0.99)	0.024
Employment Status (Employed full or part time vs. Other)	1.00 (0.92, 1.09)	0.952
Homelessness (Yes vs. No)	1.03 (0.88, 1.21)	0.724
Injection Frequency (0–10 vs 11–21)[1]	1.00 (0.90, 1.12)	0.972

Predictor	Relative Risk (95% CI)	P-value
Injection Frequency (0–10 vs. 22 or more)[1]	1.11 (1.02, 1.22)	0.015
Injection Frequency (11–21 vs. 22 or more)[1]	1.11 (1.01, 1.23)	0.038
Prior Incarcerations (Yes vs. No)[2]	1.00 (0.83, 1.22)	0.979
Relationship Status (Married or Living with Sexual Partner vs. Other)	1.00 (0.92, 1.08)	0.942
Site (Indonesia vs. Ukraine)	1.16 (1.02, 1.33)	0.027
Site (Indonesia vs. Vietnam)	0.91 (0.82, 1.01)	0.066
Site (Ukraine vs. Vietnam)	0.78 (0.70, 0.88)	<0.001

Table A2:

Clinical Benefits – Partners

Predictor	Relative Risk (95% CI)	P-value
Age (10 year increments)	1.10 (1.04, 1.17)	<0.001
Arm (Intervention vs. SOC)	0.97 (0.88, 1.07)	0.558
Education (Completed Secondary School or Beyond vs. Did Not Complete Secondary School)	0.97 (0.88, 1.06)	0.472
Employment Status (Employed full or part time vs. Other)	1.05 (0.95, 1.16)	0.335
Homelessness (Yes vs. No)	1.13 (0.94, 1.36)	0.205
Injection Frequency (0–10 vs 11–21)[1]	1.06 (0.94, 1.19)	0.381
Injection Frequency (0–10 vs. 22 or more)[1]	1.14 (1.03, 1.27)	0.014
Injection Frequency (11–21 vs. 22 or more)[1]	1.08 (0.98, 1.20)	0.105
Prior Incarcerations (Yes vs. No)[2]	0.98 (0.79, 1.21)	0.817
Relationship Status (Married or Living with Sexual Partner vs. Other)	0.90 (0.82, 0.98)	0.013
Site (Indonesia vs. Ukraine)	1.13 (0.97, 1.32)	0.121
Site (Indonesia vs. Vietnam)	0.70 (0.62, 0.80)	<0.001
Site (Ukraine vs. Vietnam)	0.62 (0.54, 0.71)	<0.001

Table A3:

Social Benefits – Indexes

Predictor	Relative Risk (95% CI)	P-value
Age (10 year increments)	1.05 (0.95, 1.17)	0.304
Arm (Intervention vs. SOC)	1.24 (1.12, 1.38)	<0.001
Education (Completed Secondary School or Beyond vs. Did Not Complete Secondary School)	1.03 (0.90, 1.19)	0.629
Employment Status (Employed full or part time vs. Other)	1.05 (0.93, 1.19)	0.436
Homelessness (Yes vs. No)	0.81 (0.62, 1.07)	0.136
Injection Frequency (0–10 vs 11–21)[1]	0.85 (0.72, 1.02)	0.079
Injection Frequency (0–10 vs. 22 or more)[1]	0.97 (0.83, 1.14)	0.693
Injection Frequency (11–21 vs. 22 or more)[1]	1.13 (1.00, 1.29)	0.058

Predictor	Relative Risk (95% CI)	P-value
Prior Incarcerations (Yes vs. No)[2]	1.10 (0.89, 1.36)	0.382
Relationship Status (Married or Living with Sexual Partner vs. Other)	0.99 (0.88, 1.11)	0.841
Site (Indonesia vs. Ukraine)	0.91 (0.77, 1.08)	0.291
Site (Indonesia vs. Vietnam)	0.87 (0.74, 1.04)	0.121
Site (Ukraine vs. Vietnam)	0.96 (0.82, 1.12)	0.567

Table A4:

Social Benefits – Partners

Predictor	Relative Risk (95% CI)	P-value
Age (10 year increments)	1.16 (1.06, 1.27)	<0.001
Arm (Intervention vs. SOC)	0.83 (0.71, 0.98)	0.024
Education (Completed Secondary School or Beyond vs. Did Not Complete Secondary School)	1.14 (0.97, 1.34)	0.110
Employment Status (Employed full or part time vs. Other)	1.04 (0.91, 1.20)	0.538
Homelessness (Yes vs. No)	1.26 (1.03, 1.55)	0.026
Injection Frequency (0–10 vs 11–21)[1]	1.04 (0.87, 1.25)	0.659
Injection Frequency (0–10 vs. 22 or more)[1]	1.06 (0.89, 1.25)	0.524
Injection Frequency (11–21 vs. 22 or more)[1]	1.01 (0.88, 1.17)	0.860
Prior Incarcerations (Yes vs. No)[2]	0.92 (0.71, 1.19)	0.536
Relationship Status (Married or Living with Sexual Partner vs. Other)	0.94 (0.83, 1.07)	0.350
Site (Indonesia vs. Ukraine)	0.87 (0.72, 1.05)	0.142
Site (Indonesia vs. Vietnam)	0.80 (0.66, 0.97)	0.021
Site (Ukraine vs. Vietnam)	0.92 (0.77, 1.10)	0.351

Table A5:

General Benefits – Indexes

Predictor	Relative Risk (95% CI)	P-value
Age (10 year increments)	1.01 (0.97, 1.06)	0.568
Arm (Intervention vs. SOC)	1.12 (1.07, 1.18)	<0.001
Education (Completed Secondary School or Beyond vs. Did Not Complete Secondary School)	0.95 (0.91, 0.99)	0.029
Employment Status (Employed full or part time vs. Other)	1.01 (0.95, 1.07)	0.735
Homelessness (Yes vs. No)	1.00 (0.88, 1.14)	0.973
Injection Frequency (0–10 vs 11–21)[1]	0.97 (0.90, 1.03)	0.327
Injection Frequency (0–10 vs. 22 or more)[1]	1.06 (1.00, 1.11)	0.035
Injection Frequency (11–21 vs. 22 or more)[1]	1.09 (1.02, 1.17)	0.015
Prior Incarcerations (Yes vs. No)[2]	0.96 (0.82, 1.13)	0.637
Relationship Status (Married or Living with Sexual Partner vs. Other)	0.99 (0.94, 1.05)	0.783

Predictor	Relative Risk (95% CI)	P-value
Site (Indonesia vs. Ukraine)	1.33 (1.22, 1.45)	<0.001
Site (Indonesia vs. Vietnam)	1.05 (1.01, 1.09)	0.027
Site (Ukraine vs. Vietnam)	0.79 (0.72, 0.86)	<0.001

Table A6:

General Benefits – Partners

Predictor	Relative Risk (95% CI)	P-value
Age (10 year increments)	1.07 (1.03, 1.11)	0.001
Arm (Intervention vs. SOC)	0.97 (0.90, 1.04)	0.329
Education (Completed Secondary School or Beyond vs. Did Not Complete Secondary School)	0.99 (0.93, 1.06)	0.792
Employment Status (Employed full or part time vs. Other)	1.00 (0.93, 1.07)	0.984
Homelessness (Yes vs. No)	1.05 (0.89, 1.24)	0.545
Injection Frequency (0–10 vs 11–21)[1]	1.06 (0.98, 1.16)	0.152
Injection Frequency (0–10 vs. 22 or more)[1]	1.07 (1.00, 1.15)	0.049
Injection Frequency (11–21 vs. 22 or more)[1]	1.01 (0.93, 1.09)	0.850
Prior Incarcerations (Yes vs. No)[2]	1.07 (0.92, 1.24)	0.375
Relationship Status (Married or Living with Sexual Partner vs. Other)	1.02 (0.96, 1.09)	0.518
Site (Indonesia vs. Ukraine)	1.69 (1.53, 1.88)	<0.001
Site (Indonesia vs. Vietnam)	1.06 (1.01, 1.12)	0.027
Site (Ukraine vs. Vietnam)	0.63 (0.56, 0.70)	<0.001

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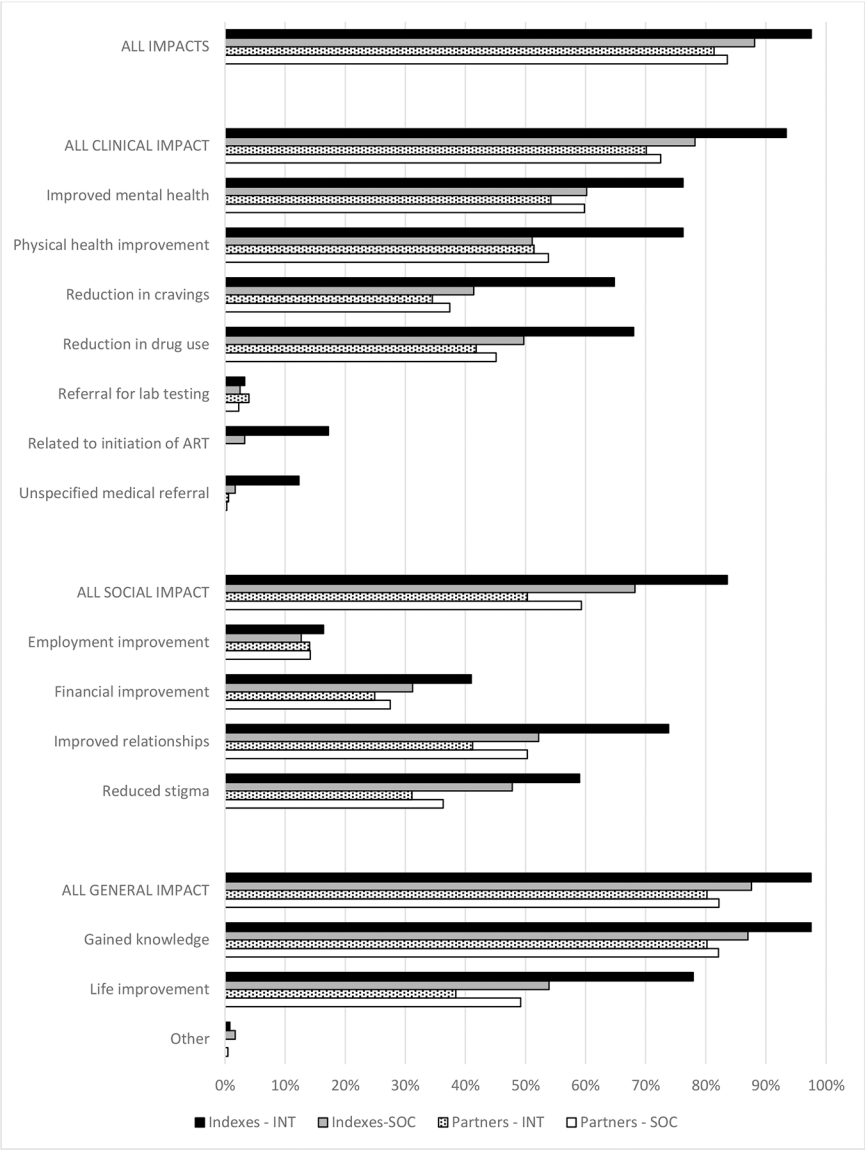

Figure 1:
Percentage of Participants Reporting Benefits by Study Cohort and Arm

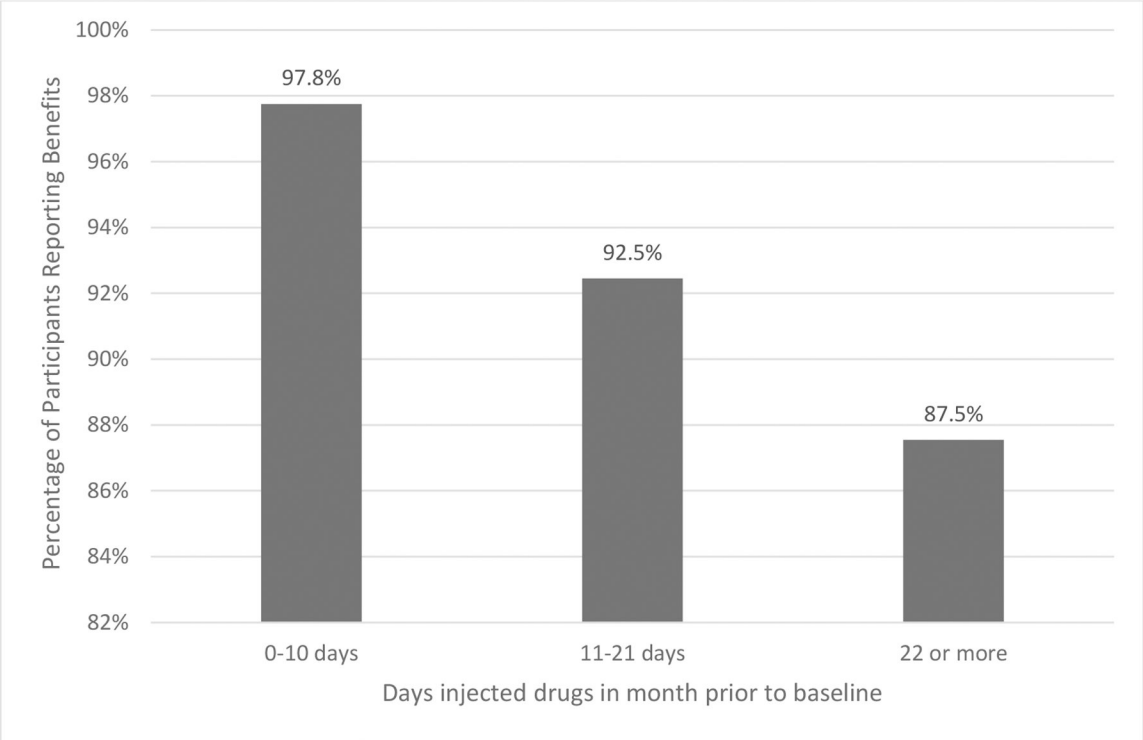

Figure 2:
Percentage of Index Participants Reporting Any Benefit by Prior Injection Frequency

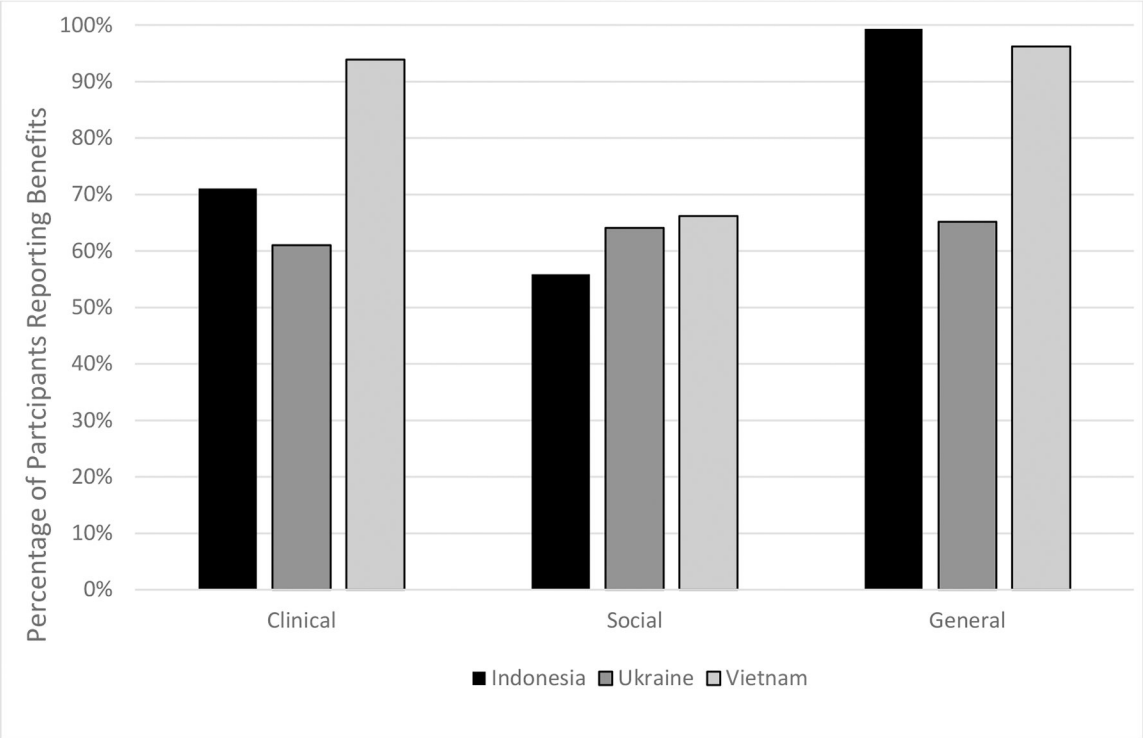

Figure 3:
Participants Reporting Aggregated Benefits by Site

Table 1:

Baseline Characteristics of Participants

	Indexes N (%)	Partners N (%)
Enrolled	484	774
Self-identified gender		
Female	75 (15.5%)	89 (11.5%)
Male	409 (84.5%)	685 (88.5%)
Age (years)		
18–19	1 (0.2%)	5 (0.6%)
20–29	80 (16.5%)	215 (27.8%)
30–39	317 (65.5%)	391 (50.5%)
40+	86 (17.8%)	163 (21.1%)
Highest education level		
Did Not Complete Secondary School	182 (37.6%)	247 (31.9%)
Completed Secondary School or Beyond	302 (62.4%)	527 (68.1%)
Relationship status		
Married or Living with Sexual Partner	238 (49.2%)	387 (50.0%)
Other	246 (50.8%)	387 (50.0%)
Unemployed in last 3 months		
Yes	291 (60.1%)	431 (55.7%)
No	193 (39.9%)	343 (44.3%)
Employment status		
Employed full or part time	273 (56.4%)	479 (61.9%)
Other	211 (43.6%)	295 (38.1%)
Homeless in last 6 months		
Yes	35 (7.2%)	59 (7.6%)
No	449 (92.8%)	715 (92.4%)