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Nomor : 1039A-c / D.5 / FP / I / 2019

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Tugas	:	Menulis Artikel Jurnal Internasional Bereputasi "Reported Participation Benefits in International HIV Prevention Research with People Who Inject Drugs"
Waktu	:	Tahun 2019
Tempat	:	Journal Ethics & Human Research. Penerbit : Wiley, 2019. Edisi 41(5). ISSN : 10.1002/eahr.500030
Lain – lain	:	Harap melaksanakan tugas dengan sebaik – baiknya dan penuh rasa tanggung jawab

Demikian surat tugas ini dibuat untuk diketahui dan dipergunakan sebagaimana mestinya.

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Dekan,

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E&HR

Reported Participation Benefits in International HIV Prevention Research with People Who Inject Drugs

Jeremy Sugarman, Ilana Trumble, Erica Hamilton, Riza Sarasvita, Kostyantyn Dumchev, Ha Viet, Irving Hoffman, William Miller, and Brett Hanscom

ABSTRACT Given ethical concerns about research involving people who inject drugs and those affected by HIV, identifying potential participation benefits is important. We evaluated participant-reported benefits in a trial conducted in Indonesia, Ukraine, and Vietnam that assessed an intervention combining psychosocial counseling and referral for antiretroviral therapy and substance use treatment for HIV-infected people who use drugs. Reported benefits were aggregated into three groups: clinical (antiretroviral therapy, reduced cravings, reduced drug use, lab testing, medical referral, mental health, physical health), social (employment, financial, relationships, reduced stigma), and general (gained knowledge, life improvement). Overall, 438 index participants (90.5%) and 642 injection partners (83.1%) reported at least one benefit. Significantly more index participants who received the study intervention reported at least one benefit versus those who received the standard of care. Clinical trial participation can provide broad direct and indirect benefits for stigmatized populations, which has implications for assessing the ethical appropriateness of studies with such populations.

KEYWORDS Human subjects research, HIV clinical trials, research risks, research benefits, people who inject drugs

Sugarman, J., et al., "Reported Participation Benefits in International HIV Prevention Research with People Who Inject Drugs," *Ethics & Human Research* 41, no. 5 (2019): 28-34. DOI: 10.1002/eahr.500030

Given concerns about the social risks and ethics of conducting research with people who inject drugs and 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 interventions and indirect benefits related to participation. In a previous phase III randomized controlled HIV prevention trial in China and Thailand that enrolled people who injected drugs in order to compare long-term and short-term medication-assisted treatment and counseling, 77% of those enrolled reported positive social impacts related to trial participation.[1] This stood in stark contrast to scant reports of negative social impacts (n = 4). All 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 about social impacts 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 contexts. However, whether such benefits are realized in related research in different settings and with different interventions is unclear.

In this article, we evaluate reported participation benefits in a clinical trial conducted in Indonesia, Ukraine, and Vietnam that included HIV-infected

people who were injecting drugs. 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,[3] assessed the feasibility of an intervention combining psychosocial counseling and supported referral for antiretroviral therapy (ART) and substance use treatment in preventing the transmission of HIV by people who inject drugs to their identified injection partners (that is, people with whom they share needles). 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 or the study intervention. Details about HPTN 074 and initial results of the trial are reported elsewhere.[4] However, very briefly, the standard of care consisted of referrals to HIV and medication-assisted drug-use 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, and provision of condoms. The study intervention included the standard of care plus system navigation designed to enhance use of these services, psychosocial counseling, and immediate initiation of ART for HIV. Injection partners in both study 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.[5] The amounts varied based on site 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.[6]

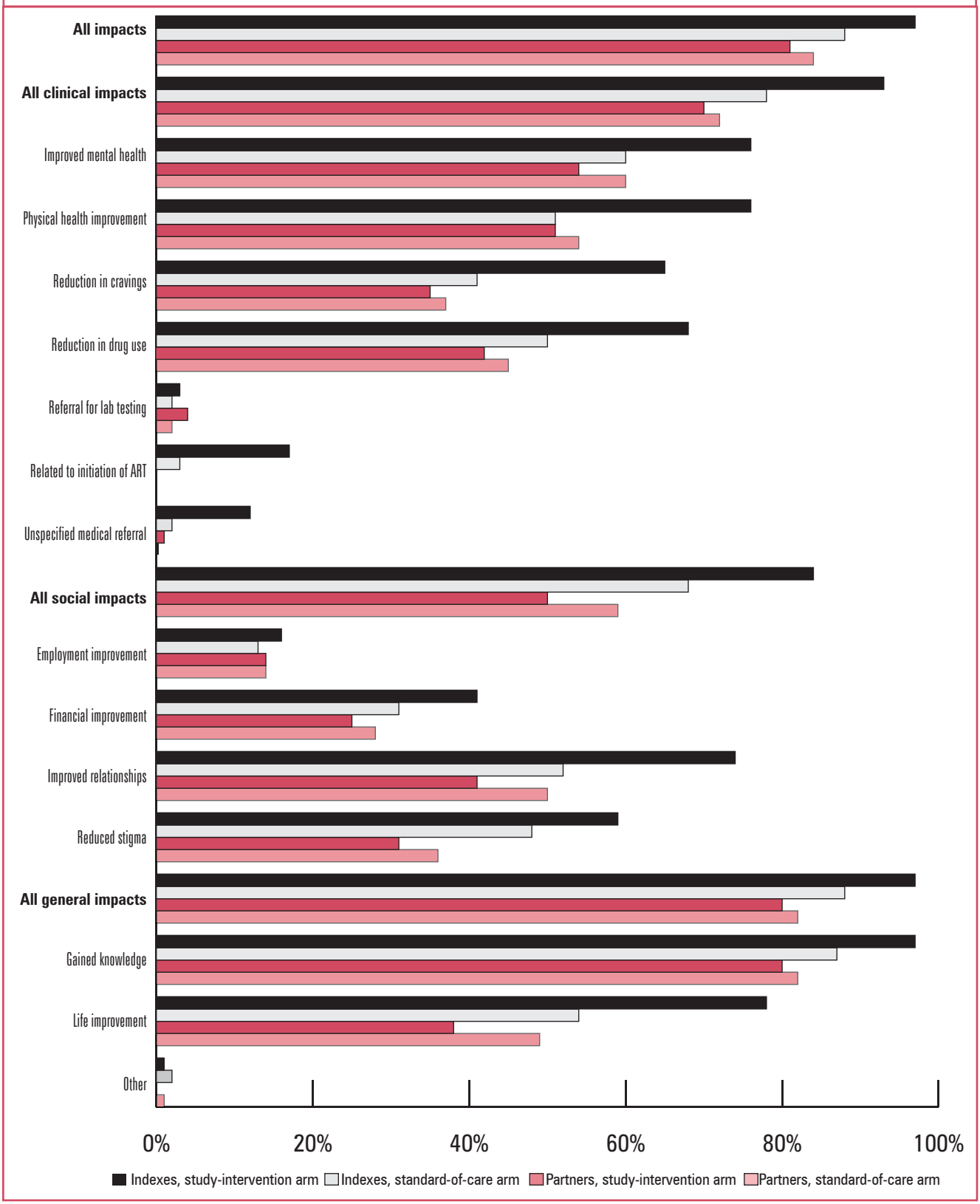
STUDY METHODS

Based on the participation benefits reported in a prior international collaborative HIV prevention trial involving people who inject drugs,[7] benefits related to trial participation were assessed at each of 7 to 11 study visits, depending on when participants enrolled in the study (those who enrolled earlier had a longer follow-up period). Specifically, the scheduled visits were for screening, for 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 obtained inductively 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. Specifically, reports of "Other" benefits were reviewed and coded with consensus among two authors (JS, IT).

Reported social benefits included improvements related to employment, finances, relationships, and stigma, even though, other than providing knowledge-based interventions about care and prevention options, no study components were designed specifically to promote such effects.

Reported benefits were aggregated for analysis into three groups: clinical (concerning initiation of ART, drug use, cravings/withdrawal, lab testing, medical referral, mental health, and physical health), social (concerning employment, finances, relationships, and stigma), and general (gained knowledge and life improvement). The binary outcome of whether participants reported experiencing a benefit at least once after the baseline visit was examined. 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 in-

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

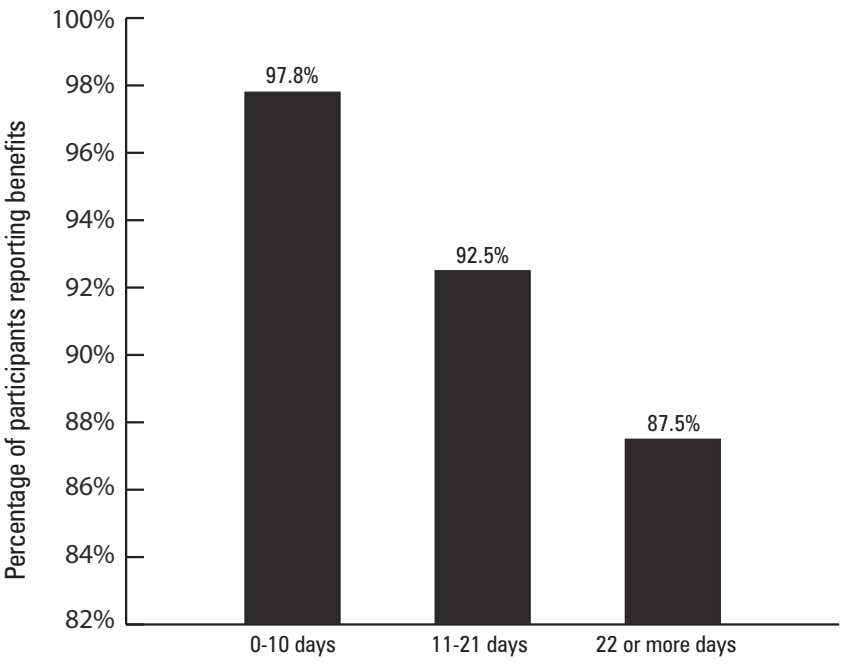


tensity, and prior incarcerations) and reports of benefits.

STUDY RESULTS

The study enrolled 502 index participants, with reported benefit data available for 484 of them; of these, 122 were assigned to the study intervention and 362 to the standard of care. The study also enrolled 806 injection partners, with reported benefit data available for 774 of them; of these, 177 were assigned to the study intervention and 597 to the standard of care. Table 1 (available online; see the "Supporting Information" section below) 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% of indexes and 4.0% of partners), those for whom we did not have these data were more likely to be men, less educated, and single and to have a history of unemployment, as compared to the overall study population (data not shown).

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

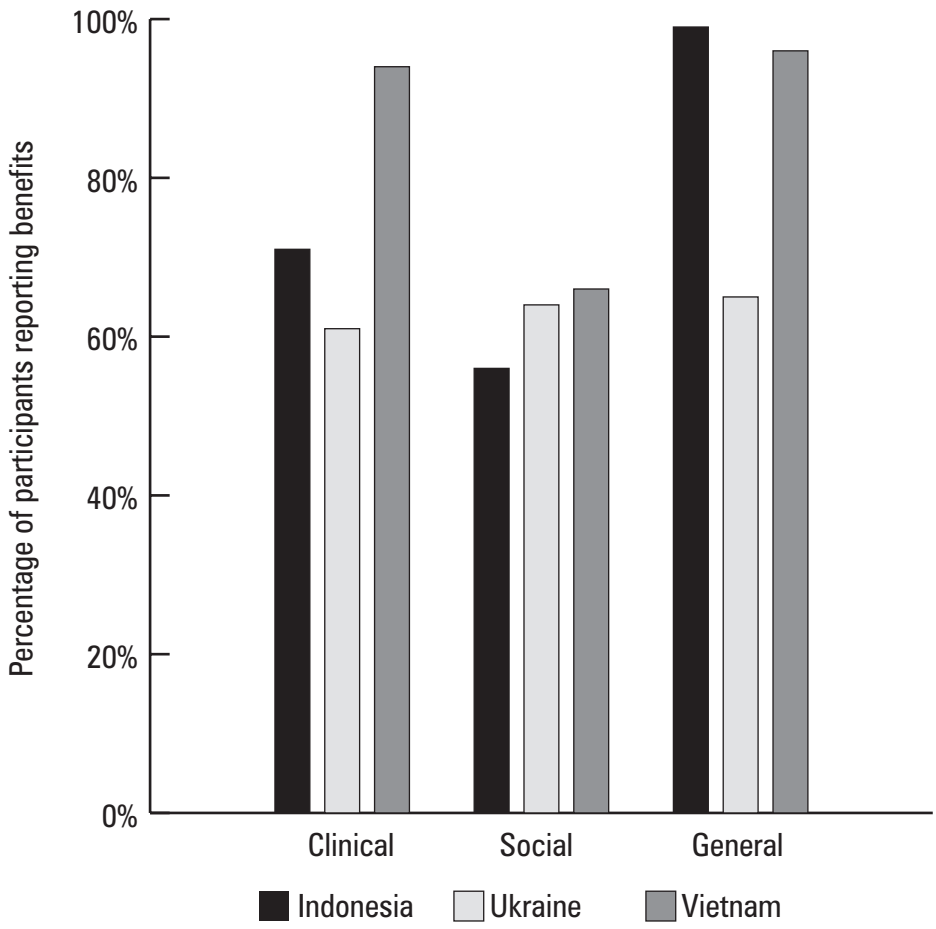


A substantial majority of trial participants reported at least one benefit from study participation. This included 438 index participants (90.5%) and 642 partner participants (83.1%). Figure 1 depicts the types of benefits and the proportions of participants who experienced those benefits at any time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

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

Finally, multivariate Poisson regression modeling (including 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 sociodemographic factors and self-reported benefits. Complete results are included in the appendix (available online; see the "Supporting Information" section below). However, drug-use intensity was found to be related to benefit reporting among index participants. Specifically, for the lowest versus highest injection frequency groups, clinical relative risk (RR) was 1.11 ($p = 0.015$), social RR was 0.97 ($p = 0.693$), and general RR was 1.06 ($p = 0.035$). Figure 2 shows the percentage of index participants reporting any benefit

Figure 3.
Participants Reporting Aggregated Benefits by Site



by prior injection frequency, with those who engaged in the least intensive drug use reporting more benefits (chi-square test p-value = 0.012) than those who engaged 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 was variability among study 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). In particular, 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 research 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 described 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 to be gained from the study. Nonetheless, consonant with widespread efforts in clinical trials and clinical practice to assess patient-reported outcomes,[8] these findings suggest that the clinical outcome measures of the primary study (such as use of ART and 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 associated with employment, finances, relationships, and stigma. This is remarkable given that, other than providing knowledge-based interventions about care and prevention options, no study interven-

tions were designed specifically to promote such salutary social effects that are especially complex given the research context. Although the relationship between 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 of a trial in which participants are treated with respect while engaged in an endeavor that is of important scientific and social value.

Because ART uptake in the trial was highest in Vietnam, it is not surprising that the reported clinical benefits were highest there compared to those reported at other trial sites. However, it is unclear why the proportion of particular benefits differs somewhat by site. While these are likely due to local context (for instance, the Vietnamese site was rural, while the Indonesian and Ukrainian sites were not), further qualitative work is needed to assess these findings.

Although our findings are largely consistent with those in the abovementioned study conducted in China and Thailand with people who inject drugs,[9] they should be interpreted with some limitations in mind. First, it is conceivable that the high proportion of reporting of benefits could be due at least in part to a social response bias when study staff members ask participants about benefits of research participation. 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, or something else. 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. 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 gathering of information about 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 people who inject drugs and who are affected by HIV in particular as well as other research that involves key 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 paying 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.[10] However, with few exceptions,[11] the standard approach to weighing risks and benefits in clinical research privileges physical risks and benefits.[12] Nonetheless, while incommensurable with clinical benefits, the potentially profound social benefits reported here may for some participants have enormous value. 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.

Clinical trial participation can provide broad benefits to stigmatized populations such as people who inject drugs and 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 research participation. ♦

SUPPORTING INFORMATION—TABLE 1 AND APPENDIX

Table 1 and the appendix are available in the "Supporting Information" section for the online version of this article and via *Ethics & Human Research*'s "Supporting Information" page on The Hastings Center's website: https://www.thehastingscenter.org/supporting-information-ehr/.

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ACKNOWLEDGMENTS AND DISCLAIMER

We would like to thank the participants in HPTN 074 for their invaluable contributions to this research. Ethics approval was obtained at all research sites and at the University of North Carolina, Chapel Hill.

This work was supported by the National Institute of Allergy and Infectious Diseases and the National Institute on Drug Abuse of the National Institutes of Health (NIH), HPTN Leadership and Operations Center (UM1AI068619) and the University of North Carolina at Chapel Hill Center for AIDS Research (P30AI50410). The content is solely the responsibility of the authors and does not necessarily represent the official views of the NIH.

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Reported Participation Benefits in International HIV Prevention Research with People Who Inject Drugs

Jeremy Sugarman, Ilana Trumble, Erica Hamilton, Riza Sarasvita, Kostyantyn Dumchev, Ha Viet, Irving Hoffman, William Miller, and Brett Hanscom

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%)
Education				
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 three 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 six months				
Yes	35	(7.2%)	59	(7.6%)
No	449	(92.8%)	715	(92.4%)

Appendix

Reported Participation Benefits in International HIV Prevention Research with People Who Inject Drugs

Jeremy Sugarman, Ilana Trumble, Erica Hamilton, Riza Sarasvita, Kostyantyn Dumchev, Ha Viet, Irving Hoffman, William Miller, and Brett Hanscom

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 after 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. standard of care)	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)*	1.00 (0.90, 1.12)	0.972
Injection frequency (0-10 vs. 22 or more)*	1.11 (1.02, 1.22)	0.015
Injection frequency (11-21 vs. 22 or more)*	1.11 (1.01, 1.23)	0.038
Prior incarcerations (yes vs. no)#	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

For all tables:
* The number of days individuals injected drugs in the month prior to baseline.
# Incarcerated (in jail or prison for involuntary detoxification or another form of incarceration) for some period during the three months prior to baseline.

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. standard of care)	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)*	1.06 (0.94, 1.19)	0.381
Injection frequency (0-10 vs. 22 or more)*	1.14 (1.03, 1.27)	0.014
Injection frequency (11-21 vs. 22 or more)*	1.08 (0.98, 1.20)	0.105
Prior incarceration (yes vs. no)#	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. standard of care)	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)*	0.85 (0.72, 1.02)	0.079
Injection frequency (0-10 vs. 22 or more)*	0.97 (0.83, 1.14)	0.693
Injection frequency (11-21 vs. 22 or more)*	1.13 (1.00, 1.29)	0.058
Prior incarcerations (yes vs. no)#	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. standard of care)	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)*	1.04 (0.87, 1.25)	0.659
Injection frequency (0-10 vs. 22 or more)*	1.06 (0.89, 1.25)	0.524
Injection frequency (11-21 vs. 22 or more)*	1.01 (0.88, 1.17)	0.860
Prior incarceration (yes vs. no)#	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. standard of care)	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)*	0.97 (0.90, 1.03)	0.327
Injection frequency (0-10 vs. 22 or more)*	1.06 (1.00, 1.11)	0.035
Injection frequency (11-21 vs. 22 or more)*	1.09 (1.02, 1.17)	0.015
Prior incarceration (yes vs. no)#	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
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. standard of care)	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)*	1.06 (0.98, 1.16)	0.152
Injection frequency (0-10 vs. 22 or more)*	1.07 (1.00, 1.15)	0.049
Injection frequency (11-21 vs. 22 or more)*	1.01 (0.93, 1.09)	0.850
Prior incarceration (yes vs. no)#	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