MEETING REPORT

WHO/UNAIDS CONSULTATION FOR EASTERN EUROPE AND CENTRAL ASIA | 16-18 JUNE 2010

Ethical engagement of people who inject drugs in HIV prevention trials

UNAIDS
JOINT UNITED NATIONS PROGRAMME ON HIV/AIDS
UNHCR UNICEF WFP UNDP UNFPA UNODC ILO UNESCO WHO WORLD BANK

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List of Acronyms used in this report

Acronym	Definition
ART	Antiretroviral therapy
EC	Ethical considerations in biomedical HIV prevention trials guidance document, UNAIDS/WHO (2007)
GP	Guidance point
GPP	Good participatory practice guidelines for biomedical HIV prevention trials, UNAIDS/AVAC (2007)
GP	Guidance point
ICESCR	Covenant on Economic, Social and Cultural Rights, 1966
NGO	Non-governmental organization
NSP	Needle and syringe programme
OST	Opioid substitution therapy
PrEP	Pre-exposure prophylaxis
RDS	Respondent-driven sampling
STI	Sexually transmitted infection
TB	Tuberculosis
UN	United Nations
UNAIDS	Joint United Nations Programme on HIV/AIDS
UNODC	United Nations Office on Drugs and Crime
WHO	World Health Organization

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Note about this report:

On the 16-18 June 2010, the World Health Organization (WHO) and the Joint United Nations Programme on HIV/AIDS (UNAIDS)[i] convened a regional expert stakeholder consultation in Istanbul, Turkey. The purpose was to explore specific challenges related to the meaningful engagement of people who inject drugs in HIV prevention trials and to identify strategies that can be - or have been – employed to creatively and ethically address these challenges. The consultation was the first of three meetings to be convened in regions with a higher risk of HIV transmission among people who inject drugs.[ii] This meeting report summarizes the discussions and recommendations from the Istanbul consultation with the Eastern Europe and Central Asia region.

The objective of the consultations is to contribute towards the development of specific evidence-informed, rights-based international ethical guidance for the meaningful engagement of people who inject drugs in biomedical HIV prevention trials for inclusion in the United Nations guidance on trial conduct. Such guidance is considered to apply in principle to behavioural and structural HIV prevention trials and would bee expected to also apply when such trials involve people who inject drugs. HIV prevention trials are an important foundation for fighting the HIV/AIDS epidemic and reducing the risk of infection. Ethical guidance is intended to be of support to people who inject drugs participating in these trials. Recommendations from the consultations are intended to promote positive change in civil legislation, to inform national research guidelines within the framework of accepted legal rules, and to be included among the existing ethical guidelines that govern international research.

INTRODUCTION

Background and meeting objectives

People who inject drugs represent a key population at higher risk of HIV infection in many settings around the world. Some types of substance use are associated with higher levels of sexual risk behaviour which increase the risk of HIV infection, however, people who inject drugs are exposed to a substantial risk of parenteral HIV transmission and merit special consideration.[iii] Indeed, UNAIDS estimates that outside sub-Saharan Africa, approximately one-third of all HIV infections are related to injecting drug use.[iv] Data suggest that an estimated 15.9 million (range 11.0-21.2 million) people inject drugs worldwide (2007), with an estimated 3 million being HIV positive.[v] Of the 148 countries in which use of injecting drugs was documented, 120 (81%) also reported HIV infections in the country, with prevalence being higher than 40% in nine countries.[vi] At the same time, coverage for HIV prevention, treatment and care for people who inject drugs remain very low globally, with only a few exceptions. A recent review of global needle and syringe programme (NSP) coverage suggests that in the countries hardest hit by injecting-related HIV epidemics such as the Russian Federation, Georgia, Thailand, and Indonesia, fewer than 5 sterile syringes per injecting drug user are distributed per year, while less than 10% of people who inject drugs report access to NSP.[vii] It is important to acknowledge that there are marked differences between and within countries with respect to syringe availability, as some countries allow for the provision of syringes to people who inject drugs through pharmacies.[viii] Regionally, injecting-related HIV epidemics continue to grow, particularly in Eastern Europe, including the Russian Federation, and Central and Southeast Asia.[ix] UNAIDS estimates that approximately 1.5 million people are living with HIV in Eastern Europe and Central Asia and, in 2008, there were approximately 110,000 new HIV infections in the region, primarily among people who inject drugs. [x] Injecting drug use is also emerging as a risk factor in some countries in southern and eastern Africa, due to a shift in drug trafficking routes.[xi]

Providing people who inject drugs with access to proven, effective HIV prevention tools is therefore a critical global public health issue, and both UNAIDS and WHO are committed to protecting people who inject drugs from becoming infected with HIV as a matter of their human right to health.[xii] To increase current knowledge of how best to implement existing and anticipated prevention methods, and to ensure that new and better prevention methods become available in the future, there is an urgent need for scientifically rigorous and ethically sound biomedical HIV prevention trials with people who inject drugs. Ethical guidance is needed to support their involvement in such trials, as well as in behavioural and structural HIV prevention trials.

The development, evaluation, and future introduction of novel HIV prevention strategies involving people who inject drugs (such as drug use treatments, vaccines, microbicides, pre-exposure prophylaxis, and others) is potentially complicated by a number of behavioural and epidemiological factors. From a molecular epidemiology point of view, there is evidence that the spread of HIV among people who inject drugs is characterized by extremely complex patterns of variation of the virus with rapid shift and emergence of new genetic sub-types and recombinant forms[1]. Transmission patterns among people who inject drugs may also be complicated due to exposure to HIV via different and parallel routes (e.g. injecting drug use combined with risky sexual behaviour), and interactions with other infections, including tuberculosis (TB) and hepatitis B and C, all of which may alter the efficacy of biomedical prevention strategies.

Lessons learned from previous and ongoing HIV prevention trials also show that large numbers of volunteers need to be recruited to take into consideration multiple behavioural and epidemiological factors that can influence the efficacy of candidate tools and interventions. Furthermore, results from biomedical prevention trials so far indicate that

[1] Reference to molecular epidemiology to be added to end notes: Do the HIV-1 subtypes circulating in Italy resemble the Red Queen running in Carroll's novel? Ciccozzi M, Bon I, Ciotti M. New Microbiol. 2010 Apr;33(2):179-81 .

partial efficacy is the most that could be anticipated from any of the new biomedical tools and interventions under development. Clearly, no HIV prevention strategy is likely to be highly effective on its own.[xiii] There is a need to combine multiple approaches taking into account the particular characteristics of people who inject drugs communities, including the structural and environmental factors that shape individual risk practices and vulnerabilities to HIV infection.[xiv]

While it is clear, therefore, that people who inject drugs need to be included as participants in biomedical, behavioural, and structural HIV prevention trials, there are numerous challenges to their meaningful engagement. These challenges, broadly characterized as legal, regulatory, structural, social, and logistical, and the strategies that have been or could be employed to overcome them, were explored during the 3-day consultation recorded in this meeting report. As a result of these discussions, participants developed a series of recommendations towards the development of specific rights-based and evidence-informed ethical guidance for the meaningful engagement of people who inject drugs in HIV prevention trials. Following further regional consultations in Asia and the Americas, the guidance document will be finalized as a supplement to the existing UNAIDS/WHO ethical guidance document *Ethical considerations in biomedical HIV prevention trials* (2007)[xv]. It will inform future revisions of the UNAIDS/AVAC *Good participatory practice guidelines for biomedical HIV prevention trials* (2007).[xvi] The regional consultations will also result in a scientific manuscript for publication and broad circulation.

Legal challenges and strategies

Many challenges to HIV prevention trials with people who inject drugs are related to the illegality of drug use and to the application of harsh law enforcement and punitive measures (including the death penalty in some countries), which, in large measure, can be attributed to the adoption of the 1988 United Nations Convention Against Illicit Traffic in Narcotic Drugs and Psychotropic Substances.[xvii] In many countries, including Russia, legal barriers limit access to proven risk reduction modalities such as needle and syringe programs (NSP) and opioid substitution therapy (OST). In addition, overdose antidotes, such as naloxone, may not be available or supported by government programmes. Likewise, national regulations or policies governing research funding may restrict access to certain risk reduction methods. For example, until recently, the use of US federal funds, including research funds to purchase injecting equipment, was prohibited.

It is important to be aware that in some countries there are not only legal barriers but among both the public and authorities, including medical authorities, there is often a strongly-held conviction that drug addiction is not so much misfortune or a public health issue, as it is the fault of an individual person. It is presumed, consequently, that risk reduction methods such as NSP or OST only encourage and facilitate drug use instead of treating or reducing the risk involved in drug injecting practices. Some people suggest that any attempts to treat illicit drug users are counterproductive because they encourage people to be less vigilant about the dangers of drug injecting. These views do not accord with the evidence, i.e. treating people with OST does not lead to increased drug use and addiction has generally long been accepted as a disease rather than a moral flaw. It is nevertheless important to recognize and acknowledge these beliefs as significant, even primary, obstacles when carrying out trials.

Strict anti-drug laws, regulations and enforcement procedures may also expose people who inject drugs to hefty fines or imprisonment, impose mandatory registration and reporting duties, and drive people who inject drugs underground – thus creating a hidden and hard-to-reach population[xviii]. In turn, these, can influence people's willingness to participate in HIV prevention trials, hamper

researchers' recruitment efforts, and affect the willingness of those already enrolled in trials to utilize risk reduction and treatment referral services. Overly-vigilant, harsh, and intrusive regulatory measures and policing activities may compromise the ability of researchers to ensure the confidentiality and right to privacy of research participants. Regulatory measures might, for example, require the mandatory reporting or registration of any person known to be injecting drugs, while police might visit trial facilities, interrupt interviews, arrest and/or subsequently prosecute participants. Ensuring the confidentiality and privacy of research participants requires thoughtful consideration across the life cycle of a research project, from the early stages of trial design and community involvement (GP 2), to recruitment processes (GP 7), and throughout the conduct of the trial and subsequent follow-up.

In general, people who inject drugs are considered a vulnerable group due to stigma and discrimination related to their drug use, and this vulnerability is compounded by the risks of drug law enforcement and police action. A trial might increase a participant's risk of exposure to social harms in the absence of advance steps and special measures to protect their rights, safety, and welfare. Formative research should include analysis of legal and regulatory frameworks and political and social conditions – including those related to gender and ethnicity - so as to assess specific local determinants of vulnerability prior to commencement of a prevention trial (GP 8).[xix] Researchers should also be aware of their own subtle prejudices against people who inject drugs. Trial researchers and sponsors need to appreciate the daily realities and lived experiences of people who inject drugs, including probable tension in relationships with families, communities, and authorities. Research involving people who inject drugs takes place within these complex contexts, and researchers' loyalty should lie with the participants in their study and protection of their rights and dignity. In this respect, consultation participants felt that researchers have an advocacy role.

The EC guidance document[xx] clearly states that HIV prevention trials should not be conducted when conditions affecting potential vulnerability may be so severe that the risk outweighs the benefit of conducting the trial with that population or when a survey of local laws indicates insurmountable legal barriers (p. 13). Further, trials should not be conducted in places where there are insurmountable legal and regulatory barriers to providing *state of the art risk reduction methods* (see further below: 'Standard of Prevention'), or where researchers cannot guarantee protection of participants' rights and safety (see further below: 'Confidentiality'). A related question for further discussion, therefore, is whether and under what conditions research in closed settings such as prisons, jails, detention centres, and compulsory drug dependency treatment centres, should take place (p. 14). At the same time, however, given the importance of including people who inject drugs in HIV prevention trials, engaging with governments and community representatives to find creative ways for research to be ethically conducted under less-than-ideal circumstances is crucial. Researchers and sponsors will need to consult national Ministries of Health to discuss and gain permission to conduct a trial. Discussions should include how to design ethical trial conduct procedures taking into account existing legal and regulatory frameworks that may affect or limit research conduct or relationships with study participants and that place study participants at risk. Where indicated, similar discussions may need to occur with other authorities, such as with local police and other recognized law enforcement agencies. It should be recognized that this may not be realistic in some countries and localities.

Researchers may choose to explore the possibility of obtaining legal exemptions from local criminal law enforcement agencies for the HIV prevention trial in order to protect participants, study team investigators, assistants, field workers, and

service providers. This may be under either prosecutorial discretion as to which laws to enforce and which not, or public health emergency provisions in international treaties and national and local laws. For example, investigators in Canada obtained a temporary exemption from the country's federal laws, for the purpose of an evaluation of the effect of a medically supervised injecting facility on levels of HIV risk behaviour among people who inject drugs. This exemption was challenged and subsequently revoked during the study period.[xxi] Similarly, in Australia, special legislation was enacted to permit a medically-supervised injecting facility to function as a pilot project. Of note, such legal exemptions might not be respected by some members of the police force, thereby creating a situation in which participants have a false sense of security but are, in fact, exposed to an even greater risk of arrest. It may create inequity if trial participants enjoy impunity while non-participant drug users do not. Such a situation could result in trial participants being pressured by drug-traffickers to purchase, carry, and store drugs for others, thus enhancing their exposure to legal and other types of risk.

To conclude, HIV prevention trials involving people who inject drugs should be conducted within the legal constraints of the particular locality and should not be undertaken where researchers are unable to overcome legal barriers to the conduct of ethical research, despite their best efforts. Before commencing a trial, research teams should undertake formative research to assess the feasibility of conducting the trial under the existing legal, social, and political conditions, identify and minimize risks of law enforcement interventions during the trial, and make considered plans to create a safe and enabling environment for the trial to take place. Because the legal and regulatory framework in a given setting influences the capacity to provide an evidence-based standard of care/prevention, including access to NSP and OST, the ethical considerations should be weighed in advance of commencing research.

Community participation challenges and strategies (GP 2)

The lack, or perceived lack, of community involvement in trial planning can lead to the halting and abandonment of research projects, as occurred in Cambodia, Thailand and Cameroon.[xxii] For this reason, and because in principle it is important that people be engaged in decisions that affect their lives, it is essential to consult communities of people who inject drugs in order that they participate in the trial through transparent and meaningful participatory processes from the very beginning. If, however, engagement is to be meaningful, it must go beyond simply eliciting the voices of people who inject drugs community representatives. Consultation participants who had experience in HIV prevention trials as people who inject drugs representatives found, that in their experience, their suggestions or demands were rejected and that their participation was largely symbolic. In order for communities to have meaningful input into trial design and protocols prior to commencement and to participate in an ongoing fashion in monitoring and implementation, it is important to seek out and value the opinions of appropriate community representatives.

The inclusion of people who inject drugs in HIV prevention trials can pose special participatory challenges because of their specific vulnerabilities which render them hard-to-reach or a 'hidden' population. It may, for example, be difficult to identify community organizations, representatives, or spokespersons in localities where legal actions against people who inject drugs and stigma are severe and where, as a result, the development of leadership among people who inject drugs may have been inhibited. Secondly, individuals and their networks might be reluctant to take part in a community consultation for fear of being exposed to legal or social risks. Thirdly, as with many other communities, people who inject drugs are not monolithic; they differ across geographical regions and their

lifestyles and behaviour differ depending on their age, gender, sexual preference, social status, and type(s) of drug(s) used. As a result, self-appointed 'community representatives' may, in fact, represent a narrow group of people who inject drugs or may not be working in the best interests of everyone in the community. Finally, in some communities, structural and social barriers may have resulted in low levels of education and lack of personal communication skills among people who inject drugs making it difficult for them to engage with confidence in research discussions and decision-making activities. It is also important to be aware that because the community of people who inject drugs is largely trial naïve, current levels of clinical trial literacy are low.[xxiii]

Meeting participants were very clear that while *former* injecting drug users might seem to be more capable and less vulnerable to legal risk, researchers should act under a strong presumption that priority should be given to engaging *active* users in the participatory process. They may have much better and more up-to-date understanding of the local context, the risks involved and the current priorities of people who inject drugs. Provisions should be made to offer capacity building and training programs for both former *and* active drug users early on in the trial design phase. Both former and active drug users are key members of any community advisory mechanism, such as a community advisory board or community advisory group, constituted prior to the commencement of a trial. Researchers, and all other relevant stakeholders, such as sponsors, governments and funding organizations, should be aware that preparatory activities building trust and capacity at the community level require time and resources and should be included in research budgets.

As previously stated, researchers should engage in a formative research process prior to the beginning of a trial in order to determine community interests, acceptability, and willingness to participate so as to assess the feasibility of the study.[xxiv] Consultation participants noted that it is important to acknowledge the problem of obtaining funding for such formative research. Most funding agencies will fund research only if the proposed research has been worked out in great detail, for example, numbers of subjects, how participants will be recruited, and specified follow-up methods, etc. This requirement for great detail – with few funds - means that the formative research must be limited to figuring out a detailed research plan with little or no opportunity for the community to influence most aspects of the trial design and conduct. As stated by a participant,"[i]f we want community involvement early in the research process, then we need to have funding that begins very early in the research process."

Research teams should also participate in training to gain a better understanding of the issues facing trial participants. They should have knowledgeable people on their staff to ensure an understanding of potential research participants and the contexts in which they live. This includes knowledge of their culture and lifestyles, stigma among and between people who inject drugs themselves, and patterns of prejudice and discriminatory attitudes in the larger community. Researchers in all settings, but particularly settings where human rights violations against people who inject drugs have been documented, are advised to commission or conduct a human rights impact assessment of their proposed operational procedure and survey the relevant laws and regulations which could affect the trial and trial participants. Participants noted that researchers are unlikely to know how to conduct such an assessment and that a human rights impact assessment guide should be available. Researchers may need training on how to carry out such an assessment if they are expected to use and/or understand it. One participant noted that while the broad frame of such an analysis is clear, they do not know a single researcher who would know how to actually apply such an assessment in a real-world research situation.

As part of the formative research process, researchers should map the larger community in which people who inject drugs live, so as to ascertain how relevant decisions are made, and determine which persons might play a constructive role in supporting and facilitating the HIV prevention trial. It is critical to engage local authorities, including public health officials and police, where possible, to reduce harm and prejudice to participants and researchers. It may also be necessary to address discriminatory attitudes of health care providers. Community advisory mechanisms could also include caring and trusted leaders or members of civil society, such as medical professionals and human rights non-governmental organisation (NGO) activists. Particular efforts should be made to involve women and others sensitive to gender issues, including those related to the involvement of female sex workers who inject drugs.

In engaging appropriate representatives of the community of people who inject drugs, researchers are advised to be responsive to community needs and wishes. It is important to be open-minded to changes in attitudes, perspectives, and methodologies that would make the research more culturally appropriate, increase accessibility, and facilitate community cooperation by building trust and allaying concerns. Engagement mechanisms may include hiring interpreters, partnering with existing networks of people who inject drugs, and working with the media, if appropriate. Once identified, potential representatives should be asked (it should not be assumed) if they are prepared to represent their community openly, and researchers should ensure representatives are well informed of the extent to which they are able to guarantee protection of their safety and welfare.

Researchers should be aware that advocates for people who inject drugs might not have faith in the potential impact of evidence-based science to bring about change in government policy. Nonetheless, HIV prevention trials involving people who inject drugs across the life cycle of a research study, as community representatives, trainers for academic staff members, research assistants, peer educators, and field workers, help to mobilize communities and can offer motivation and hope. Benefits to the individuals who become involved in research studies, as either community representatives or team members, include empowerment, reduction of stigma, training and acquisition of new skills, and the possibility of increased employability.[xxv]

The involvement of people who inject drugs as staff on research teams also contributes significantly to various aspects of the research. Research shows that respondents appear to give more weight to recruiting information that is communicated by peers than to that communicated by study staff.[xxvi] If provided with adequate training, employing people who inject drugs as recruiters and interviewers may also contribute to validation of primary data at the point of collection, since some participants may be more likely to disclose to peer rather than non-peer interviewers. That said, people are sometimes reluctant to disclose particular issues to peers or members of their community, preferring instead to share very personal issues with a professional or someone they do not know. A second caution is the importance of finding ways of ensuring that confidentiality is not breached when peer or community members are part of the research team. Research teams need to be equally vigilant in ensuring confidentiality in behavioural research where a breach of confidentiality may reveal participant behaviours that may be heavily stigmatized within the community of people who inject drugs itself.

When researchers involve persons who *formerly* injected drugs in trial conduct, they need to take into consideration the heavy emotional burden that might be

entailed in fieldwork, such as the risk of relapse. To avoid or minimize such risks, researchers should ensure access to appropriate supervision and support resources (individual and group). Whether people who inject drugs or people who previously injected drugs but no longer do so are brought onto the research team, it is important that they be provided with proper training, remuneration, and support.

Recruitment of participants (GP 7) - retention and follow-up

Recruitment by treatment centre staff or researchers

Recruiting people who inject drugs into HIV prevention trials can pose specific challenges due to legal and law enforcement issues (discussed above) and to social marginalization and special vulnerabilities, for example sex workers who inject drugs may be even more isolated and suffer even greater stigma because of their occupation. While recruitment by service providers in treatment centres is very common, such recruitment can pose special problems in relation to voluntariness of participation. As with all trials where recruitment of vulnerable people is conducted in medical or treatment-related facilities, it is important that trial enrolment is not, nor is understood to be, a condition of access to treatment since this would compromise trial participants' right to refuse or withdraw their consent to participate. For this reason, it is often considered inadvisable for caregivers and service providers to recruit research participants. Instead, researchers might educate members of the community of people who inject drugs to become peer educators and assistants who are able to provide accurate information about the trial and identify and recruit potential participants. In any event, where the trial is conducted in association with a treatment centre or other type of organization providing services to people who inject drugs, it is important to emphasize that refusal or withdrawal of consent to participate will not carry jeopardise the continuation of treatment in any way.

Researchers might also ask participants to bring in friends, or to name others whom they know to be drug users so that they can contact them independently. One consultation participant noted that this type of approach, i.e. nomination and identification of potential participants to researchers, is unlikely to be approved by institutional review boards. Study personnel need to clarify with the first person whether the friend/potential volunteer they are naming knows that the participant is a drug user, and also to be cautious in approaching the friend, so as to protect the privacy of both the informant and the candidate. Another participant noted that 'bringing in friends' (peers) and naming and giving contact information are very different activities and need to be thought of quite differently when considering the ethics of each.

Respondent-driven sampling and other social network recruitment approaches

Innovative approaches to recruiting participants who are people who inject drugs include strategies that incorporate low-threshold interactions,[xxvii] social network approaches,[xxviii] including respondent-driven sampling (RDS), or other methods that engage directly with people who inject drugs.[xxix] Recruitment methods such as these - RDS, snowball, chain referral, and other direct approaches by researchers or peers - can reach people who do not attend public venues and can lead to rapid recruitment of research participants. Among these methods, perhaps the main advantage of RDS is that it is theoretically able to recruit a population from which unbiased estimates can be calculated. Although there is no published evidence of the effectiveness of RDS in recruiting participants for clinical trials or cohort studies, peer sampling (snowball sampling) is documented to be effective in recruiting subjects for trials and cohort studies, and as noted below, the ethical issues in snowball sampling and RDS are essentially identical.

Respondent driven sampling starts with a small group of diverse 'seeds' and trains them in the specifics of the study and how to recruit peers. Seeds can recruit up to three peers and are paid for their own participation and for each peer who volunteers for the trial. One participant asked for clarification as to whether the peer has to actually enrol in the trial or simply show up for possible recruitment. The concern was the possibility of there being great pressure to have the peer actually enrol. The response to this was that in a study in India[2], all volunteers/peers that showed up were paid regardless of whether they enrolled. "If we were not to do, it would mean that very quickly the entire community would know the 'right' answers to the recruitment questions that they would need to give, in order to get paid." Participants may be identified through local NGOs and service providers or at public venue hot spots. In the latter case, individuals might be homeless and might not have official identification documents, and researchers will need to adopt some kind of alternative identifying system, such as unique physical identifiers, which may or may not involve face recognition software or phalange measurement. Peers are supposed to participate in the study as part of their training to recruit others. Similarly, only persons who participate in later waves are asked to recruit new subjects

One potential issue, albeit not an ethical issue, is that because people are not recruited through direct approaches by the research team (including peer researchers) but by their peers (who because of the 'waves' may not be known to peer researchers), they may be less likely to engage and be retained. There are also issues in relation to confidentiality related to the incentive payments to participants whose referrals are eligible for trial participation (in effect a disclosure of serostatus). One participant noted that RDS is unique, if recruiters not only recruit other individuals within their networks but also learn whether those persons participate and then collect the secondary incentive only if their recruits follow through[3]. Another participant cautioned against only discussing RDS in any guidance document as it then appears as if it is the preferred recruitment methodology.

Confidentiality may be breached if seeds learn that the people they brought did not meet the eligibility criteria and were screened-out from participation in the study. Likewise, confidentiality can potentially be breached when it is clear that someone has been enrolled in the study. It was noted that this danger is not limited to RDS but also occurs with, for example, a standard snowball technique. In general, the risks and benefits of RDS in recruiting participants for prospective observational studies and clinical trials have not yet been fully assessed and, as noted previously, the effectiveness of RDS in recruiting and retaining (key) participants in clinical trials and follow up studies is not documented. At the same time, there are strong proponents of RDS and there are multiple publications on ethics/risks and benefits in RDS. These risks and benefits are not fundamentally different from other peer recruitment methods that have been used for decades. One participant voiced that discussions of the ethical and technical issues related to RDS should be discussed separately in order to reduce confusion and misinterpretation.

Retention and follow-up

HIV prevention trials are often conducted over long periods of time and if treatment clinic staff are also involved in the research they may have an interest in high retention rates. They may overtly or subtly pressure individuals to

[2] Assessment of sexual behaviours and sexual networks of injecting drug users in Delhi and Imphal (A. Sarna, W. Tun,W. et al

[3] For a discussion of ethics and RDS see De Jogn et al. American Journal of Public Health 2009 99 (9).

continue participating and participants may find it difficult to refuse to do so. At the same time, researchers should be aware that when trials are conducted over long periods of time, participants might continue to participate because they are being paid to do so, but without adhering to the trial product regimen, thereby compromising the scientific validity of the trial. One participant noted that if more accurate estimates of HIV incidence likelihood in HIV prevention trials were made prior to the trial, there would be less felt need to pressure participants to remain in the study over such a long period of time because the study design would have anticipated a sufficiently high number of participants to allow for accrual and loss to follow-up. However, unequal loss to follow-up between experimental and comparison groups may compromise a trial's power to draw conclusions. Further, HIV incidence in a trial may be lower than expected, as has been the case in several microbicide trials in Africa, leading to an unexpected extension of a trial for a longer period of time, which may make it more difficult to retain participants.

Researchers need to make plans in relation to loss to follow-up, since people might suddenly be difficult to locate for various reasons including relocation, incarceration, hospitalization, death, or other reasons.[xxx] In general, steps should be taken to ensure that efforts to follow participants who do not show up for trial visits are done with the prior consent of participants, so as not to feed suspicion and mistrust of trial operations. At enrolment and each subsequent visit, participants should be asked to name at least one trusted person who can be contacted without breach of their confidentiality, in case they do not present for a scheduled trial visit, If the participant consents, research staff may seek the collaboration of family members, sexual partners - recognizing however that there may be ethical issues related to partner notification in relation to seroconversion - or co-dependents to encourage ongoing participation in the study. Where recruitment or follow-up involves street outreach and visits to homes and prisons, researchers need to consider the safety of team personnel. One participant noted that "if the study recruits true peers, and by that I mean that they belong to the study population both in terms of risk group and geographic locality, people from the community itself, then this whole issue is handled by them. Peers handle the tracking and follow-ups of subjects through their own system of networks within the community. And this can be done at a frequency that will not be achievable by "staff". We have found that a single peer worker can keep track of up to 25 clients on a daily basis 7 days a week, and the number s/he can handle increases as the frequency of contact drops."

Vulnerable populations (GP 8) - prisoners

There was insufficient time to adequately deal with the question of trial conduct in prisons, including, for example, whether there should be research in prisons – or detention centres - at all, whether confidentiality is possible and the ability/inability to provide an adequate standard of care/prevention – such as sterile injecting equipment. As expressed by one participant, "[F]or me an adequate standard of care/prevention is non-negotiable – if this minimum cannot be provided trials should not be conducted in this setting." Another participants stated that "we should emphasize the importance of ensuring access to the highest standard of prevention (as discussed for research outside prisons). It is important that research can only be carried out in prison settings if the research team is able to ensure access to the accepted standard, such as clean needles, condoms etc." One participant noted that Art. 29, part 3 of "The Foundations of Legislation of the Russian Federation on Protection of Citizen' Health" clearly prohibits any kind of research on prisoners. It is unclear for purposes of this report whether this means that already enrolled participants who are incarcerated during research can be followed in prison or whether they are precluded from continuation.

Despite not being able to deal fully with the issue and ethics of research in prisons and other locked settings, a number of points were raised. Researchers should expect that some trial participants will be incarcerated during the course of the trial and researchers need to adopt an incarceration protocol for such an event. It should include plans for follow-up of incarcerated individuals so as to continue their participation and provide them with the trial product and optimal care while in prison without compromising their right to confidentiality or placing them at risk of discrimination or harm because of their drug usage and trial participation. For example, prison officers may want to know the results of urine drug screening, which might lead to punishment. In such case, researchers should consider the balance of the benefits and the risks to incarcerated participants, and not proceed where the risks are not justified. Similarly, prison authorities might demand that interviews with inmates be conducted in the presence of a guard, and this has the potential of jeopardising the confidentiality and security of trial participants. Further, it is also critical that the prisoners not be able to overhear each other during interviews. Researchers should negotiate with the authorities about conducting research procedures in a way that keeps participant's confidentiality but if this cannot be guaranteed in the prison context, the trial should be not conducted.

Researchers should plan to include ongoing staff visits and risk-reduction counselling during incarceration and include these plans in the protocol. They might also advocate for the designation of an independent physician to provide treatment and care inside the prison, and for a representative of the community of people who inject drugs to sit on the prison review board. They might seek assistance from available legal aid services to ensure the protection of participants' rights while incarcerated. A remaining question is whether this standard/activity/engagement is maintained in the correctional setting when the trial finishes and/or whether it is extended to benefit non-trial participants during the conduct of the trial. Further, researchers should address the issue of referral for post-release care and support, including ways to reduce the risk of overdose and death for those who had stopped injecting in prison and may revert to injecting drugs on release. For example, they might ensure contact with peer staff team members upon release for support or for facilitation of reconnecting with family, or negotiate places in half-way homes and shelters for trial participants. If "peers" are current users (as discussed above) meeting with them could provoke craving and relapse. Supportive services should be available, including referrals for medical and/or substance use treatment..

In the informed consent process, researchers should disclose to candidates the provisions of the protocol in the case of incarceration. This includes whether it will be possible to provide sterile injecting equipment or dispense OST in the prison, and whether treatment for withdrawal symptoms can be provided in prison. One participant noted that "[S]ome of this will depend on which prison(s) people are sent to – for example in the state I live in there are ~25 different prisons in a huge geographic spread. What happens if you enrol trial participants in a prison that can meet the required standard of care but they are subsequently transferred to one that does not? Do researchers need to ensure that standard of care is available at all potential prisons in the jurisdiction?"

Prevalence and incidence of HIV in prison populations are higher than in the general population. Injecting drug use may be less prevalent than in the community but the risks are higher because prevention programs are rarely available, multi-person syringe use with greater numbers of other users may occur, and other behaviours take place that carry a high risk of HIV transmission, including unprotected sex and tattooing.[xxxi] As a general ethical rule, research studies that can be conducted elsewhere in the general population (such as

phase I and phase II trials) may not be conducted in prisons or detention centres. Further, early trials are assessing safety, and in the case of HIV vaccines immunogenicity, of candidate HIV prevention tools or interventions and should be conducted in populations not at risk for HIV acquisition.

The question of whether research should be conducted in illegitimate closed extra-judicial settings where people who inject drugs are placed without their expressed consent or without a trial, such as the compulsory drug dependency treatment centres existing in China and South-East Asia, should be addressed in any guidance developed. There was agreement expressed by some participants that trials should not be conducted in settings where conditions violate basic human rights. The discussion was, however, short and a more nuanced and full discussion will be needed for the development of guidance.

Where a trial is designed specifically to be conducted in and for the direct potential benefit of the participants and other prisoners, ethics committee approval may be given, despite it contradicting country regulations concerning research with prisoners and not addressing the issue of compulsory drug dependency treatment centres. A study might, for example, propose to investigate means to prevent hepatitis C transmission in specific prison conditions. It can, however, also be argued that it is clear that sterile injecting equipment in prisons has been proven to stop hepatitis C transmission and so this may not be the best example of research that should be conducted. Agreement is needed on whether it is ethical to conduct trials of interventions known to be effective over and over again. It would be relevant to conduct trials comparing different delivery models of risk reduction services for their suitability in closed settings.

Researchers should give due consideration to various ethical aspects, including minimizing risks to participants, guaranteeing confidentiality, and protecting the inmates from undue influence and coercion to participate or retaliation for refusing to cooperate. One option is to appoint a suitably qualified prisoner advocate, with expertise in ethics where possible, to represent participants' concerns before the prison authority or institutional review board responsible for approving the trial.

Women (GP 9)

Women provide one example of a specific minority group of drug users. They suffer from double stigma and discrimination both within society and the community of people who inject drugs itself.[xxxii] Standard prevention and treatment programs, such as NSP or drug rehabilitation programs, may not be adapted to women's special needs for services such as child care, appropriate hours of operation, and provision for, or referral to, reproductive health services. Women may therefore experience difficulty in accessing and interacting with health care services and this might encourage mistrust in research. Researchers need to consider all these factors in order to include women who inject drugs in HIV prevention trials. Recruitment may be facilitated by means of independent, low-threshold service facilities in which women trust.

While it was agreed that women who inject drugs should be included in trials, it was not clear in what proportion, that is, whether the proportion of women in a trial should reflect their representation in the population under investigation which may preclude sex-specific analyses if the proportion is low. It could be ethically permissible to not include them or, better yet, to over-recruit women so that sex-disaggregated analyses are possible. One participant questioned whether this point was needed in ethical guidance at all since it was a technical research question and another pointed out that inclusion criteria and issues related to

women and minorities are often a standard item for most institutional review boards.

Women in HIV prevention trials should be informed if there is a potential risk to them or the foetus in the event of pregnancy. Excluding women unless they agree to use contraception to prevent pregnancy during the trial has been an issue in microbicide trials – women who become pregnant are typically taken off product. Earlier toxicology studies would help inform the necessity to avoid exposure to a product during pregnancy. Researchers should guarantee that women are provided with access to sexual and reproductive health services. Often women have additional behavioural risks due to limited ability to negotiate safer sex and vulnerability to physical and sexual violence. Research plans and trial designs should provide counselling services on strategies to protect against violence, including couple communication skills and problem-solving techniques.

Researchers need to pay special attention to the involvement of female sex workers who inject drugs in HIV prevention trials given that these women suffer additional stigma and are less likely to utilize health care services. Whether the issues male sex workers face are similar and require similar responses was not discussed. Female sex workers are likely to have greater difficulty in attending clinics and trial sites during standard operating hours, and are at an increased risk of arrest and abuse by police. Their inclusion as participants might require collaboration with human rights NGOs, medical treatment facilities, legal aid services, and prison authorities to reduce the risk of rape and other forms of violence should they be incarcerated during the course of the trial. One participant noted that including sex workers who inject drugs raises the issue of appropriate remuneration, particularly given the potential loss of income incurred by women as a result of study visits. More generally, it was recommended that this document needs to discuss and establish appropriate remuneration of people who inject drugs who participate in clinical trials as a general principle. Many institutional review boards are still loathe to remunerate drug users and many organizations, especially health clinics, have policies that prevent cash reimbursements for people who use illicit drugs. Such practices/policies are inherently discriminatory and unhelpful. Helping institutional review boards and funders to realize the importance of adequate and respectful incentives for participants who are people who inject drugs is something that both advocates and researchers need to work together on. For a discussion of remuneration see p. 23).

Adolescents (GP 10)

There are sound scientific reasons for including adolescents in HIV prevention trials. At the same time, the inclusion of adolescents who inject drugs adds further layers of ethical and legal complexity. It is imperative that trials are conducted in compliance with protective laws and regulations applicable at the trial sites, including those related to the legal age of consent. Community acceptance and preparedness is essential if adolescents are to be successfully enrolled in HIV prevention trials. Locally relevant cultural beliefs and practices must also be identified and considered when determining the acceptability of research studies involving adolescents who inject drugs. Researchers might include in the study plan a mechanism for the appointment of an advocate or representative of the interests of the adolescents.

As a general rule, the informed consent of a parent or legal guardian will be required, in addition to the assent of the adolescent. There are, however, cases of ‘emancipated minors’ where parental consent is unnecessary. Knowledge of the relevant laws is essential. If, for example, adolescents are not living with their family but are living on the streets, obtaining parental consent may be

impossible. Their inclusion in a trial is possible if local laws provide for 'emancipated minors'. The same would apply where adolescents have parents but there is no official documentation of the relationship. In other cases, often parents will not be aware of their child's injecting drug use so that enrolment of the adolescent would compromise his or her right to confidentiality of information disclosed or discovered in the recruitment process. This may also apply to information collected during the conduct of the trial. Researchers, therefore, should seek the adolescents' permission to disclose the adolescent's use of injecting drugs before making contact with parents, and if they are not willing to do so, they should not be included in the study. Further, as a general rule, parental consent will be required for medical treatment provided - although treatment for sexually transmitted diseases in many settings is an exception - and this would apply also to the provision of NSP and OST[4]. One participant noted that parental consent for NSP or OST could be difficult to obtain and thus many adolescents would not have access to these risk reduction measures. Another noted that in the US, provision of drug abuse treatment to adolescents often does not require parental consent but was not certain if the standards were different elsewhere, for example in Eastern Europe and Central Asia. The applicable local laws would be the determining factor. When community conditions are not favourable and legal constraints pose insurmountable challenges, it may not be possible to enrol adolescents in a trial in a particular area. Researchers should undertake formative research in order to identify and address these conditions prior to making plans for a trial involving individuals below the legal age of consent.

Standard of prevention (GP 13)

The ethical principle of beneficence obligates researchers to minimize risks to trial participants. In HIV prevention studies, researchers should ensure that appropriate counselling and access to available state-of-the-art services for HIV reduction are provided to all participants. These include proven HIV prevention methods, including behavioural counselling and other reproductive health services (family planning, pregnancy and childbirth services) for women. Comprehensive counselling should include basic principles of safer sexual practice, education concerning reproductive and sexual health, including sexually transmitted infections (STI), and strategies to reduce sexual and domestic violence.

With regard to people who inject drugs, counselling should address drug risk behaviours and, specifically, injecting practices. Additionally, access to appropriate HIV risk reduction measures should include the 9 interventions as stated in the WHO, UNAIDS and *UNODC Technical Guide for countries to set targets for universal access to HIV prevention, treatment and care for injecting drug use*.[xxxiii] Further, researchers should ensure participants have access to overdose prevention and management information and, where indicated and available, naloxone should be made readily available.

That said, where laws and regulations prohibit access to NSP or OST, both of which are on the list of universal access interventions, researchers may face the dilemma of competing legal constraints and ethical demands of providing an adequate standard of prevention for people who inject drugs. As a minimum threshold requirement, access to free-of-charge sterile injecting equipment should be regarded as essential, fundamental, and basic to the ethical conduct of an HIV prevention trial conducted among people who inject drugs, in addition to the provision of condoms and HIV risk reduction information. If legal barriers to

[4] Note that one participant asked whether NSP and OST should be considered as medical treatment or as risk reduction. This will need clarification.

the provision of sterile injecting equipment are insurmountable, a trial should not be undertaken. This consideration is in context of an HIV prevention trial; the consultation did not address this issue *vis-a-vis* prevention research more generally. One participant noted that this risk reduction counselling should include information and counselling on other blood-borne viruses.

In some instances, pilot studies of already proven methods have been undertaken to bring about change in law and policy by producing local evidence of the benefit of introducing a measure in a certain locality. However, it is not ethical to conduct trials of HIV prevention interventions that have been proven to be effective over and over again. One participant noted, however, that countries may not be prepared to accept evidence of effectiveness from outside their own countries and trials. Another noted that we may need to define what is meant by 'effective'. Researchers should not experiment with proven interventions, *although it is ethically acceptable* to conduct implementation feasibility and acceptability studies of a proven measure so as to investigate models of service delivery, in order make sure that it is useful for people who inject drugs. One participant pointed out that the stance that it is unethical to test proven interventions would seem to declare current research on buprenorphine plus counselling versus placebo plus counselling to be unethical. This research is being conducted primarily to increase likelihood of political acceptance of buprenorphine in countries where it is not currently available. While there are fundamental ethical problems with doing such research, researchers may respond that: 1) increasing political acceptance is a legitimate goal of research, and 2) all of the subjects in the research potentially benefit—even the placebo group is getting counselling which they would not receive in the absence of the research. Participants recommended a nuanced discussion of this issue to evaluate models of service delivery and to consider, for example, additional implications, such as whether both experimental and comparison groups would get the medication after the trial if the trial did show that buprenorphine reduced HIV infection.

Care and treatment (GP 14)

Sponsors and investigators have an obligation to ensure that participants who become infected with HIV during the course of a trial have access to HIV care and treatment regimens from among those internationally recognized as optimal, including antiretroviral therapy (ART). The obligation to ensure treatment to those who are medically eligible also extends beyond the life of a trial. Researchers may encounter difficulties in ensuring optimal care if the trial is to take place in a country in which the local standard of care is not optimal, due to limited resources or country priority-setting. Research with people who inject drugs can pose additional challenges when discriminatory policies and practices or attitudes of health care providers pose barriers or even block access to treatment for people who inject drugs, violating human rights principles. It is absolutely crucial that agreements among key stakeholders, including representatives of people who inject drugs, on the provision of care and treatment for those who seroconvert be reached in advance of trial commencement. As one participant noted, there is not always consensus on who is responsible to provide care and treatment – research staff or via a referral mechanism – and so advanced agreement is absolutely crucial.

Moreover, trials may involve drug injecting participants who suffer other health conditions that are related to drug use and require attention and care. These include co-infection with viral hepatitis, for which treatment is highly expensive. Targets for universal access to prevention, care and treatment for people who inject drugs can be found in the previously mentioned *Technical guide* developed

by WHO, UNODC and UNAIDS.[xxxiv] This document determines a package for the prevention, treatment and care of HIV among injecting drug users that includes nine interventions (see box below). One participant noted that it may be difficult to remove this list from its context (i.e. targets for universal access) and make it a list of conditions for clinical trials. "If agencies and donors can't seem to implement this should we be expecting researchers to do this?"

1. Needle syringe programmes
2. Drug dependence treatment (OST and other)
3. HIV testing and counselling
4. Antiretroviral therapy
5. Prevention and treatment of sexually transmitted infections
6. Condom programs for people who inject drugs and their sexual partners
7. Targeted information, education and communication for people who inject drugs and their sexual partners
8. Diagnosis and treatment of or vaccination for viral hepatitis
9. Prevention, diagnosis and treatment of tuberculosis

There may also be additional ethical obligations which are not covered by the list. For example, in order to ensure prevention of overdose, the participants should be provided with naloxone or other overdose antidote. Consideration should also be given to the issue of interaction of illegal substances that people who inject drugs use with trial products as well as provided treatments (such as antiretroviral therapy and tuberculosis medications). Antiretroviral therapy alone may not be sufficient for opioid dependent patients; treatment for other psychiatric problems related to illicit drug injecting might be indicated. It should also be recognized that general HIV prevention, testing and treatment (including monitoring of immune status and viral load) services may be less accessible for people who inject drugs than for other groups[xxxv] and there was a discussion about whether research should be used as an opportunity to help them engage with these services (for example psychological support and counselling for themselves and family members). If people are homeless and living on the street, they may also have basic needs for water and food, and the statement was made that researchers have an ethical obligation to take care of those who help them get data. In response, it was noted that while "this is an admirable statement, it is not applied in high income countries and probably could not be applied in low/middle income countries." In some research with homeless drug users in US, a drop-in centre was provided where people could rest, have coffee (and, when funds were available for this in the research budget, take a shower). Crisis counselling was made available when emergencies arose in their lives, and people who inject drugs were provided referrals to local services. But there was not any real capacity to provide for basic needs such as food.

Behavioural research often takes a public health approach with a prescriptive definition of trial participants for effective community level.[xxxvi] This means that the trial does not only involve those recruited and enrolled, but that it includes all the people who use drugs in the community even though they are not all identified. Ideally, therefore, the aim of researchers should be to establish a standard of care in the entire community. But the financial constraints of limited funding for social science research and evidence-based public health programs raise practical questions of feasibility. (See further below – 'Availability of outcomes' and 'A rights-based approach')[5].

[5] See also Treloar et al in Vaccine 2010

Control groups (GP 15)
It is unethical to conduct a study where a proven risk reduction package is not provided to the control group. If the measure is known to be effective, it is unethical to randomize participants into a control group and deprive them of a potentially life-saving intervention. Meeting participants discussed one study which was deemed to be unethical because it did not provide or inform the respondents about HIV risk reduction measures that were available to those in the intervention group in a separate locality. Recognizing that the group without access to risk reduction measures was getting infected with HIV, concerned advocates brought in clean syringes to distribute. While the study is purported to have contributed to the development of a NSP where there had not been any previously – a very positive outcome – existing ethical guidelines do not support holding back a known risk reduction measure.

One participant noted that consideration should be given to a "stepped wedge" design, in which interventions are phased in to communities in a random order. This is generally considered ethical as all communities eventually receive the HIV intervention, even if communities do not receive the intervention at the start of the study. It is often used when there are not sufficient resources to begin the intervention simultaneously in all communities[6].

Further discussion is needed on the issue of appropriateness of using randomized clinical trial designs in trials of interventions with previous sound evidence of effectiveness and life-saving potential. Such designs, it was asserted, are often used on political ("advocacy") grounds. It was not clear at the consultation if consensus was reached on the whether there are, if ever, conditions in which it is ethical to conduct trials which withhold known successful interventions for advocacy grounds. At the same time, it seemed generally clear that, as with the case of NSP trials described above, it would be unthinkable to deny one group of people with whom researchers have established contact stable provision of a lifesaving intervention. There seemed to be more doubts that the same is the case for naloxone trials or buprenorphine/placebo trials. As one participant noted in comments on the draft report, "I think I understand the political implications and the fact that there may be nuances in interpretation, but generally, I'm not convinced with the argument that these people "would die anyway" and we can provide them with this great chance to die in the sake of their communities and other lives saved. People could die, BUT we already established access and had a chance to save their health and possibly lives by providing what we know works. What do I feel as a researcher having to randomly allocate people in the cohorts of more chance to live / more chance to die? And then establishing monthly and sometimes years relations, sometimes friendships with people in the study and having to lose some of them just because they didn't have enough luck to be in my live group – it just seems too much. So I think what was missing in our consultation - and subsequently the report - is a discussion of the difficultness of this situation for researchers in the drug field with RCT being the standard of evaluation, and politically demanded in many cases, but so ethically unacceptable… and alternative designs that could be suggested in these situations – maybe not so scientifically ideal (but the science is behind these interventions already!!), but ethically appropriate."

Informed consent (GP 16)

[6] For more on phased interventions, see, for instance: Statistical design of THRio: a phased implementation clinic-randomized study of a tuberculosis preventive therapy intervention: Moulton LH, Golub JE, Durovni B, Cavalcante SC, Pacheco AG, Saraceni V, King B, Chaisson RE.Clin Trials. 2007;4(2):190-9.

Each participant should provide voluntary informed consent at each stage of an HIV prevention research study, including screening, testing for HIV status, follow-up and monitoring. Informed consent is a process of ongoing communication and researchers should ensure that participants continue to understand and to participate freely throughout the progress of the study.

Competence and capacity to understand information
The general presumption is that all adults are competent to give informed consent. In the case of people who inject drugs, that capacity might be impaired by intoxication, withdrawal, or comorbid mental health issues. Clinically significant cognitive impairment makes it impossible to obtain informed consent. Sometimes participants will not be fully conscious, and are unable to understand the information that is communicated to them. At other times participants will arrive at the trial site in poor condition, perhaps high or intoxicated, but demonstrating good understanding when asked questions. Research team members should receive training so they are able to recognize temporary and long-term cognitive impairment and mental health issues, and assess levels of intoxication at baseline and at subsequent follow-up and whether participants are able to give ongoing informed consent to trial procedures. Research assistants who are themselves former or current injecting drug users may be best-placed to recognize capacity.

Researchers should be aware that often participants lack research literacy and do not understand the difference between diagnostic testing, treatment, and research. They may possess misconceptions about people who inject drugs the nature of research, confusing studies with treatment intervention programs. People who inject drugs who have previous experience of clinical trial research may demonstrate greater understanding of underlying trial constructs, such as placebo or equipoise, than trial-naïve people who inject drugs, but may refuse to accept them.[xxxvii] The point was also made that while important, we should not just be concerned with individual clinical trial literacy but rather with more broadly building community capacity in clinical trial literacy[7].

Researchers need to take responsibility for explaining trial methodologies and their implications, and to conduct comprehension tests in order to ensure that participants fully understand what is entailed in their participation in the study. For example, when they are in need of money or drugs, volunteers are perhaps more likely to cooperate enthusiastically without truly understanding the meaning of simple trial concepts such as home visits or telephone calls. It is the responsibility of the researcher to verify that participants actually understand the benefits and risks of participation. Comprehension tests can also serve as a tutoring tool, and should include several control questions. One participant asked whether a low test result would, in all cases, exclude the potential participant even if participation could be beneficial to the participant[8]. It was suggested that the requirement of a test be treated as culturally specific one: there are cultures which accent a person's autonomy, but in other cultures more weight is given to beneficence.

Remuneration for participation
Researchers should not expect people who inject drugs to participate in HIV prevention trials without remuneration, since that would be exploitative and inconsistent with practices in biomedical HIV prevention trials involving other populations. They should also consider offering remuneration for the screening

[7] See Treloar et al. in press. *Vaccine*
[8] (Note: if there is true equipoise, this is not an issue. The issue is simply the consequences of a low test score regardless of benefit.)

process. One participant noted that it is probably important to provide a justification for this as it is not standard practice. Potential benefits, including access to health care services where indicated, are to be distinguished from participant compensation. Remuneration for participation is not unethical and does not amount to undue inducement so long as it reflects fairly the burden of participation, such as the time, effort and inconvenience associated with study visits, on a scale similar to that offered to participants in other research. At the same time, if a study involves significant risk the offer of large sums of money can amount to undue inducement. In most cases, financial remuneration provides an incentive to participate but will not be coercive or at a level such as to undermine the individual's autonomy or capacity to provide voluntary informed consent.

Motivations for study participation include altruism and financial benefits, and in some settings, people who inject drugs are reluctant to enrol in research trials without financial incentives. When determining the amount, researchers should consider that it may be the case that participants associate higher payment with higher risk. Higher remuneration may also lead to increased speed of recruitment and risk of false subjects (those who do not actually fit the criteria) which should be considered as an issue of study management At the same time, the experience of some participants who took part in the consultation was that many people's motivation to cooperate with researchers can be altruistic, and the stereotype of a person enrolling in a study for cash to buy a next 'fix' may be a discriminatory prejudice[9].

Remuneration for participation may take different forms, such as cash honorarium payments, food coupons, phone cards, stamps for free prescriptions, or access to health care services. The latter could also be provided to participants as part of a broader obligation and not considered to be part of remuneration. In the case of homeless people, shelter and food program access may constitute a form of remuneration. Concerns about providing cash remuneration because it will be used to buy drugs, can be contested, since food coupons and phone cards can also be converted into cash and become a second currency. That said, the larger issue can be framed as one of choice and respect over control: cash payments convey the message that people who inject drugs are respected as members of the larger community and respects their right to exercise choice on how to spend the money they earn. On the other hand, it was surmised that coupons or vouchers could be seen to connote a humanitarian relationship. In choosing the form of remuneration, researchers should take into consideration participant preferences and local conditions. For example, in some locations cash payments will be subject to income tax, and this could compromise confidentiality. Cash payments may also require additional security measures at the trial site, and study staff may feel safer and more comfortable with coupons or cards. At the same time, participants might prefer cash to vouchers, because vouchers lose much of their cash value when sold[10]. What is more, where coupons or vouchers are issued especially for a particular study, they might identify their holders and compromise their confidentiality. A suggestion was made to advise that the nature and amount of remuneration can be best determined in pre-study consultations with the community,[xxxviii] and that the issue of remuneration for screening be discussed separately.

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[9] For further discussion see Fry C, Treloar C, Maher L. (2007). Applied communitarian ethics for harm reduction: Promoting a dialogue within the field. Drug and Alcohol Review 26:553-555; Fry C, Treloar C, Maher L. (2005). Ethical challenges and responses in harm reduction research. Drug and Alcohol Review 24:449-459.

[10] Maher et al. 2010 *International Journal of Drug Policy*

Disclosing risks of participation
During the informed consent process, researchers should disclose all the known risks of trial participation. This includes a discussion of trial procedures in the case of incarceration due to charges and convictions unrelated to the trial, including the extent to which researchers can guarantee .full protection of participants' confidentiality. In particular, they should ensure that participants understand circumstances in which OST, if provided, might be discontinued, so as to warn of the risk of reversion to the use of illegal drugs. They should address further the issue of referral to medical treatment centre if testing positive for HIV or any other STI, and the issue of partner notification, including to spouses, sexual partners, and drug users with whom injecting equipment has been shared.

Ordinarily trial participants would be given a copy of the signed informed consent form for their own safekeeping, but participants who inject drugs might not want to keep a copy for fear of exposure. Researchers should ask whether they prefer that the research team alone keeps the signed consent form and provides them a copy on request or if they want a copy for their personal records. The possibility of oral informed consent, often done in cross-sectional studies - should also be discussed. Signature on the informed consent form may be an issue if people feel uncomfortable leaving their signature, particularly if participation in the trial is intended to be anonymous. People should be given a possibility to avoid signing documents, including the informed consent form, as long as the questions of consent can be verified by other means and consent is documented as having been provided for legal protection of the research team.

Confidentiality (GP 18)
HIV prevention trials in general require researchers to develop and maintain procedures to protect the personal data of participants and maintain the confidentiality of information collected. Researchers may need to take heightened data protection measures when trials involve people who inject drugs, so as to protect information of participants' drug use or other illicit behaviour from disclosure to law enforcement or other authorities or the public. To protect the privacy of trial participants, identifiable personal data should be collected only by people who have signed a confidentiality agreement. Ideally, personal identifying information of candidates and participants should be protected by double codes for anonymizing participants. The keys to the codes should be kept in a secure and safe place. No identifiable information should be stored at the research site or on the trial's database, so that it cannot be found in the event of a police raid. Similar measures should be taken also to protect data that are held by peer outreach workers.

Concerns were expressed about the potential for authorities to confiscate confidential trial information and data, including, for example, electronic databases and computers. Given these concerns, researchers might consider the feasibility of approaching relevant local authorities to receive official permission or support for conducting the trial, prior to its start, so as to ensure the safety of participant information. For example, in the USA a "certificate of confidentiality" may be issued by the Public Health Service, stating that staff members of the research project may not be compelled to provide any identifying information about participants that the project has collected.

Researchers also should be aware of legal exceptions to their duty to maintain confidentiality, including conflicting duties to report individuals' health status under public health laws and regulations. Likewise, child protection laws might require them to report abuse and neglect of adolescents who participate in trials, or of participants' children. Researchers must verify that participants understand

the limits of their power to guarantee full protection of confidentiality and privacy. A specific statement about confidentiality and partner notification may be needed.

Availability of outcomes (GP 19)
In biomedical HIV prevention trials in which the intervention is proven to be successful, steps should be taken to make the tool or intervention available as soon a possible to all trial participants. When pharmaceutical companies test a new drug, they generally agree that, if the drug is effective, they will provide the drug at no cost to research participants after the trial. However, they do not take on the responsibility of providing the infrastructure that may be needed to supply the drug safely. Likewise, behavioural researchers are generally willing to make the materials needed for the intervention (manuals, videos, staff training procedures, etc.) free of charge at the end of a trial but do not have the resources for providing staff, facilities, etc. By the same token, it would be unethical to withdraw a behavioural intervention in a study with people who inject drugs that is shown to be beneficial during the study. If the findings of the trial are not taken on by government and the community, then people who inject drugs are not going to benefit. Researchers should negotiate agreements about standard of prevention during the trial and following its closure whether the intervention is found to be effective or not. Plans for access to an effective trial product should be made before the trial commences, so that any knowledge of benefit that helps to strengthen HIV prevention among people who inject drugs continues to be available to all participants in the trial in which it was tested, as well as to others in the local community of people who inject drugs, after the trial is completed. One participant noted that '[w]e need to think this through – for example what about where research shows that an intervention is efficacious but the intervention is expensive (e.g. medically supervised injecting centre) or the government is hostile to the intervention and refuses to fund it regardless of the evidence.' In keeping with standard expectations, researchers also need to consider communications strategies for informing communities and media of trial results,. Participants and global partners should be informed before the public, and special attention should be paid to confidentiality concerns. It was noted that informing participants may be difficult as some may no longer be contactable.

Financial resources for behavioural intervention trials are limited and it is difficult to secure commitments for additional funds so as to provide the effective behavioural intervention on a post-trial basis. National governments may not agree to include the newly proven intervention in standard HIV prevention programs, and city level governments are even less likely to do so. Concern was expressed that researchers cannot take on responsibilities that are not feasible. Applying the same ethical standards as those applied to biomedical trials would impose exaggerated expectations and have the potential to cripple behavioural research. On the other hand, not negotiating post-trial access to a potential behavioural intervention would suggest a 'research for research' approach which would itself be unethical.

There was a view that funding issues are merely practical constraints that should not negate or reduce the ethical obligation of researchers to provide participants with post-trial access. Therefore, behavioural scientists need to find creative ways to promote ownership of results by communities of people who inject drugs, and to partner with NGOs and some of the 'deep pockets of the world', so as to plan in advance how to roll-out an intervention if it proves to be effective, as a joint responsibility. If governments cannot afford, or do not have the political will, to fund the intervention, foundations could be sought out. Researchers might also prepare a dissemination plan in collaboration with existing services so as to establish a good standard of care in the community that can be continued.

A rights-based approach

A rights-based approach draws inspiration from the obligation of governments to respect, protect, and fulfil human rights under UN covenants, conventions, and declarations. The most relevant document in the present context is the International Covenant on Economic, Social and Cultural Rights, 1966 (ICESCR). Article 12 of the ICESCR articulates the right to health as "the right of everyone to the enjoyment of the highest attainable standard of physical and mental health." The article also refers specifically to the prevention, treatment, and control of epidemic diseases, and this should be considered as a core obligation. At the same time, Article 2 of the ICESCR recognizes constraints of limited resources, and it provides as an overriding principle that the obligation of states is to take steps, to the maximum of their available resources, "with a view to achieving progressively the full realization of the rights recognized under the present Covenant". The principle of 'progressive realization' is relevant to the obligations of researchers in HIV prevention trials, to provide HIV risk reduction methods, and care and treatment, as well as to post-trial access to study interventions that have been demonstrated to be safe and effective.

The principle of 'progressive realisation" recognizes that steps need to be taken to fulfill the obligation, but it does not have to be done all at once. It is analogous to the concept of ethical 'aspiration', as opposed to an ethical 'obligation'. If a course of action is described as an ethical obligation (expressed in terms such as 'should', 'must' or 'will'), then normally the action should be done, and while exceptions to that course of action are permissible, these exceptions require a strong ethical justification. For example, a certain obligation may conflict with a higher or same level obligation, so that they cannot be both fulfilled simultaneously. A course of action expressed in terms of an ethical aspiration (expressed in terms such as 'making good faith efforts') implies that following the course of action to pursue the ethical ideal is admirable or commendable. In this context, the practical application of the concept needs to be carefully thought through. It is important to consider, for example, whose responsibility is it for progressive realisation - the next set of trial researchers? Is there an expectation that each trial must improve on the last in terms of progressive realisation?

At the very least, access to sterile injecting equipment is a threshold essential element for conducting HIV prevention trials with people who inject drugs, together with the provision of condoms, risk reduction counselling, and education. Some would argue that the researcher is obligated also to ensure trial participants' basic needs for food and water although this, as discussed earlier, is difficult to put into practice and goes beyond what is standard in many trials. Other components in HIV risk reduction and care and treatment packages may be addressed as a matter of 'progressive realisation' if they cannot be provided at once. Exactly how this works is unclear – is it within the trial or over time, between different trials?

It is worth noting that it took several years for a consensus to form as to the obligation to provide ongoing antiretroviral therapy to participants who acquired HIV infection during the course of a biomedical intervention trial. During the interim period, there were countries in which trials did not take place because they could not implement the standard of care. In other cases, researchers negotiated with sponsors and government to create an earmarked fund for antiretroviral therapy in case a participant became infected, so that trials could proceed. In most cases, the standard of care developed faster in the country, and there was no need to use the fund.

Conclusions and recommendations

Providing access for people who inject drugs to effective HIV prevention tools is a critical global public health issue. Given the specific vulnerabilities of people who inject drugs, including legal risks, stigma and discrimination, their inclusion in HIV prevention research trials poses ethical and participatory challenges that require special consideration.

(1) General conclusions

1.1 Many challenges to HIV prevention research with people who inject drugs are related to the illegality of drug use and aggressive law enforcement measures and policing practices. Additional challenges are posed by legal barriers to accessing proven HIV risk reduction methods, such as access to sterile injecting equipment and opioid substitution therapy and access to overdose antidote drugs. Given that researchers loyalty must lie with study participants and the ethical conduct of a trial, researchers will need to reach an agreement before a trial begins with host country national Ministries of Health and law enforcement agencies on a range of issues, including but not limited to participant safety and confidentiality and risk reduction packages offered to participants and relevant others.

1.2 Trials should not be conducted in places where there are insurmountable legal and regulatory barriers to access or provision of free-of-charge sterile injecting equipment for participants, or where researchers cannot guarantee protection of participants' rights and safety.

1.3 If community engagement is to be meaningful, it is important that the concerns of community representatives of people who inject drugs be taken seriously and heeded, and it is not sufficient merely to elicit their voices. Communities should be meaningfully engaged early and continuously across the entire life cycle of the research project.

1.4 Research teams working with people who inject drugs should be respectful and open to learning about the social, structural, and legal environment of people who inject drugs. This will include becoming knowledgeable about prejudice and discriminatory attitudes faced by people who inject drugs.

1.5 Researchers should adopt an incarceration protocol for the event of trial participants being arrested in the course of a trial, so as to continue their participation while in prison, if they consent. Researchers should ensure that this occurs without compromising their right to confidentiality vis-à-vis prison personnel or placing participants at risk of discrimination or abuse because of their health status. Note that for some trials, e.g., a couples counselling trial, continuation while incarcerated is simply not feasible. .

1.6 As a general ethical principle, trials that can be conducted elsewhere in the general population may not be conducted in prisons. Phase I and early phase 2 trials of safety should not be conducted in prison settings. If, however, the research is designed specifically for the prison setting and for the direct potential benefit of the participants and other future prisoners, ethics committee approval may be given. In such cases, researchers should give due consideration to various ethical aspects of minimizing risks to participants, guaranteeing confidentiality, and protecting the inmates from undue influence and coercion to participate, including retaliation for refusing to cooperate. Researchers should also consider the importance of ensuring prisoners access to the standard of prevention and treatment available in the community. Whether research should be conducted in compulsory drug dependency treatment centres, requires a

different and in-depth discussion. We have not considered these centres in the term ‘prison’.

1.7 The environment and services related to the research should consider the special needs of women who inject drugs in terms of child care, provision for or referral to reproductive health services, and appropriate hours of clinic operation, and provide also for counselling services on strategies to protect women against violence.

1.8 The inclusion of women who engage in sex work might require collaboration with human rights NGOs, legal aid services, and prison authorities to reduce the risk of rape and other forms of violence while in jail. It was also questioned whether this should be restricted to ‘jail’ settings and further whether this is a research issue, or more fundamentally a human rights and legal issue.

1.9 If adolescents are not living with their families their inclusion in a trial will be possible only if allowed as ‘emancipated minors’ under local law. When constraints of protective child laws pose insurmountable challenges, it may not be possible to include this group in prevention trials.

1.10 Researchers should not conduct trials with proven interventions with the aim of bringing about change in law and policy. This does not preclude conducting implementation research.

1.11 In terms of standard of prevention, access to sterile injecting equipment should be regarded as essential and a minimum threshold requirement for the ethical conduct of HIV prevention trials among people who inject drugs, together with the provision of condoms, risk reduction counselling and education.

1.12 In terms of treatment and care, researchers have an obligation to ensure provision of treatment for co-infections, in addition to the provision of antiretroviral therapy, for participants who acquire infection during the trial[11].

1.13 Other components in HIV and risk reduction and care and treatment packages, such as OST, may be addressed as a matter of ‘progressive realisation’ of human rights requirements if they cannot be provided at commencement of the trial.

1.14 Behavioural scientists need to find creative ways to encourage ownership of results by communities of people who inject drugs, and to partner with NGOs, sponsors and governments, so as to plan in advance how to achieve progressive realization of the rights of participants to packages of HIV and risk reduction methods, and care and treatment- This includes post-trial dissemination of and access to behavioural interventions that have been demonstrated to be safe and effective.

(2) Recommendations for background conditions for conducting HIV prevention trials involving people who inject drugs

2.1 Before commencing a project, researchers should undertake a formative ‘preparedness’ study to assess the feasibility of conducting a study under the reigning legal conditions, identify and minimize risks of law enforcement

[11] Note: this point as written did not receive unanimous support as it is too sweeping and unclear in its operationalisation.

interventions, and make considered plans to create a safe and enabling environment for the study to take place.

2.2 To ensure appropriate community representation, researchers should include capacity building and training programs in their early plans. The preparatory activity of building trust and capacity at the community level requires funding, and should be included in research budgets.

2.3 HIV prevention trials should involve people who inject drugs throughout their design, implementation, and management – as community representatives, trainers for research personnel, research assistants, peer educators, and field workers.

2.4 At enrolment and each subsequent visit, participants should be asked to name a trusted person who can be contacted without breach of their confidentiality, in case they miss a scheduled trial visit.

2.5 Where recruitment or follow-up involve street outreach and visits to homes or prisons, researchers need to consider the safety of their team members.

2.6 In the informed consent process, researchers should openly discuss with potential participants the possibility of incarceration unrelated to the trial and the provisions of the protocol, including, for example, if it will be impossible to provide access to sterile injecting equipment or dispense OST in the prison, and whether treatment for withdrawal symptoms can be provided.

2.7 Researchers should seek the permission of adolescent participants to disclose their injecting drug use status before making contact with parents, and if they are not willing to do so, they should not be included in the study.

2.8 Research team members should receive training to distinguish issues of life style, temporary cognitive impairment and mental health consequences of drug abuse, and to assess levels of intoxication at base line and at subsequent sessions and capacity of participants to give ongoing informed consent to trial procedures. It is the responsibility of the researcher to verify that participants actually understand the benefits and risks of participation.

2.9 In choosing the form of remuneration for participation, researchers should take into consideration participant preferences and local conditions.

2.10 Within the informed consent process, researchers should disclose all the known risks of participation, including legal and regulatory requirements to declare infectious diseases to public health authorities or report child abuse, sexual violence or other intimate partner violence to police authorities. This may include notification of sexual partners and of peers with whom injecting equipment is shared, if testing positive for any STI or blood-borne infection. Researchers should make clear any limits on their power to guarantee full protection of participants' confidentiality.

2.11 Researchers should ask whether participants prefer to keep a copy of the informed consent form on record with the research team, rather than receive it for their own safekeeping for fear of exposure.

2.12 Researchers need to take heightened data protection measures when trials involve people who inject drugs. Identifiable personal data should be protected by double codes, and the keys to the codes kept in a secure and safe place. No identifiable information about people who inject drugs should be stored

at the research site or on the study's data base, nor carried by peer outreach workers.

2.13 As the standard of prevention, counselling should address drug risk behaviours and, specifically risk injecting practice, and HIV prevention. Risk reduction packages should include access to sterile injecting equipment and OST. Additionally, researchers should provide access to naloxone or other appropriate antidote drug to prevent death from overdose.

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[i] The consultation was convened by the HIV Vaccine Initiative (HVI), the joint WHO-UNAIDS programme of the WHO Initiative for Vaccine Research (IVR) and the Office of the Chief Scientific Officer (CSO) of UNAIDS,

[ii] The second consultation will be held in November 2010 in Kuala Lumpur Malaysia (Asian region) and the third is planned for Buenos Aires Argentina in March 2011.

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