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Ethical engagement of people who inject drugs in HIV prevention trials

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Note about this report

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This report represents the opinions expressed by the participants of this consultation and does not necessarily reflect the official positions of the World Health Organization or the Joint United Nations Programme on HIV/AIDS.

List of acronyms and short forms used in this report

Acronym or short form	Definition
ART	Antiretroviral therapy
CAB	Community advisory board
CDDC	Compulsory drug detention centre
DSMB	Data and safety monitoring board
Ethical Considerations	Ethical considerations in biomedical HIV prevention trials, guidance document, UNAIDS/WHO (2007)
GPP	Good participatory practice guidelines for biomedical HIV prevention trials, UNAIDS/AVAC (2007)
GP	Guidance point
HCV	Hepatitis C virus
HPTN	HIV Prevention Trials Network
HVI	HIV Vaccine Initiative
ICCPR	International Covenant on Civil and Political Rights
ICESCR	International Covenant on Economic, Social, and Cultural Rights
IEC	Information, education, and communication
IPV	Intimate partner violence
MAT	Medically assisted treatment
MMT	Methadone maintenance treatment
MSM	Men who have sex with men
NGO	Non-governmental organisation
NSP	Needle and syringe programme
OST	Opioid substitution therapy
PWID	People who inject drugs
PrEP	Pre-exposure prophylaxis
RDS	Respondent-driven sampling
REC	Research ethics committee
RSP	Regular sexual partner
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

Background in brief

On 12-13 December 2010, the World Health Organization (WHO) and the Joint United Nations Programme on HIV/AIDS (UNAIDS),ⁱ in partnership with the Centre of Excellence for Research in AIDS (CERiA) and the AIDS Vaccine for Asia Network (AVAN), convened a regional stakeholder consultation specifically focusing on the Asian region with the objective of exploring challenges to meaningful engagement of people who inject drugs in HIV biomedical HIV prevention trials and other HIV prevention research, and to identify strategies that can be employed or have been employed to creatively and ethically address these challenges.

The objective of the consultation was to contribute towards the development of human rights-based and evidence-informed international ethical guidance for meaningful engagement of people who inject drugs in biomedical HIV prevention trials and other HIV prevention research. The meeting was held in Kuala Lumpur, Malaysia, in conjunction with the '*Lancet* Series Symposium on HIV in people who use drugs'.ⁱⁱ held on 10-11 December 2010. The scientific papers presented at the symposium provided a highly relevant evidence base for consideration at the regional consultation.

The Kuala Lumpur consultation was the second of three planned meetings to be convened in different regions with a higher risk of HIV transmission originating from and among people who inject drugs. The first consultation was held in Istanbul, Turkey (June 2010) with a focus on the Eastern Europe-Central Asia region; the third will be convened in the Latin American-Caribbean region in April 2011. This meeting report summarizes the discussions and recommendations from the consultation in Kuala Lumpur.

INTRODUCTION

HIV transmission among people who inject drugs

On the cusp of the fourth decade of the AIDS epidemic, people who inject drugs represent a key population at the highest risk of HIV exposure in many settings around the world. While the numbers of new HIV infections and HIV-related deaths are declining in many countries, especially those in sub-Saharan Africa, due to changes in risk behaviour and increased access to antiretroviral therapy (ART), several regions and countries do not fit this overall trend.ⁱⁱⁱ There is an alarming increase in HIV incidence and HIV-related deaths in Eastern Europe and Central Asia, where drug injecting is a major mode of HIV transmission fuelling new epidemics among people who inject drugs and their sexual partners. Indeed, outside sub-Saharan Africa, 30% of people living with HIV were infected through contaminated injecting drug equipment. In some countries in South East Asia, the HIV prevalence among people who inject drugs is over 40%.^{iv}

The need for advocacy, policy development, and legal and ethical guidance to support the inclusion of people who inject drugs in trials of novel biomedical HIV tools and other HIV prevention research.

The high HIV prevalence among people who inject drugs clearly represents a global health challenge. It is therefore crucial to involve this population and their representatives in all stages of relevant HIV prevention research and clinical trials to evaluate the safety, and efficacy of potential new interventions specifically in this population.

Meaningful and ethical engagement of people who inject drugs in biomedical HIV prevention trials and other HIV prevention research is, however, a very complex task, in part because governments and research entities adhere to highly variable legal, ethical, and regulatory policies and practices that often serve as impediments to the participation of people who inject drugs in trials and other HIV prevention research. One of the burning and controversial issues, for example, is related to definition of the standard HIV prevention package that must be offered to trial participants. In particular, access to sterile needle and syringe programmes and opioid substitution therapy is not, legally provided in many countries, despite their proven effectiveness as HIV risk reduction methods.

There is, therefore, an urgent need for practical international normative guidance for ethical engagement of people who inject drugs in HIV prevention research and clinical trials. The urgency of this need is underscored both by: 1) the rising numbers of people who inject drugs and related HIV transmissions, particularly in Eastern Europe, Asia and parts of Latin America, and 2) the growing movement calling for an evidence-informed, human rights-based approach towards the development of and access to prevention and treatment programmes for people who inject drugs. This guidance needs to address challenges originating not only at the individual level, but also those derived from societal and governmental levels, such as sub-optimal resource allocation and barriers posed by punitive drug laws and harsh policing practices.

The consultation process

WHO and UNAIDS actively promote the development of sound scientific and ethical frameworks to support HIV prevention research and clinical trials with a special focus on low- and middle-income countries and key populations at higher risk of HIV exposure. Two recent products are the 2007 UNAIDS/WHO document *Ethical considerations in biomedical HIV prevention trials* (hereafter - Ethical Considerations)^v and the 2007 UNAIDS/AVAC publication entitled *Good participatory practice guidelines for biomedical HIV prevention trials (GPP)*. These guidance documents, however, do not consider with enough specificity the challenges of engaging people who inject drugs in biomedical HIV prevention trials and other HIV prevention research. Therefore, in 2010, UNAIDS and WHO embarked on a consultation process to develop guidance which would specifically address these challenges, based on respect for human rights, the best available scientific evidence, and regional experiences with high levels of HIV transmission among people who inject drugs. The first of three consultations was held in Istanbul, Turkey (June 2010) with key stakeholders from the Eastern Europe-Central Asia region. Based on the recommendations from this first meeting, a guidance point with commentary was drafted.

The second consultation brought together key stakeholders in the South and South-East Asia region in Kuala Lumpur, Malaysia on 12-13 December 2010. The broad objective of the consultation was to further refine the ethical guidance drafted in Istanbul, while also addressing issues of special importance for the Asian region. The consultation was organised in conjunction with the 'Lancet Series Symposium on HIV in People Who Use Drugs', held at the University of Malaya on 10-11 December 2010. Presentations and discussions at the symposium supplied an evidence base for the deliberation on ethical guidelines for biomedical HIV prevention trials and prevention research.^{vi}

This report summarizes deliberations, conclusions, and recommendations from the Kuala Lumpur consultation. A third consultation will be held in the Latin American-Caribbean region in April 2011. The three meeting reports will form the basis of a discussion/policy paper for publication in an open access journal.

Emerging considerations

HIV prevention is a dynamic and rapidly changing field as evidenced by recent new trial findings. Between the Istanbul and the Kuala Lumpur meetings encouraging results were reported from two large biomedical HIV prevention trials. On 19 July 2010, at the International AIDS Conference in Vienna, results were announced from the microbicide trial conducted by the Centre for the AIDS Programme for Research in South Africa (CAPRISA). The trial assessed safety and effectiveness of a 1% tenofovir vaginal gel formulation for the prevention of HIV acquisition in women. This double-blind, randomized controlled trial compared 1% tenofovir gel ($n = 445$ women) with placebo gel ($n = 444$ women) in sexually active, HIV-uninfected 18- to 40-year-old women in urban and rural KwaZulu-Natal, South Africa. The vaginal gel reduced HIV acquisition by an estimated 39% overall, and by 54% in women with high gel adherence.^{vii}

Not long after, on 23 November 2010, the iPrEx trial published results providing the first evidence that pre-exposure prophylaxis (PrEP) can reduce the incidence of HIV infection. The trial study evaluated the impact of oral PrEP in tablet form among men and transgender women who have sex with men. A total of 2,499 individuals participated in the six-country study. All participants received a

comprehensive package of prevention services designed to reduce their risk of HIV infection throughout the trial, including HIV testing, intensive safer sex counselling, condoms, and treatment and care for sexually transmitted infections (STIs). Half of the participants also received a daily tablet containing a combination dosage of two widely used antiretroviral medications, while the other half received a placebo. Individuals assigned to take the active agent experienced an average of 43.8% fewer HIV infections than those assigned to take the placebo tablet.^{viii}

It is understood that no single HIV prevention strategy or intervention will be effective on its own. A multi-faceted combination approach will be necessary to halt and reverse the HIV epidemic. These trial results add important new components to the combination prevention package of biomedical, behavioural, and structural strategies that should be at the centre of any response to HIV. However, more research among people who inject drugs is necessary as their numbers have been few in published trials to date.

Ethical considerations

(1) General

At the Istanbul consultation, participants developed recommendations for ethical engagement of people who inject drugs in HIV prevention research by addressing and applying the guidance points (GPs) of the Ethical Considerations guidance document to a wide range of legal, regulatory, structural, social, and logistical challenges. In contrast, discussions in Kuala Lumpur primarily focused on three key questions with high relevance for the Asia region, namely:

- (1) Whether there should be a minimum threshold requirement for risk reduction modalities offered to both experimental and control arms, without which trials may not be conducted as a matter of ethical principle? If so, what should that minimum requirement include? (GP 13 – standard of prevention);
- (2) Whether - and under what conditions – biomedical HIV prevention trials and other HIV prevention research among people who inject drugs can be conducted ethically in prisons and compulsory drug detention centres? (GP 8 – vulnerable study populations); and
- (3) Whether certain forms and amounts of remuneration for participating in research compromise the voluntariness of participation or the quality of the research? (GP 16 – informed consent).

In addition, several overlapping themes that had been discussed in depth during the Istanbul consultation, arose again during the Kuala Lumpur consultation, namely: **community participation** (GP 2), **informed consent** (GP 16), **inclusion of adolescents** (GP 10), and **care and treatment** (GP 14).

Community participation (GP 2) and informed consent (GP 16):

People who inject drugs, like all other populations, should be involved in the entire research life cycle, from the initial stages of conceptualizing a research

study to protocol development, trial conduct, and results dissemination. The challenges of doing so were discussed at the Istanbul consultation^{ix}. At the KL consultation, participants made the point that involving people who inject drugs in research from the very earliest stages will result in better research design and better methods and tools that are culturally sensitive to the specific affected population. This can also facilitate ready and reliable access to hidden populations. Participants at the Kuala Lumpur consultation noted it would be inappropriate ('paternalistic') to exclude people who inject drugs and their organizations from the initial planning phase in order to avoid disappointing the community if the research does occur because of lack of funding, for example.

Participants at Kuala Lumpur also emphasised the need to include representatives of people who inject drugs in community advisory boards (CABs). Questions were raised about the feasibility of participation by prisoners or detainees in such bodies, given risks of reprisal by authorities. In general, as noted at Istanbul, researchers should ensure that community representatives are well informed of any limitations they have in guaranteeing their safety and welfare. It was suggested that researchers should adopt protocols/appropriate procedures that would specify how volunteers are protected from potential action by police or other authorities as a result of their participation as CAB members. For example, in some behavioural studies in Central Asia, researchers provided a letter to CAB members confirming that they were involved in a research study.

Another question was raised about the feasibility of community engagement and obtaining informed consent in China, where regions affected by HIV are often remote and the level of education may be extremely low. Village leaders often lack high school education, traditional Chinese healers rather than physicians serve the population, and participants are often illiterate. Although similar conditions pertain in some parts of Africa, there has been successful community engagement and lessons have been learned about communication with communities and participants.

Children and adolescents (GP 10):

Minors who inject drugs are extremely vulnerable to HIV infection, particularly if they are homeless and living on the streets rather than with their parents or other guardian. In such cases, obtaining informed consent can be very challenging. Some participants suggested that adolescents at high risk of HIV exposure should be able to participate in trials even if obtaining parental consent is not practical. National and local laws must, however, be considered in any research conducted with this cohort, and researchers should consult and negotiate with national authorities prior to considering the inclusion of children and adolescents in trials or other prevention research. No recommendations on this point were made additional to those in the existing Ethical Considerations document or in the discussions in Istanbul.

Care and treatment (GP 14):

People who inject drugs experience multiple health problems, including co-morbidities, such as tuberculosis (TB), hepatitis C virus (HCV), and mental illness, but they often lack treatment resources. Therefore, researchers should be concerned about these co-morbidities and should include the possibility of providing for their treatment, as required, in their planning.

Similarly, women who inject drugs are at a significant risk of intimate partner violence (IPV), which is in itself can be a risk factor for HIV exposure. Participation in a research project or clinical trial may increase women's risk of physical or sexual abuse by a partner. Researchers should be aware of this concern and train study staff to monitor for signs of IPV. They should ensure that safety protocols and treatment resources are in place to help women who experience or are at risk of IPV. In general, behavioural evidence indicates a need to address relationship dynamics between men and women in drug injecting contexts, and their association with higher HIV risk for female partners, whether or not they themselves inject drugs.^x The implications for the design of biomedical HIV prevention trials and other HIV prevention research, even as regards male participants, require further nuanced discussion.

If researchers do not provide treatment services themselves, they should identify and negotiate with agencies that can provide *trusted* care in the locality and/or identify local infrastructures where services could be made available. Creating linkages with existing agencies and local services for referral purposes is essential. To further facilitate access to existing services for participants, research teams can produce a resource manual and provide contact information. Advance preparation by researchers is necessary to ensure that receiving agencies are able and willing to handle increased referrals. It was suggested that biomedical HIV trials and other HIV prevention research involving people who inject drugs should set in place a referral process to legal services for research participants, including to legal aid or other free or low-cost legal services available in the locality.

(2) Standard of prevention (GP 13)

Standard of prevention discussions raise many questions which cannot be answered readily as a matter of principle. For example:

- Should researchers provide people who inject drugs with access to risk reduction methods, as standard of prevention, that are not yet available in the community or country where the trial is taking place, so as to upgrade local standards?
- Should trials introduce risk reduction modalities where sustainable access cannot be ensured after the trial ends?
- Should new scientifically validated HIV prevention and risk reduction tools be provided if they are not yet approved by that country's national regulatory authorities?

At the Istanbul consultation, participants discussed whether investigators should conduct trials where there are real or perceived¹ legal restrictions on the provision of proven risk reduction strategies, such as access to sterile needles and syringes. An example of a creative solution to this dilemma is the ongoing Bangkok Tenofovir PrEP study, which is a collaboration between the Bangkok Metropolitan Administration, the Thailand Ministry of Public Health and the USA Centers for Disease Control and Prevention (CDC). The USA federal ban on funding access to sterile needles and syringes – no longer in effect - affected a number of HIV prevention trials. USA-funded researchers could not provide

¹ An example of a perceived legal restriction would be where a regulation is interpreted very broadly so as to apply far beyond its intention. The interpretation of the previous USA federal ban on funding sterile injecting equipment provides a good example of a perceived broad legal restriction.

sterile needles and syringes, as part of the standard prevention package for trial participants. CDC interpreted this ban as providing the possibility that other research collaborators could provide such injecting equipment. As a result, the trial did not include a needle-syringe programme (NSP) but Thai NGOs provided sterile injecting equipment in the community independently of the trial, making it available *de facto* to all trial participants.

Other related questions that arose at the Kuala Lumpur meeting with regard to standard of prevention in trials involving people who inject drugs were:

- Is it ethical to conduct a trial with people who use opiate drugs and randomly assign them to an arm that has only HIV counselling and testing?
- Should investigators conduct research on proven risk reduction interventions solely for the sake of gathering evidence to gain local political acceptance?

Participants agreed that it could be ethically acceptable to conduct feasibility or implementation studies of a proven modality in order to assess feasibility and optimal service delivery models. On the other hand, it would be unethical to design a study with separate intervention and control arms in which a proven risk reduction method is not provided to the control group.

Researchers' dilemma

This question of what should be considered as a standard HIV risk reduction and prevention package to be provided to all arms in an HIV prevention trial can pose a major dilemma for researchers. On the one hand, most HIV prevention trials are end-point driven and are designed to conduct comparative evaluation of HIV incidence rates in active and control groups. The sample size of such trials is highly dependent on numbers of participants who are anticipated to become infected with HIV. On the other hand, there is an ethical *obligation* to help people in both the active and the control arms to remain uninfected by providing known effective prevention methods. However, as more risk reduction methods are added to the HIV prevention package, the less likely it is that trial participants will acquire HIV infection, thereby necessitating a larger and/or longer trial to ensure that the trial is adequately powered and the trial results are statistically significant. Increasing the size of a trial or prolonging the conduct of a trial result in increased costs of the trial, either by increasing the timeframe required for recruitment of sufficient numbers of volunteers or by increasing the length of time that they are followed. This can result in an overall delay in obtaining definitive trial results. However, the participants of the Kuala Lumpur consultation felt that the expense and longer duration of a trial cannot serve as major reasons to override the obligation to provide – or ensure the provision of – proven HIV prevention methods. Specifically with regard to biomedical HIV prevention trials and other research involving people who inject drugs, the primary question that arises is about definition of what comprises proven risk reduction methods and whether they can be provided in the research context in a manner that is safe, sustainable, adequate, and respectful?

The risk reduction package

As at the Istanbul consultation, reference was made to the nine interventions of the 'comprehensive package for the prevention, treatment and care of HIV

among people who inject drugs' articulated in the WHO, UNODC and UNAIDS Technical Guide, 2009.^{xi} While researchers may aim to provide all these interventions in HIV prevention research, this may not always be technically feasible. The question is, whether there are components in the package of risk reduction modalities that are non-negotiable. In other words, should there be a minimum threshold requirement for risk reduction modalities that are offered to both experimental and control arms of a study, without which trials could not be conducted as a matter of ethical principle?

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^{xii}

Access to Sterile Needle and Syringe Programmes

The Ethical Considerations guidance point GP13 states: "all participants must receive appropriate counselling and access to state-of-the-art HIV risk reduction methods." It also states that biomedical HIV prevention trials should not be conducted where a survey of local laws and regulations indicates insurmountable legal barriers (p. 13). The Istanbul consultation recommended that access to 'free-of-charge' sterile injecting equipment should be regarded as a minimum threshold requirement, and that a trial should not be undertaken if legal barriers to the provision of sterile injecting equipment were insurmountable.^{*} At Kuala Lumpur, participants agreed that 'access to sterile needles and syringes' without law enforcement interference is a must both during and after the completion of the trial. However, it was not necessarily the duty of researchers to provide sterile needles and syringes themselves or to guarantee that access is free-of-charge, so long as access is assured and affordable elsewhere in the community. Thus, people might have access to affordable sterile needles and syringes that are not provided by the researchers, through either low cost pharmacy sales or free provision outside the trial setting. Discussants at Kuala Lumpur concluded further that researchers are encouraged but not obliged to ensure people have access to all sterile injecting equipment such as cookers and water, as this may not be possible or prove onerous in resource-poor settings. An ethical obligation to provide all the equipment might undermine the possibility of conducting important trials.

^{*} Note the comment in the Istanbul meeting report: "This consideration is in the context of an HIV prevention trial; the consultation did not address this issue *vis-à-vis* prevention research more generally." Neither did the Kuala Lumpur consultation address the question directly with regard to behavioural and structural HIV prevention research.

Voluntary counselling, information, education, and communication

Many participants thought it necessary to emphasize that all risk reduction modalities should be offered including drug dependency and risk reduction counselling, and HIV counselling and testing, noting that 'counselling' is fraught with bad connotations and experiences for some people who use drugs. Others stressed the need for information, education, and communication (IEC) on access to community resources and services - including treatment for HIV, drug use, and STIs, as well as IPV and sexual and reproductive health. Participants stressed that trial participants must be free to accept or decline the offer of any or all of these risk reduction methods.

Sexually transmitted infections: Participants considered that diagnosis and treatment of STIs are risk reduction measures for trial participants who inject drugs. Some suggested that the package of prevention modalities should include syphilis screening and treatment, because of evidence that HIV spread is slower among people who inject drugs in countries with low syphilis rates.

Food and water: While the Istanbul consultation produced a suggestion that researchers should also address the basic needs of people who inject drugs for food and water, participants at the Kuala Lumpur consultation agreed that provision of food and water on site should be an ethical obligation for conducting HIV prevention research among people who inject drugs.

Naloxone: Most participants at Kuala Lumpur agreed that access to naloxone to reverse opiate overdose should be a minimum threshold requirement for engaging opioid-dependent people as trial participants, since it would be unacceptable to allow people to die from overdose in the course of a trial. But some participants noted that providing naloxone can be expensive and involve complicated regulatory issues. For example, in Australia, naloxone requires a prescription and legal administration is currently limited to doctors and paramedics.

Opioid substitution therapy: There is scientific consensus that for people who inject drugs, NSP and OST are essential for HIV prevention. Researchers should engage in advance planning and discussions with relevant stakeholders to negotiate provision and access to all three modalities if they are not already available and accessible in the locality. But there was disagreement as to whether researchers have an ethical obligation to provide or ensure provision of OST to opioid-dependent participants who want it, as a minimum threshold requirement without which the research may not be conducted as a matter of ethical principle.

On the one hand, OST is recognized as one of the most effective programmes available for the treatment of opioid dependence and a critical component of efforts to prevent the spread of HIV among people who inject drugs. When OST is appropriately dosed and managed for medication interactions, it enhances adherence to ART, treatment for co-morbidities, and retention in HIV care, reduces illicit heroin use and decreases drug-related HIV risk behaviours, including injecting frequency and the use of contaminated injecting equipment.^{xiii} On the other hand, it is expensive, requires appropriate dosage and management of medication interactions, requires government cooperation for import and distribution, and is often delivered under controlled, strict conditions. Registration of those enrolled in OST can, when undertaken by regimes with

harsh drug policies and policing practices, compromise confidentiality, safety, and life opportunities.

Ideally, voluntary access to OST should be ensured for participants during a trial and post-trial access conditions should be negotiated before the start of a trial or research project. However, in some countries and settings the provision of OST may be illegal, while in others it may be impossible to ensure appropriate long-term post-trial access to OST. Some participants thought that countries that refuse to provide OST should not serve as locations for research, since research should build on existing demonstrated standards of prevention and researchers can find enough sites that do provide OST. Others thought that it was wrong to prevent populations from having access to potentially effective interventions and other benefits of participating in research as a result of restrictive country policies. One participant suggested, at the very least, that researchers, community members, and the UN family have an ethical and scientific obligation to advocate for OST where it is not available to trial participants.

Summary

In summary, there was consensus at Kuala Lumpur that it is unethical to conduct research in situations where there is no access to sterile needles and syringes, and that researchers must provide male and female condoms; voluntary counselling and testing; information, education, and communication; STI diagnosis and treatment; and food and water on site. But there was disagreement about the ethical obligation to provide OST and naloxone.

At the same time, it was understood that some of the more controversial risk reduction modalities provided as standard of prevention in HIV prevention trials would be negotiated in advance on a case-by-case basis with relevant stakeholders. Clearly, the specific components of the risk reduction package would also depend on the modality that is being tested. For example, it does not make sense to talk about OST when discussing HIV prevention among amphetamine users.

In conclusion, the following text was suggested as part of the commentary to a new guidance point on people who inject drugs for the Ethical Considerations guidance document:

“In HIV prevention studies, researchers should ensure that appropriate voluntary counselling and access to evidence-informed services for risk reduction are provided to all participants. With specific regard to people who inject drugs, counselling should address drug risk behaviours, safe injection practices, safer sex options, and prevention of intimate partner violence. Access to sterile needles and syringes, provision of medical opioid substitution or medically assisted therapy for opioid dependence, and diagnosis and treatment of sexually transmitted infections, especially syphilis, are relevant risk reduction measures for trial participants who inject drugs (see GP 13: Standard of Prevention). Additional measures include providing male and female condoms, making food and water available at the research site, educating participants to identify symptoms of overdose and manage them, and providing access to naloxone as an antidote for opioid overdose. Where laws and regulations prohibit access to sterile needles and syringes or opioid substitution treatment, researchers should make every reasonable effort to solve the conflict between local legal constraints and the ethical requirement to provide an adequate standard of prevention. Trials should not proceed if barriers to the provision of sterile needles and syringes are insurmountable.

While it is ethically acceptable to conduct feasibility studies of a proven preventive modality in order to assess optimal service delivery models, it can be unethical to design and conduct a study with separate intervention and control arms, in which state-of-the-art services for risk reduction are not provided to the control group.”

(3) Closed settings (GP 8– vulnerable study populations)

One of the key questions that was specifically discussed at the Kuala Lumpur consultation was whether research could be conducted in the closed setting of compulsory drug detention centres. As a general ethical rule, research that can be conducted in the general population should not be conducted in closed settings – i.e., all facilities of involuntary detention by authorities, including police cells, jails, prisons, and forced treatment, detoxification or rehabilitation centres, whether for adults or juveniles – because individuals are held captive under conditions that may compromise voluntariness of participation. For example, safety and immunogenicity (Phase I and II) trials should not take place at all in closed settings, because there are many other settings in which they can be conducted.

It is worth mentioning in this respect that Article 7 of the International Covenant on Civil and Political Rights (ICCPR) forbids the conduct of scientific experimentation without the free consent of participants, as a particular instance of torture:

“No one shall be subjected to torture, to cruel, inhuman, or degrading treatment or punishment. In particular, no one shall be subjected without his free consent to medical or scientific experimentation.”

Incarceration in prisons and other closed settings increases the risk of HIV exposure because of multiple factors, including disruption of social networks and inadequate treatment of mental illness that may put inmates at a greater risk of substance-use disorders.^{xiv} Moreover, imprisonment is often associated with interruption of ART and OST, and most incarcerated HIV-positive drug users have restricted or no access to any type of therapy. At the same time, the question whether to initiate research in closed settings raises complex nuanced issues. Inmates or detainees must not be simply a convenience sample, recruited because they are a ‘captive’ population unlikely to be lost to follow-up. Likewise, research should not be conducted among detained or incarcerated people who inject drugs with the intention of obtaining information about people who inject drugs outside the closed setting. Given the vulnerability of prisoners and detainees and the potential for ethical abuses inside closed settings, emphasis should be on building capacity to conduct HIV prevention research in community settings, with appropriate resources.

(a) Prisons

In general, the involvement of prisoners in any form of research that poses more than minimal risk, or is not intended to benefit the individual prisoner or prisoners as a class, is presumed to be unethical. At the same time, there are circumstances in which research inside prisons can be justified. In the USA, for example, federal regulations^{xv} define certain categories of permissible research, which include the study of possible causes, effects, and processes of incarceration and of criminal behaviour; the study of prisons as institutional structures or prisoners as incarcerated persons; and conditions particularly affecting prisoners as a class, including HIV, drug use, tuberculosis, hepatitis, and mental illness. In any event, studies conducted inside prisons should set up referral mechanisms and ensure appropriate follow-up plans and continuum of care.

Prisoner representatives

The USA federal regulations require that the research ethics committee (REC), known in the USA as the institutional review board (IRB), must include a prisoner or a prisoner representative. Participants at the Kuala Lumpur meeting suggested, in addition, that investigators should ensure that trial data and safety monitoring boards (DSMBs) include prisoner representatives as members, although it was noted that DSMBs are generally composed of statisticians and safety experts who must follow pre-determined trial stopping rules and are bound by confidentiality. They might also establish an independent community advisory board of former inmates, prison guards, and judges to review and evaluate the study.

Safety and confidentiality (GP 18)

Among other things, prison officials have a duty to maintain safety and to protect all individuals within the environment, including researchers. Thus researchers seldom have free choice with regard to the conditions in which they conduct research inside the prison. For this reason, among others, prison conditions can pose challenges to the ethical obligation of researchers to protect participants' confidentiality. For example, prison authorities might require an officer to be present at all times when an inmate is involved. If the issue is safety, researchers need to negotiate with prison administrators so that participant confidentiality is not compromised. Researchers can employ various techniques, such as the use of audio-computer assisted self-interviews, or conducting interviews behind a window which allows observation without hearing the conversation. Research should not place an already highly vulnerable population at even greater risk of harm. Therefore, safety issues for research participants should also be of concern to investigators.

Prison research protocols

Research in prisons with people who inject drugs poses very specific challenges which research protocols must address. Protocols must give due consideration to issues of voluntariness of consent; strategies for the protection of confidentiality; access to risk reduction packages (e.g., sterile needles and syringes; condoms; OST; monitoring, management, and reporting of adverse events (e.g. availability of medical care and access to such care after hours); and responsibilities to report abuses in prisons.

Incarceration protocols

Researchers should prepare incarceration protocols in advance, not only for community research in case participants are detained in the course of the study, but also for research that starts in prison in case individuals are released and get re-incarcerated. The incarceration protocol should address the reporting and managing of adverse events and continuing access to risk reduction modalities for participants who become incarcerated.

In case of incarceration in a prison (as well as in case of detention in a CDDC), researchers should ask whether following participants into the closed setting entails any incremental risk to those individuals above that which they can be expected to experience regardless of the research. For example, there might be concern that researchers' inquiries about individuals will be taken as interference from 'foreigners' and place participants at risk of reprisal by prison or detention authorities. In an HPTN study in China, opiate injectors were recruited from the community and participants in one arm were to receive HIV testing and counselling every 6 months for 2 years. Researchers were aware that

participants were at risk of incarceration because of their drug use, but did not anticipate that participants would be imprisoned not because of the trial but due to unrelated ethnic tensions. Over twenty participants were detained in a detoxification centre, and the question was whether researchers should follow them or whether it would place them at an incremental risk. In fact, most were released following the investigators' inquiries about this issue.

Following release

Upon participants' release from prison or from another closed setting, researchers should 're-consent' participants, both in order to verify with participants that consent to participate during the period of incarceration or detention was truly voluntary, and to obtain informed consent for continued participation. Re-consent should occur even when the study is taking place in the community and participants gave initial informed consent to the incarceration protocol. An interview with participants post-release also serves to provide an opportunity for researchers to hear from participants what the conditions in prison were like and thereby increase the researchers' understanding of the conditions under which prison research is conducted.

It is known that the first few weeks after release from closed settings pose a much higher risk of opioid overdose, and increased use of potentially contaminated injecting equipment in community settings where there is limited access to sterile injecting equipment. Therefore, researchers should also make plans for post-release activities to assist participants in the transition to the community. These plans might include funding for a social worker or preparation of a resource manual to link participants to available community services, such as NSP and OST. People might also benefit from knowing where they can receive naloxone in case of need. Similarly, when women are discharged they need information about how to access shelters if they are subjected to IPV and abuse. For juveniles, in particular, community connections are needed as a safety net upon release from detention.

(b) Compulsory drug detention centres

In compulsory drug detention centres (CDDCs) researchers must first consider the basic legitimacy of the setting. These facilities are often administrative detention centres operating outside the review of the judicial system. As opposed to incarceration in prisons, detainees are unlikely to have appeared before a judge or to have a right of appeal before a court of law. The catalogue of so-called 'treatment' in many of these facilities includes military-type drills, physical exercises, and experimental treatment that lacks scientific evidence to support its effectiveness. In some places, CDDCs are essentially drug-free forced labour camps, where detainees report routine violations of human rights, including beating, food deprivation, and psychological and physical abuse. Conditions might be cruel, inhuman, or degrading. Infractions such as talking back to staff can be punished in discipline rooms where detainees are placed in stress positions, severely beaten or tasered. Typically detoxification is not assisted medically and there are those who view this, in itself, as a form of torture.

Can there be meaningful engagement with community when the community representative is a foreman who beats the detainees? Is it possible to obtain voluntary informed consent in conditions where refusing to follow orders is punishable by torture, and can researchers protect those who refuse to participate from retaliation? How realistic is it to require access to risk reduction methods when minimal conditions of human dignity are not observed and

detainees say “we want not to be beaten and not to starve” or “there was only a little rice”? In practical terms, the system might be so systematically dehumanizing that meeting the basic ethical standards for HIV prevention research would be difficult if not impossible.

Research in CDDCs poses a dilemma of ‘the rotten compromise’. On the one hand, conducting research in these settings may be seen to give them legitimacy. There is a humanitarian impulse to help to alleviate suffering, but perceived collaboration by researchers might perpetuate the wrong. It could be argued that if we want to learn about these environments it is better to intervene with people post-release, and ask them then to find out what is going on. On the other hand, research can play a role in documenting and reporting abusive conditions and introducing mechanisms to improve conditions and thus benefit the detainees. For example, one participant at Kuala Lumpur suggested that an intervention in one such facility had actually resulted in an improvement in prevention, treatment, and care.

Humanitarian principles

How do we balance potential benefits and risks of research in such settings? First and foremost, it should be clear that ethical research cannot be conducted with people being tortured—if torture is occurring in the facility, research should not. In brief, research should not commence if there is reason to believe that research participants will be tortured. If research is being planned, researchers should insist on unimpeded access to participants without advance notice, to be sure that they are not being maltreated. If the researcher becomes aware of cruel, inhuman, or degrading treatment which he or she cannot stop, the research must stop. Therefore, there must be a protocol for reporting and responding to adverse events related to torture, cruel, inhuman or degrading treatment, and coercion (in addition to medical adverse events). The reporting requirements should be communicated in advance to the directors of the facilities, and researchers should interview detainees upon release to ensure an accurate understanding of the conditions within the closed setting in which they are conducting research.

There was general agreement that if research is conducted at all within CDDCs, it must observe several humanitarian ethical principles that should be negotiated in advance with the relevant authorities:

- a) Researchers must have unimpeded access to detainees without advance notice to authorities and without the presence of a custodian or guard within hearing distance (unless requested for the protection and safety of the research staff).
- b) Informed consent must be obtained at a face-to-face meeting in the absence of any custodian. The research can take place only if researchers are assured that refusal to participate will not prejudice the individual and can guarantee that no data about individuals will be shared.
- c) Research cannot be conducted in facilities where torture or cruel, inhuman, or degrading treatment occurs. If researchers learn of such violations of human rights, they will challenge them and stop the study in that facility if the practice does not cease.
- d) Detention authorities may not make public use of the research collaboration so as to justify the existence of the facility or suggest endorsement of its approach to drug dependence.
- e) Publication of papers, reports, and findings does not require approval or vetting by detention and governmental authorities.

(4) Remuneration for participation in research (GP 16 – informed consent)

To what extent does remuneration for participating in research compromise the voluntariness of participation or the quality of the research? The ethics of remuneration to people for participating in research remains controversial. Many research ethics committees (RECs) judge that providing more than the most basic remuneration or paying cash to people who inject drugs will have inevitable negative consequences, but these concerns are not evidence-based. One North American study found that neither the magnitude nor the mode of payment had a significant effect on drug use frequency among study participants. Most often reported uses of remuneration were for debts and household or personal needs. Moreover, higher remuneration and cash payments resulted in higher follow-up rates, increased satisfaction with the study, and a greater willingness to participate in future research. An ongoing hepatitis C (HCV) preparedness study in Australia found a range of motivations for study participation but the two most important were altruism and financial remuneration. Participants viewed remuneration for participation in research as an opportunity to generate legitimate income and to “do something useful”.^{xvi}

Remuneration can be reimbursement for expenses (e.g. transport), compensation for time, or incentives for follow-up. In general, the amount of remuneration should reflect the burden of participation such as the time, effort, and inconvenience associated with study visits and procedures. Funders generally agree to reimburse expenses without receipts, but it is harder to get approval to compensate people for their time and effort. Nonetheless, there is a growing agreement that it is appropriate and respectful to pay people who inject drugs for the time they spend providing data, which incurs opportunity costs for them. There is less agreement about the form or amount of remuneration.

Scale of remuneration

Participants at Kuala Lumpur suggested that remuneration should be on par with the work people do, i.e. salaries. If it is too low, it may mean that those most easily recruited may be those most in need who may be less likely to take great care in providing information. Moreover, if people feel undervalued or exploited, it undermines the community’s willingness to support research.

On the other hand, if the level of remuneration is too high, it can amount to undue inducement and can compromise the voluntariness of participation. It may also affect the quality of the data since there is a danger of double enrolment and repeat participation in different trials at the same time by the same individual, as seen among women in South Africa. For example, in the Bangkok tenofovir PrEP trial the level of payment to participants is equivalent to that of a salary, so it is difficult for people to withdraw from the study. In addition, participants are paid a transportation cost for coming every day. Community representatives think participants are being paid too much and that the incentives to return to the study are too high. They suggested that a scale based on the minimum wage in the country and the time spent would make more sense.

Community consultation

Community consultation in advance of the trial may be helpful in determining both the form and level of remuneration. It is important to ask prospective trial participants what they think is fair. It is discriminatory to avoid cash payments out of concern that the money may be spent on drugs. One form of payment is

conditional cash transfers, whereby participants are paid for performing or abstaining from certain actions, or for obtaining certain outcomes. In an Australian HCV preparedness study, input from participants led to changes in the amount and form of remuneration which improved the ethics and acceptability of the study, maximizing recruitment and retention.^{xvii} In a study in Indonesia to assess methadone clinic treatment, researchers discussed whether to offer participants cash, coupons, or vouchers. They asked a methadone support group which would be better and the groups' members answered that they would prefer to get part in cash and part in the form of free methadone treatments.

Conclusion

The Ethical Considerations guidance document has evolved in its scope. Its first version in 2000 addressed HIV vaccine trials. The revision in 2007 addressed biomedical HIV prevention trials. The three regional consultations, one of which is the Kuala Lumpur consultation will inform the content of a supplementary guidance point specific to ethically engaging with people who inject drugs in biomedical HIV prevention trials. Many of the issues discussed at Kuala Lumpur and summarized in this report would apply to all HIV prevention research with people who inject drugs, e.g., providing information about community services resources. However, there are also many issues that would not apply to all HIV prevention research, e.g., a cross-sectional community risk behaviour survey would not need an incarceration protocol. The Ethical Considerations guidance document stated that its guidelines specifically address trials of novel biomedical HIV preventive approaches but that they are also relevant to those engaged in behavioural research. This document and its recommendations should be read in a similar spirit.

Of note, ethical guidance is often vague and leaves leeway for discretion, judgment, and common sense given the conditions and circumstances of a particular research project. When researchers are asked to 'address' issues, this means that they should give due consideration to the weighing and balancing of competing values.

Concern was expressed that some ethical requirements might be impractical and lead to a reduction in the quantity of research. The risk is that if the ethical standard is unachievable it will either be dismissed or lead to labelling good work as unethical. The HIV Prevention Trials Network (HPTN) suggests an approach that distinguishes between ethical obligation and ethical aspiration. For example, there is an ethical obligation, or a moral requirement, to provide a risk reduction package of 'effective, comprehensive, and locally sustainable' services. But the actual content of the package is an ethical aspiration, and depends on the outcome of pre-trial negotiations with relevant stakeholders, which will reflect the practical constraints that are inherent to the political, economic, social, and cultural conditions in any given locality.^{xviii} The language of 'must' implies an obligation, while the language of 'should' implies an aspiration.

Where ethical guidance is aspirational, it is akin to a 'rebuttable presumption'. This means that special justification is needed if the standard is not met. If that is the case, researchers should engage in a deliberative process with relevant stakeholders, document the deliberations over the conflicting ethical obligations, and explain why they chose to depart from the guidance.

Finally, participants asked: What is the power of the ethical guidance? How do we get researchers to follow the document? All research proposals undergo prior

review by a research ethics committee and the new guidance point will be included in training and capacity building programmes for these committees. Some participants at Kuala Lumpur suggested there is also room for monitoring mechanisms to evaluate whether ethical obligations are met in actual practice, similar to the DSMB mechanism for following adverse medical events.

Key recommendations

1. Researchers should involve people who inject drugs in the research process across the entire research life cycle, including representation on community advisory boards (CABs). It is inappropriate to exclude people who inject drugs from the initial planning phase for the 'paternalistic' purpose of avoiding disappointment if the trial does not take off.
2. Researchers must provide participants with male and female condoms and voluntary HIV counselling and testing (VCT) throughout all stages of research.
3. Researchers must also offer confidential voluntary counselling on risk reduction issues, and information, education, and communication (IEC) on accessing a variety of community resources and services, including treatment for sexually transmitted infections (STIs), intimate partner violence (IPV), and sexual and reproductive health.
4. Researchers must provide access to sterile needles and syringes for trial participants, if participants do not have ready and affordable access through either pharmacy sales or free provision outside the trial setting.
5. Feasibility and implementation studies on proven risk reduction methods such as needle and syringe programmes may be carried out to assess optimal service delivery models. It is unacceptable to withhold proven risk reduction methods from participants in any trial arm.
6. While opioid substitution therapy (OST) is a proven HIV risk reduction intervention for people who use opioids, in some countries and settings it may be illegal or impossible to ensure appropriate long-term post-trial services. Researchers should negotiate the provision of OST, or other types of medically assisted treatment, with relevant stakeholders on a case-by-case basis before the start of the research. At the very least, researchers must advocate for OST where it is not available to research participants in their community.
7. In trials with people who are dependent on opiates, researchers should ensure that naloxone is available to participants as an antidote for opiate overdose.
8. Researchers should provide screening and treatment for sexually transmitted infections, and especially for syphilis, in the package of HIV risk reduction modalities.
9. Researchers should address the vulnerability of people who inject drugs to co-morbidities such as tuberculosis, hepatitis C virus, and in the case of women to a heightened risk of intimate partner violence. Researchers must provide either the appropriate treatment or linkage to services that are available in the community. Advance preparation by researchers may

be necessary to ensure receiving agencies are able and willing to handle increased referrals.

10. Researchers should set in place an active referral process for participants in need of legal services.
11. Researchers should provide food and water on-site to participants.
12. In community-based trials, the risk of participants being incarcerated for non-trial related activities can be high and an incarceration protocol should be designed for that possibility. Incarceration protocols should be prepared in advance also for trials that start in prison, in case individuals are released and get re-incarcerated. The incarceration protocol should address the reporting and managing of adverse events and continuing access to risk reduction modalities for participants who become incarcerated.
13. When research is conducted in a prison, the research ethics committee should include a prisoner representative. In trials, investigators should ensure that prisoner representatives also serve as members on the data and safety monitoring board (DSMB), although it was noted that DSMB members are statisticians and safety experts who must follow pre-determined trial stopping rules and are bound by confidentiality.
14. Protocols for research in prisons and other closed settings must give due consideration to issues of voluntariness of consent; strategies for the protection of confidentiality and safety of participants; access to risk reduction packages (e.g., sterile needles and syringes, condoms, and OST); monitoring, management and reporting of adverse events (e.g. availability of medical care, and access to such care after hours); and responsibilities to report abuses in prisons.
15. Where studies are conducted inside prisons and other closed settings, researchers should make plans to assist participants in the transition to the community and to address the known increased risks of injecting and sexual behaviour, intimate partner violence, and opioid overdose on release from detention.
16. Upon release from prison or detention, researchers must verify with participants that consent to participate during incarceration was voluntary and obtain informed consent for continued participation.
17. Whether research should be conducted in compulsory drug detention centres (CDDCs) is highly controversial. If research is to be conducted at all, researchers must observe the following humanitarian principles and negotiate them in advance with the relevant authorities:
 - a. Researchers must have unimpeded access to detainees without advance notice to authorities and without the presence of a custodian or guard within hearing distance (unless requested for the protection and safety of the research staff).
 - b. Informed consent must be obtained at a face-to-face meeting in the absence of any custodian. The research can take place only if researchers are assured that agreement to participate or refusal to participate will not prejudice the individual and they can guarantee that no data about individuals will be shared.

- c. Research cannot be conducted in facilities where torture or cruel, inhuman, or degrading treatment occurs. If researchers learn of such violation of human rights, they should challenge it and stop the study in that facility if the practice does not cease.
- d. Detention authorities must not make public use of the research collaboration so as to justify the existence of the facility or suggest endorsement of its approach to drug dependence.
- e. Publication of papers, reports, and findings will not require approval or vetting by detention or governmental authorities.

18. The amount of remuneration to people who inject drugs for participating in research should reflect the burden of participation. It is discriminatory to avoid cash payments out of concern that the money may be spent on obtaining drugs. Community consultations in advance of the research may be helpful in determining both the form and level of remuneration.

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 Adviser to UNAIDS (CSO)

ⁱⁱ The 'Lancet Series Symposium on HIV in People Who Use Drugs' was co-sponsored by the Centre of Excellence for Research in AIDS (CERiA) and brought together most of the lead authors of the scientific papers published in the Lancet Special Series on HIV in People Who Use Drugs, many of whom were able also to participate in the consultation. The Special Series was launched at the International Conference in Vienna, 2010.

ⁱⁱⁱ UNAIDS Report on the global AIDS epidemic 2010, p. 8

^{iv} C. Hankins, Global HIV epidemic among people who inject drugs. Presentation at Lancet Series Symposium on HIV in People Who Use Drugs, 10 December 2010, University of Malaya, Kuala Lumpur. Statistics from UNAIDS, AIDSinfo 2010.

^v This ethical guidance document is an update and revision of an earlier guidance document entitled *Ethical considerations in HIV preventive vaccine research* (2000).

^{vi} HIV in people who use drugs. *The Lancet*. July, 2010.

^{vii} Quarraisha Abdool Karim et al. Effectiveness and Safety of Tenofovir Gel, an Antiretroviral Microbicide, for the Prevention of HIV Infection in Women. *Science*. 2010; 329(5996):1168-1174

^{viii} Robert M. Grant et al. Pre-exposure Chemoprophylaxis for HIV Prevention in Men Who Have Sex with Men. *N Engl J Med* 2010;363:2587-99.

^{ix} WHO-UNAIDS. Istanbul Meeting Report (2010). Unpublished. Reports from the three consultations will form the basis for a scientific article in an open source publication with a target date of late 2011.

^x El-Bassel et al. HIV and women who use drugs: double neglect, double risk. *The Lancet*, 2010; 376:312-313; S. Kumar. Transmission of HIV from people who inject drugs to their sexual partners in the Asian region. Presentation at Lancet Series Symposium on HIV in People Who Use Drugs, 11 December 2010, University of Malaya, Kuala Lumpur

^{xi} Technical guide for countries to set targets for universal access to HIV prevention, care and treatment for injecting drug users. Geneva: WHO, UNODC and UNAIDS, 2009.

^{xii} Ibid.

^{xiii} Altice et al. *The Lancet* 2010 376: 367

^{xiv} Altice et al. *The Lancet*. 2010; 376:382

^{xv} USA 45 CFR 46.301 et seq.

^{xvi} Maher L. Payment and participation in research of people who use drugs illicitly. *AIVL Research & Policy Update*. 2010; 6:5-7. <http://tinyurl.com/24erlcb>

^{xvii} Maher L et al. Using ethnographic fieldwork to inform hepatitis C vaccine feasibility studies. *International Journal of Drug Policy* 2010;21(3):194-201.

^{xviii} HIV Prevention Trials Network (HPTN) Ethics Guidance for Research, 2009, guidance point 9.