Overcoming key obstacles to adolescent involvement in HIV Vaccine & Microbicide trials:

A roadmap for stakeholders

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Background

Adolescents form a major part of the HIV epidemic. More than half of all new infections occur among people under the age of 25[1]. Young women are especially vulnerable to HIV, especially in Sub-Saharan Africa, partly due to inter-generational, transactional or coercive sex. There are differences (both biological and behavioural) between adults and adolescents that make it difficult to predict adolescent responses to prevention products without enrolling them in trials. However, adolescents are also a vulnerable group because of their limited life experience and evolving autonomy. This dual vulnerability makes it impossible to ignore adolescent enrolment in trials, yet makes their enrolment sensitive and complex. Although no HIV vaccine trials have enrolled adolescents to date, adolescents have been enrolled in certain microbicide trials.

There have been numerous academic articles published on adolescent enrolment in HIV vaccine trials[2] and a few on microbicide trials[3]. There have also been a number of consultations that have debated the issue for HIV vaccines and microbicides. However, there have been limited efforts to debate issues of common concern to both fields, and facilitate sharing across these fields.

In April 2007 an award was made to the HIV AIDS Vaccines Ethics Group to host a consultation between stakeholders in HIV vaccine and microbicide trials to debate adolescent enrolment and promote sharing across fields. This forum, funded by the Bill and Melinda Gates Foundation through the Global Campaign for Microbicides, was held in Durban, South Africa on September 5th and 6th 2007. This consultation brought together stakeholders from HIV vaccine and microbicide fields that were conducting or planning adolescent trials. This included sponsors, investigators, community and government representatives, civil society organisations, and legal and ethics experts. The consultation highlighted several core problems common to both fields. **A detailed report is available for download** at http://www.global-campaign.org/clientfiles/ReportGCMconsult(Adolescents)Sep07.pdf

Prior to the meeting, a comprehensive review was done of all published articles on enrolling adolescents in HIV vaccine or microbicide trials. **This resource document is available for download** at http://www.global-campaign.org/clientfiles/Essack-Slack-Strode(2008)Towards-a-Roadmap.pdf.

[1] UNAIDS. (2007). *AIDS epidemic update*. Retrieved March 4, 2008, from http://www.unaids.org/en/KnowledgeCentre/HIVData/EpiUpdate/EpiUpdArchive/2007/

[2] e.g. Bekker, L-G., Jaspan, H. B., McIntyre, J., Wood, R., & Gray, G. (2005). Adolescents and HIV vaccine trials: What are the clinical trial site issues? *Journal of the International Association of Physicians in AIDS Care, 4*(4), 93-97; Jaspan, H. B., Cunningham, C. K., Tucker, T. J. P., Wright, P. F., Self, S. G., Sheets, R. L., et al. (2008). Inclusion of adolescents in preventive HIV vaccine trials: Public health policy and research design at a crossroads. *JAIDS*, 47(1), 86-92; McClure, C. A., Gray, G., Rybczyk, K., & Wright, P. F. (2004). Challenges to conducting HIV preventative vaccine trials with adolescents. *Journal of Acquired Immune Deficiency Syndromes, 36*, 726-733.

[3] e.g. Heise, L. L., & Wood, S. Y. (2005). *Rethinking the ethical roadmap for clinical testing of microbicides*. Retrieved January 29, 2007, from http://www.global-campaign.org/researchethics.htm.

Meeting participants identified four key priorities to move the adolescent agenda forward in both fields. Firstly, stakeholders need to understand the ethical-legal framework for conducting trials with adolescents. Secondly, a clearly articulated and accessible scientific justification for adolescent enrolment is required. Thirdly, there is a need for clarity on the data required to move products into adolescent trials and to get products licensed for adolescent use. Lastly, data on social harms should be collected from other trials with adolescents, e.g. Human Papillomavirus and Carraguard trials. This "roadmap" aims to take forward these issues prioritized by attendees at the consultation, and is not meant to be an exhaustive overview of key complexities. The roadmap aims to spell out the common obstacles, and describe what a range of stakeholders (see Appendix 1) can do to address these obstacles.

Currently, trials of pre-exposure prophylaxis (PrEP) are being conducted or planned with various populations including injection drug users, men who have sex with men, heterosexual men and women, and sero-discordant heterosexual couples[4]. If PrEP is found to be promising, adolescents will need to be enrolled in trials. Preparation and planning are required now in order to study PrEP in adolescents once sufficient data becomes available from current trials[5]. Ethical, legal, scientific and regulatory issues that complicate the enrolment of adolescents in HIV vaccine and microbicide trials, are likely to impact on PrEP trials with adolescents as well.

[4]Paxton, L. A., Hope, T., & Jaffe, H. W. (2007). Pre-exposure prophylaxis for HIV infection: what if it works? *The LANCET,* 370(9581), 89-93.
[5]AIDS Vaccine Advocacy Coalition (AVAC). (2008). *Anticipating the results of PrEP trials: A powerful new HIV prevention tool may be on the horizon. Are we prepared?* New York: AVAC.

(a)Ethical-legal framework

Where adolescents are to be enrolled in a trial in a particular country, the norms and standards (both legal and ethical) that govern child research must be complied with. In many settings where trials will take place, there is a lack of clarity on when adolescents can consent independently to research (that is, the age requirement or when emancipation is reached). Where adult involvement is required, there is a lack of clarity on which adults could provide consent (parents versus caregivers/ custodians). There is also some confusion around how to manage confidentiality in trials. In trials where parents give consent, complex privacy issues arise. A parent may give consent for enrolment, but adolescents may expect confidentiality for some components (such as their risk behaviour). In addition, laws that permit adolescents to independently access treatment/services within the country may support these expectations. There is also tension around how to manage confidentiality when the setting has laws about disclosures that must be reported to authorities. In some jurisdictions, there are reporting requirements that necessitate breaching confidentiality under certain circumstances. Here attendees flagged the need to know the ethical-legal matrix in which the trial is located to determine what should be reported (e.g. abuse, sexual offences like under-age sex or criminal behaviour). For both vaccine and microbicide trials, assessing the efficacy of products will be complex. While direct evaluation of efficacy would be ideal, in many settings statutory rape laws make it difficult to enrol adolescents below a certain age in efficacy studies where sexual activity is required and HIV infection is an endpoint.

Obstacle 1:
Inadequate ethical-legal systems

Many ethical-legal systems are restrictive and cannot accommodate adolescent microbicide or vaccine research. For example, in Ethiopia, a proclamation issued by the science and technology commission provides that clinical trials cannot enrol children under the age of 18 years. Furthermore, some legal systems do not have research-specific laws. This means that other laws, such as laws relating to medical treatment, have to be applied to research to establish appropriate norms. This may result in increased uncertainty. For example, in South Africa there are currently no research-specific laws in operation dealing with adolescent consent. As a result, there have been disparate approaches taken by research ethics committees. Some have equated therapeutic research with medical treatment and used the age at which children can consent independently to medical treatment (14) as the age at which they can also consent independently to therapeutic research. Others have found that the research relationship is not akin to a therapeutic one and have thus required parental consent for research until the age of 18.

Response:
Advocate for reform

In many cases inadequate ethical-legal systems that either fail to protect children or, conversely, are overly protective can only be remedied through reform. A range of Civil Society Organisations should engage in a coordinated advocacy effort to make law-makers aware of the need to reform or develop new laws regulating research with children. Law-makers and other governmental agencies will require support to identify key local issues and to ensure that revised or new laws comply with international best practice. This could be done by facilitating a meeting with parliamentarians and advising them of concerns regarding the lack of legal norms or inappropriate legal norms, and advocating for a reform process to be put in place.

Obstacle 2:
Lack of awareness of the ethical-legal framework

In many instances stakeholders are unclear about the local laws and ethical guidelines that govern child participation in research. Where this is the case, protocols may not comply with key standards or there may be inconsistent standards across trials. This is particularly the case with large-scale multinational trials that are conducted in countries that may each have varying laws and expectations regarding adolescent enrolment. For example, in South Africa given the current lack of legal clarity on the age of independent consent to research, ethics committees have applied a range of different standards regarding the age at which it is appropriate to allow adolescents to consent independently to research. Specifically, ethics committees have allowed microbicide trials to enrol adolescents with independent consent from the age of 16 whilst they have insisted that vaccine trials obtain parental consent until the age of 18.

Response:
Raise awareness by tool development & research

Ideally, trials should only take place in countries where an assessment of the ethical-legal framework has taken place and where there is as much clarity as possible on legal rights and duties. Ethics organizations like the WHO-UNAIDS African AIDS Vaccines Program Ethics, Law and Human Rights working group should develop a tool that enables countries to undertake this assessment. This tool should set out key content areas to be examined and give direction on how to assess the implications for trials.

Local Civil Society Organizations, like human rights non-governmental organisations and university law faculties, should use this tool to conduct audits to provide researchers and other stakeholders with a comprehensive assessment of laws and guidelines governing adolescent research in the host country. This ought to be done at regular intervals to ensure that stakeholders are aware of changes in the ethical-legal framework.

Best Practice

In 2005, the Ethics, Law and Human Rights Working Group of the African AIDS Vaccine Program produced an audit of the ethical-legal frameworks in Botswana, Ethiopia, Kenya, Tanzania and Uganda with a view to making recommendations on the extent to which they could facilitate trials that would protect and promote the rights of research participants[6].

Obstacle 3:
Poor application of ethical-legal norms to child trials

In some instances, there is an ethical-legal standard governing child research, stakeholders are aware of it, but have poor capacity to implement the norm. For example, the Kenyan Children's Act of 2001, section 19 states that "Every child shall have the right to privacy subject to parental guidance."[7] This gives adolescents limited rights to privacy. Applying this legal principle to HIV prevention trials enrolling Kenyan adolescents, however, would be complex. The section could be interpreted to mean that because children need parental assistance with the consent process, they would also need parental guidance regarding any information on their health status, i.e. they would not have any privacy rights within the context of a trial. It could also be interpreted to mean that when children have sufficient understanding about a particular activity (e.g. treatment for STIs) they are entitled to privacy regarding that decision.

Response:
Support stakeholders through training & tool development

In many instances researchers, regulators and participating communities need education and support to apply ethical-legal norms and standards. Ideally, this support ought to be through training on the key principles that inform the ethical-legal framework regulating child research. In addition, the development of locally relevant tools would be useful, in order to clarify how norms apply to adolescent research. International agencies like WHO-UNAIDS should assist locally based organisations with training activities which focus on developing the capacity of countries to identify the areas where the application of ethical-legal norms could be difficult, for example with regard to mandatory reporting obligations or the privacy rights of children. Civil Society Organisations, like the AIDS Vaccine Advocacy Coalition and the Global Campaign for Microbicides, and locally based human rights organisations should assist to develop tools which can be used to apply local laws to the identified issues.

[6]Grant, C., Lewis, M., & Strode, A. (2005). *The ethical-legal regulation of HIV vaccine research in Africa: A study of the regulation of health research in Botswana, Ethiopia, Kenya, Tanzania & Uganda to determine their capacity to protect and promote the rights of persons participating in HIV vaccine research*. Pietermaritzburg: Ethics, Law and Human Rights Working Group (ELH), African AIDS Vaccine Programme (AAVP).

[7]African Network for the Prevention and Protection Against Child Abuse and Neglect. (2001). *Kenyan Laws on children*. Retrieved September 18, 2008, 2008, from http://www.anppcankenya.co.ke/index.php?option=com_content&task=view&id=21&Itemid=26

Best Practice

In 2007, the HIV AIDS Vaccines Ethics Group developed a tool that spelled out the implications of laws for child researchers and ethics committee members[8]. For example, children of 14 and above can independently consent to medical treatment (South African Child Care Act, 1983), even though parental consent is required for enrolment in clinical research trials[9]. The tool explained that this means that while parents will consent for trial enrolment, children can consent independently to those aspects of the research that amount to treatment, such as treatment of STIs[8].

(B) Justification for adolescent trials

There is no question that adolescents are at risk of HIV infection. However, it is a general ethical norm that vulnerable persons (like adolescents) should only be enrolled in trials when the research question cannot be adequately answered with less vulnerable persons (like adults). Therefore research ethics committees require some justification of why adolescents *themselves* must be enrolled, before approving such trials. Civil Society Organisations and community representatives also need to be convinced of the justification of adolescent enrolment.

It has been identified that responses to HIV vaccines may be different in adolescents compared to adults[10]. For example, while product safety may not differ for adolescents, vaccines may be more effective in adolescents at lower or fewer doses than in adults[11]. Some microbicide resource documents have pointed out that adolescent girls differ from adult women, for example, their cervixes are not fully mature and they are more susceptible to sexually transmitted infections. Also their menstrual patterns differ; while they may have periods many adolescent girls do not ovulate, and lower progesterone levels may affect the vagina's immune responses[12]. It has also been argued that differences in adolescent behaviour (like douching) may impact on responses to products[13].

[8]HIV AIDS Vaccines Ethics Group, Desmond Tutu HIV Centre, & Perinatal HIV Research Unit. (2007). *Building stakeholder skills to manage legal complexities in child and adolescent research: A directory of the legal rights of minor research participants including children & adolescents*. Retrieved September 18, 2008, from http://www.saavi.org.za/childresearch.pdf

[9]Department of Health. (2006). *Guidelines for good practice in the conduct of clinical trials with human participants in South Africa*. Retrieved March 5, 2008, from http://www.doh.gov.za/docs/index.html

[10]Jaspan, H. B., Gray, G., Robinson, A. K. L., Coovadia, H. M., & Bekker, L. G. (2005). Scientific justification for the participation of children and adolescents in HIV-1 vaccine trials in South Africa. *South African Medical Journa*l, 95(9), 685-687; Jaspan, H. B., Lawn, S. D., Safrit, J. T., & Bekker, L. G. (2006). The maturing immune system: implications for development and testing HIV-1 vaccines for children and adolescents. *AIDS, 20*, 483-494; WHO/UNAIDS/AAVP International Expert Group. (2007). Executive summary and recommendations from WHO/UNAIDS and AAVP consultation on: 'The inclusion of adolescents in HIV vaccine trials', 16–18 March 2006 in Gabarone, Botswana. AIDS, 21(14), W1-W10.

[11]Cardinali, M., Lau, C., Lawrence, D., Allen, M., & Sheets, R. (2007). *Considerations for HIV vaccine clinical trials in adolescents*. Retrieved July 4, 2007, from http://www3.niaid.nih.gov/research/topics/ HIV/vaccines/PDF/ AdolescentsPaper.pdf; Jaspan, H. B., Cunningham, C. K., Tucker, T. J. P., Wright, P. F., Self, S. G., Sheets, R. L., et al. (2008). Inclusion of adolescents in preventive HIV vaccine trials: Public health policy and research design at a crossroads. *JAIDS, 47*(1), 86-92.

[12]Heise, L. L., & Wood, S. Y. (2005). *Rethinking the ethical roadmap for clinical testing of microbicides*. Retrieved January 29, 2007, from http://www.global-campaign.org/researchethics.htm

[13]Slack, C., Mamotte, N., & Essack, Z. (2008). *Ethical-legal concerns in adolescent microbicide & HIV vaccine trials: Report on an international consultation held in Durban, South Africa, September 5-6, 2007*. [Electronic Version]. Retrieved September 18, 2008, from http://www.globalcampaign.org/clientfiles/ReportGCMconsult(Adolescents)Sep07.pdf

Obstacle 4:
Adult-adolescent differences have not been clarified or communicated effectively

Consultation participants argued that, especially for microbicide trials, the scientific experts have not debated and clarified the differences in safety and efficacy that they expect between adults and adolescents for various products, for example classes of microbicides such as those that disrupt cell membranes (surfactants); those that enhance the natural defences of the vagina; and antiretroviral-based products that prevent viral replication.

Consultation participants argued that in addition to the lack of publicly available information on the anticipated differences between adults and adolescents, the available scientific justification for adolescent enrolment has not been articulated in a manner that key stakeholders, like community representatives, can understand. For HIV vaccine trials, there are some papers addressing this issue, but these are not written in a manner that key consumers such as communities can make sense of.

Response:
Improve clarity and communication about differences

Civil Society Organisations should work with researchers and other experts to clarify anticipated differences in vaccine and microbicide safety and efficacy between adults and adolescents. An expert consultation could serve this purpose, and the discussion should be made publicly available. Researchers, sponsors, international agencies (e.g. WHO-UNAIDS) and Civil Society Organisations (e.g. Global Campaign for Microbicides and AIDS Vaccine Advocacy Coalition) should develop resources in a language that is accessible to all stakeholder groups. These resources should spell out what researchers anticipate would differ for safety or efficacy for adolescents versus adults, product by product.

Best Practice
The Global Campaign for Microbicides has developed a comprehensive and accessible report based on a consultation held in 2003 on ethical issues in the testing of microbicides[14]. This document covers several issues around the ethics of microbicide trials and is available for download at http://www.global-campaign.org/

The International Partnership for Microbicides (IPM) website (http://www.ipm-microbicides.org/) offers several factsheets for download. These factsheets are written in a user-friendly manner and in a language that makes difficult concepts accessible to various stakeholders.

[14]See Heise, L. L., & Wood, S. Y. (2005). *Rethinking the ethical roadmap for clinical testing of microbicides*. Retrieved January 29, 2007, from http://www.global-campaign.org/researchethics.htm

(C) Collection of adolescent data

It will not be possible to license a microbicide or HIV vaccine for use in adolescents without collecting safety and effectiveness data from adolescents. But at what time-point in the sequence of trials should data be gathered from adolescents? And, what data should be gathered from adolescents in order to license these products?

Obstacle 5:
Lack of clarity on data needed for enrolment or licensure

There is a lack of clarity on the data needed **before adolescents can be enrolled** in trials. For HIV vaccines, the FDA guidance[15] asserts that before adolescents are enrolled, data on safety and activity is required from adults. Adolescent enrolment should be "stepwise" from older to younger adolescents.

HIV vaccine trial researchers have also made some proposals[16]. One such proposal is that sufficient adult *safety and immunogenicity* data should be gathered to warrant advancement to adult efficacy trials. At that point, safety and immunogenicity data should be gathered from older adolescents (ages 16 and 17) by co-enrolling them in adult efficacy trials. After confirming safety and immunogenicity in older adolescents, safety and immunogenicity data should be gathered from younger adolescents. It has been argued that *efficacy* in adolescents should be established by enrolling adolescents into trials as soon as possible after starting efficacy trials with adults. Either a stratum of adolescents could be added to the adult trial or separate adult and adolescent trials could be conducted. It would be ideal to gather efficacy data directly from adolescents. This is possible for older adolescents who are over the age of lawful consent to sex. However, for younger adolescents below the age of lawful consent to sex, bridging studies could be conducted. Given that correlates of immunity, for protection from HIV, have not yet been identified, bridging studies could be conducted based on state-of-the-art assays[17] (assays considered best at the time of the bridging study).

There is a single document that summarizes proposals for adolescent enrolment in microbicide trials, made at a meeting hosted by Global Campaign for Microbicides. Namely, adult phase I and II

[15]US Food and Drug Administration. (2006). *Guidance for industry: Development of preventive HIV vaccines for use in pediatric populations*. Retrieved June 22, 2007, from http://www.fda.gov/cber/gdlns/pedhiv.pdf
[16]Cardinali, M., Lau, C., Lawrence, D., Allen, M., & Sheets, R. (2007). *Considerations for HIV vaccine clinical trials in adolescents*. Retrieved July 4, 2007, from http://www3.niaid.nih.gov/research/topics/ HIV/vaccines/PDF/ AdolescentsPaper.pdf; Jaspan, H. B., Cunningham, C. K., Tucker, T. J. P., Wright, P. F., Self, S. G., Sheets, R. L., et al. (2008). Inclusion of adolescents in preventive HIV vaccine trials: Public health policy and research design at a crossroads. *JAIDS*, 47(1), 86-92.
[17]Jaspan, H. B., Cunningham, C. K., Tucker, T. J. P., Wright, P. F., Self, S. G., Sheets, R. L., et al. (2008). Inclusion of adolescents in preventive HIV vaccine trials: Public health policy and research design at a crossroads. JAIDS, 47(1), 86-92.

trials should commence and, if there is clear safety data for adults, researchers can proceed with phase I and II trials for adolescents. Once safety is established for adolescents, they can be co-enrolled in phase III trials with adults. Because numbers may be too small to establish efficacy, a full phase III trial with adolescents may be needed[18]. Attendees at our meeting argued that the developmental trajectory would be the same as for HIV vaccine trials: early trials should be conducted on adults, then once a significant signal is present to move to adult phase II/IIb trials, plans should be made to enrol adolescents, but whether this is in safety, efficacy or bridging studies depends on many factors[19].

There is also a lack of clarity on the data needed before **products would be licensed** for adolescents. For HIV vaccines, FDA guidance[20] on licensure is that licensure may be sought through 1) using adult efficacy data and 2) through paediatric efficacy studies with clinical outcomes. In the first instance, to support paediatric use of an HIV vaccine, it may be sufficient to have efficacy data indicating prevention of new HIV infections in adults as well as safety and immunogenicity data in children. In the second instance, a paediatric efficacy trial with HIV infection as clinical endpoint may be conducted, although this may not be feasible in US paediatric populations where HIV prevalence is low.

A lack of clarity on this issue is compounded by the lack of international guidance. International bodies have not issued clear standards on the minimum requirements for enrolling adolescents in trials and setting out the circumstances in which licensure would be justified.

Response:
Lobby stakeholders to outline proposals & guidance

Civil Society Organisations should advocate for researchers to meet with National Regulatory Authorities to advise them of the importance of enrolling adolescents in HIV prevention research. Civil Society Organisations also need to lobby researchers to outline further proposals and National Regulatory Authorities to issue guidance on when and how adolescents may be enrolled in such trials. International bodies such as WHO-UNAIDS should develop international minimum requirements for the enrolment of adolescents into trials and the licensure of products for use within

[18]Heise, L. L., & Wood, S. Y. (2005). *Rethinking the ethical roadmap for clinical testing of microbicides*. Retrieved January 29, 2007, from http://www.global-campaign.org/researchethics.htm
[19]Slack, C., Mamotte, N., & Essack, Z. (2008). *Ethical-legal concerns in adolescent microbicide & HIV vaccine trials: Report on an international consultation held in Durban, South Africa, September 5-6, 2007*. [Electronic Version]. Retrieved September 18, 2008, from http://www.globalcampaign.org/clientfiles/ReportGCMconsult(Adolescents)Sep07.pdf
[20]US Food and Drug Administration. (2006). *Guidance for industry: Development of preventive HIV vaccines for use in pediatric populations*. Retrieved June 22, 2007, from http://www.fda.gov/cber/gdlns/pedhiv.pdf

(D) Social harms

In addition to the physical risks associated with participation in a trial, volunteers may face social harms as a result of their enrolment in a vaccine and microbicide trial. Some of these harms may be exacerbated with adolescent participants. Potential social harms include stigma and discrimination; increased risky behaviour; and vaccine-induced seropositivity (testing false-positive on standard HIV tests) in HIV vaccine trials. Concerns about social harms may affect a volunteer's willingness to participate in a trial. Communities and parents may also be reluctant to allow their adolescents to participate due to the possibility of social harms, and ethics committees may not feel confident to approve protocols if they cannot be sure that risks are acceptably low.

Obstacle 6:
Inadequate data on potential social harms

Meeting participants observed that there is a lack of data on potential social harms for adolescents and how these harms may be experienced by them. In addition, it was noted that better tools are needed to assess social harms and sexual risk behaviours of adolescents. While there is some understanding of crude factors like condom use or mean number of sexual partners, information on adolescent sexual networking is limited. Furthermore, because different measures have been used, it is hard to draw comparisons across trials.

Response:
Collate existing data and develop common tools

Researchers and sponsors (e.g. Adolescent Trials Network) should gather data on social harms from other adolescent trials like Human Papillomavirus and Herpes suppression trials. Researchers who have conducted microbicide trials with adolescents (e.g. Population Council's Carraguard trial in South Africa) should report on the social harms experienced by adolescents. Data that indicates how reporting and responses to social harms differ between adults and adolescents will also be useful. Researchers and sponsors should develop common tools to assess harms across both adolescent vaccine and microbicide trials. For HIV vaccine trials, it is imperative that host countries develop mechanisms for long-term access to confirmatory testing for vaccine-induced seropositivity.

Best practice

The Adolescent Trials Network has a template for collecting adolescent data on social harms. Researchers, sponsors, civil society and international agencies should consider adapting this template as necessary.

Conclusions

There is broad agreement on the need to enrol adolescents into HIV prevention studies. However there are several ethical, legal, scientific and regulatory complexities that affect the enrolment of adolescents in HIV prevention trials; and several recommendations have been put forth to address these complexities[21].

This roadmap focused on taking forward four select issues that were prioritized by attendees at the ethical-legal consultation on the enrolment of adolescents in HIV vaccine and microbicide trials in September 2007. These issues are not necessarily new. They have been extensively identified in the literature and previous consultations. However, this roadmap has set out the potential activities for resolving these complexities and has linked these activities to partners/stakeholders. In doing so, it is hoped that various stakeholders will adopt these activities into their plans in order to move the adolescent agenda forward.

While we do not anticipate a vaccine or microbicide to be available for testing in adolescents for some time, these issues will be applicable for other HIV prevention products that hope to enrol adolescents. For now, it seems that PrEP candidates are the most promising and accordingly, steps must be taken to unblock the current obstacles and open up the pathway towards the development of safe and effective HIV prevention strategies for adolescents.

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[21] As summarised in Essack, Z., Slack, C., & Strode, A. (2008). *Towards a roadmap: A summary of identified ethical-legal complexities in adolescent HIV vaccine and microbicide research*. Retrieved September 18, 2008, from http://www.global-campaign.org/clientfiles/Essack-Slack-Strode(2008)Towards-a-Roadmap.pdf

Box 1:
Obstacle, potential responses and stakeholders

Issue	Obstacle	Response	Stakeholder
Ethical-legal framework	1. Inadequate ethical-legal systems	Advocacy for reform	Civil society organisations, Law-makers
	2. Lack of awareness of ethical-legal framework	Tool development for ethical-legal audits	Ethics organisations
		Audits	Civil society organisations
	3. Poor application of ethical-legal norms to child trials	Training	International agencies
		Tool development for applying norms	Civil society organisations
Justification for adolescent trials	4. Inadequate clarification of anticipated adult-adolescent differences	Expert consultation	Researchers, Civil society organisations
		Resource materials development	Researchers, Sponsors, International agencies, Civil society organisations
Collection of adolescent data	5. Lack of clarity on data needed for enrolment or licensure	Advocacy for proposals and guidance	Civil society organisations
		Proposal and guidance development	Researchers, National regulatory authorities
Potential social harms	6. Inadequate data on potential social harms	Research	Researchers and Sponsors
		Tool development	

Appendix 1: KEY STAKEHOLDERS IN TRIALS

A range of different groups have a stake in clinical trials of prevention products like HIV vaccines and microbicides[i]

Stakeholders	Potential role in HIV vaccine and microbicide trials
Researchers	Involved in conducting the study/clinical trial.
Funders	Organization(s) that fund the study/clinical trial through contracts, grants or donations.
Sponsors	Individuals, companies, institutions or organizations who take primary responsibility for initiating, managing and/or financing of a clinical trial. Sponsors are tasked with ensuring that the study design satisfies appropriate standards and that mechanisms are in place to ensure appropriate conduct and reporting; the sponsor is often, but not necessarily the principal funder.
National Regulatory Authorities (NRAs)	Statutory bodies that regulate product development – in most countries, NRA approval of the product and protocol must be obtained prior to the initiation of the clinical trial in human volunteers. NRAs also decide whether products are approved for widespread use, marketing and export/ import[ii].
Research Ethics Committees (RECs)	Independent committees responsible for ensuring the rights, safety and well-being of participants involved in a trial by reviewing, approving and providing continuing review of 1) trial protocols and amendments and 2) methods and materials used in obtaining and documenting informed consent.
Community Advisory Boards (CABs)	CABs are a group of community members (e.g. people living with HIV and AIDS, service providers and community activists) that facilitate research by 1) helping members of the community to be involved in the process of planning and running trials[iii], 2) providing advice about the design and implementation of research protocols[iv] and 3) acting as the voice of the community and trial participants.
Civil Society	CSOs comprise a range of organisations including non-governmental organisations (NGOs and Organisations (CSOs) "nonprofit organizations that aim to further the interests of the communities they serve"[v] by contributing to the ethical assessment of trials and ensuring that the community benefits by providing access to information about HIV prevention strategies[vi].
Parliamentarians/ Law-makers	Develop the legal frameworks for countries within which trials take place as well as the frameworks and guidelines for conducting HIV prevention trials.
Government agencies	Government agencies may be involved in developing clinical trial infrastructures, conducting clinical trials, and training researchers.[vii]
International agencies	Play a normative and advisory role in setting standards for research.

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