APRIL 2012

Clinical Guidance: Essential Approaches for the Conduct of IAVI Clinical Research

INTRODUCTION

IAVI conducts AIDS vaccine research in developing countries in the South, as well as countries in the North, through partnerships with qualified local institutions and investigators. IAVI establishes partnerships based on previous research experience and the ability to conduct culturally appropriate, high-quality, ethically responsible clinical research in key populations affected by the AIDS pandemic. Important elements of the partnership include a commitment from IAVI to improve or build sustainable infrastructure and training programs, and to work within the guidelines of the institution and the country's ethical and regulatory framework. Research partners commit themselves to direct oversight of research conduct, engaging communities and other key stakeholders, obtaining appropriate ethical and government approvals, and participating in protocol development, analysis, and dissemination of research findings. These commitments are detailed in written agreements.

The purpose of this document is to guide IAVI research partners in the conduct of clinical research. It outlines essential processes and practices required to conduct IAVI-sponsored research, based on the specific research and sociocultural context and the needs of the research team, study volunteers, and community. This guidance applies to clinical trials and to observational and behavioural research studies. The processes and practices described here are part of a comprehensive public health and development-focused approach to AIDS vaccine research that addresses the needs of research volunteers and communities. They also ensure that the research itself and associated capacity-building efforts and service delivery activities meet high ethical and quality standards. IAVI provides collaborators with training, materials, and other assistance to help them implement these processes.

The processes described in this document and in the institutional agreement help to ensure that individuals participating in IAVI-sponsored research are treated according to the highest ethical standards, and that the communities that host the research benefit as a whole. IAVI follows relevant guidance from the International Conference on Harmonisation's Good Clinical Practice, the U.S. Federal Policy for the Protection of Human Subjects (The Common Rule, 45 CFR Part 46), the UNAIDS/WHO guidance documents "Ethical considerations in biomedical HIV prevention trials" (2007) and "Good participatory practices for biomedical HIV prevention trials" (2007), and national regulations.

1. COMMUNITY ENGAGEMENT

Engaging communities at various levels is important for the success of clinical research. Research should contribute to the health and welfare of communities that host the research. These communities may experience such benefits as improved healthcare and HIV voluntary counselling and testing (VCT) services, as well as increased knowledge about HIV infections and AIDS vaccines. IAVI believes that it is also essential for the AIDS vaccine field to engage key national, regional, and global stakeholders, such as nongovernmental organisations (NGOs), community-based organisations (CBOs), faith-based organisations (FBOs), women's groups, policymakers, the medical community, scientists, the media, and others as appropriate. IAVI, often in collaboration with research partners, undertakes stakeholder engagement activities at the national, regional, and global levels.

A community engagement strategy serves two functions: (1) to develop a supportive community environment for research by building knowledge, trust, and a sense of ownership, and (2) to facilitate effective recruitment and retention. The knowledge and trust that is built through community engagement activities helps to minimize rumours about research that can lead to misunderstandings and even opposition, making study implementation difficult. Building community support can be particularly challenging in communities that have not participated in previous research and that may lack exposure to complex concepts of clinical vaccine

research such as informed consent, placebos, immunity, vaccines, and vaccine research.

In addition to engaging communities before and during trials and other studies, research partners should devise communications mechanisms or organize events to inform key community stakeholders about basic research information, update them on the progress of ongoing research, and disseminate research results.

At a minimum, each research partner should set up or have access to a Community Advisory Board (CAB) or a similar entity that represents the interests of the community where the research takes place and of the populations enrolled in the study. CABs can advise the research staff on a range of matters and provide valuable insights on cultural constraints and appropriate communication approaches. They also serve as an important safeguard for volunteer rights. As one CAB member from Lusaka, Zambia, put it, CABs are "the eyes of the community and the ears of research staff." It is often challenging to ensure that a CAB represents the diversity within a community and has strong links with the population that is being recruited, particularly in populations not accustomed to proactive community consultation or to clinical research with vulnerable populations. IAVI and its research partners will soon complete a CAB toolkit that can be used by research centres to develop and strengthen CABs.

Examples of community engagement mechanisms (other than CABs) include:

- Community meetings
- Informational seminars for community members
- Gender Advisory Boards
- Peer leader networks
- Community educational materials
- Media outreach
- Newsletters
- Collaboration with NGOs, CBOs, FBOs, women's groups, youth groups, etc.
- Building relationships with local influential individuals, including religious and community leaders
- Participation in community events (e.g., health fairs, cultural events, sports events, World AIDS Day, and World AIDS Vaccine Day events)
- Partnerships with local VCT and other health service providers

2. INFORMED CONSENT AND PROTECTION OF HUMAN SUBJECTS

Conducting research that involves human subjects includes the responsibility for protection of all volunteers participating in research. IAVI is committed to protecting volunteers who participate in IAVI-sponsored clinical and other research studies and follows GCP guidelines for the conduct of clinical trials, in addition to complying with U.S. Federal Policy for the Protection of Human Subjects (The Common Rule, 45 CFR Part 46) for all research on human subjects.

The process of informed consent is important for protecting human subjects. Research teams strive to ensure that all volunteers have freely given informed consent based on a clear understanding of the study and the potential risks and benefits of study participation. Before giving consent, volunteers must demonstrate that they understand the important features of the study and their role in it. As the study continues, research staff should periodically ensure volunteers' understanding and ongoing consent.

To provide potential volunteers with the optimal setting for understanding study participation and providing informed consent, the informed consent process should include the following:

- Community outreach to provide information about research to the community
- Training of staff in counselling skills for obtaining consent, and periodic supportive supervision of the counselling process
- Various methods of communication, such as group and individual counselling using visual aids like videos and flip-charts, with particular attention to difficult concepts
- Appropriate measures to ensure adequate time for volunteers to reflect on the decision to participate and, if desired, involve their partners, friends, and family
- Approaches for protecting low-literacy populations, such as allowing witnesses, determining literacy levels, and using visual tools
- Assessment of understanding before informed consent and participation
- Ongoing informed consent education, including review of key study concepts and opportunities to verbally reaffirm consent throughout the study

Obtaining review and approval for study protocols from local ethics committees and regulatory agencies is another important protection for human subjects. Research partners conducting IAVI-sponsored research must ensure that necessary regulatory agencies and local ethics committees approve all protocols, informed consent materials, and other materials presented to potential study volunteers.

Volunteers receive reimbursement for travel and other expenses related to participation. The specific amount and form of compensation should be appropriate for the local context and should be reviewed and approved by local ethics bodies to avoid undue inducement to participation. CAB input is also helpful for determining compensation amounts appropriate for the local context.

3. HIV VOLUNTARY COUNSELLING AND TESTING

All volunteers participating in IAVI-sponsored clinical studies and other research studies receive repeated,

high-quality, free HIV VCT that follows World Health Organization or national guidelines. Trained counsellors conduct VCT in a confidential setting and in a manner that respects the diverse backgrounds of volunteers.

Some research partners provide VCT to consenting couples who are married or living together to facilitate disclosure of results and to discuss joint planning for risk reduction, family planning, and care of children based on the HIV status of both parents. Often, VCT is also offered to the sexual partners of study volunteers. When protocols involve testing for early or acute HIV infection, counsellors receive specialized training in communicating the implications of test results. As the research progresses, counsellors modify the standard VCT model to build on information provided in previous sessions and include information about the risk of vaccine-induced HIV antibodies.

Pre-test counselling includes a personal risk profile and risk reduction plan, information about HIV transmission and prevention, an explanation of positive and negative test results, and informed consent procedures. Post-test counselling includes a discussion of test results and appropriate counselling, support, and referral. If the test result is negative, the counsellor gives information about the window period and re-testing, and works with the volunteer to create or alter a risk reduction plan. If the test result is positive, counselling includes identifying immediate concerns and social support, discussing disclosure, creating or altering a risk reduction plan, discussing medical follow-up, and referring to appropriate treatment and support organisations.

4. RISK REDUCTION COUNSELLING

Risk reduction counselling must be provided to all volunteers throughout their participation in IAVI-sponsored clinical trials and other research studies where HIV testing is provided. Particularly in AIDS vaccine efficacy trials, all research partners must provide the highest-quality risk reduction counselling. Risk reduction counselling should comply with national guidelines, where applicable, or WHO guidelines, as a minimum standard.

Counselling staff should have adequate levels of training in counselling skills, as well as information about prevention technologies, and should receive refresher training and ongoing supportive supervision to address skills, difficult counselling situations that arise from time to time, and occupational stress. Wherever research partners work with particularly vulnerable or stigmatised populations, or populations with special needs, counsellors should receive specialized training. IAVI can help research partners arrange such training as needed.

IAVI-sponsored research protocols require access to HIV prevention methods as part of the risk reduction counselling process. Research partners must provide adequate supplies of male condoms to all study volunteers. IAVI encourages research partners to provide female condoms as well. Where post-exposure prophylaxis (PEP) services are available, IAVI encourages referral in case of rape or other accidental exposure. Research teams should provide information and referral for male circumcision (see below). As other proven HIV prevention methods and tools emerge, IAVI will ask research partners to provide access to these as well, where feasible.

5. MALE CIRCUMCISION

Following national guidelines or, if no national guidelines exist, international recommendations (e.g., WHO), research partners should provide information about the partial protection from HIV provided by male circumcision. Interested volunteers should receive referrals to high-quality services that provide accurate counselling for circumcision and a safe procedure. In all IAVI-sponsored studies that recruit HIV-uninfected volunteers and provide HIV risk reduction counselling, such as observational cohorts and clinical trials, volunteers should receive this information when they enrol and again every six months for the duration of their study participation.

6. FAMILY PLANNING SERVICES

IAVI research partners must provide either on-site family planning services or referrals to such services. Family planning services are important because they (1) help women avoid pregnancy while they receive investigational vaccines with unknown risks to the foetus, (2) provide public health benefits from men and women participating in HIV prevention studies. Most vaccine clinical trials required that female volunteers use an effective form of family planning during the vaccination phase of the trial. In early phase vaccine trials, males are often required to use effective family planning during the vaccination phase as well. Males participating in other AIDS vaccine clinical trials, and males and females in other research studies, may also request or need family planning services.

For all phases of AIDS vaccine clinical trials, IAVI requires that women of childbearing potential (e.g., not menopausal or surgically sterile) use an effective, non-barrier form of family planning, such as hormonal methods or an intrauterine device, during the vaccination period of the trial. IAVI set this requirement because of the relatively high rate of pregnancy in earlier trials in women who reported condoms or abstinence as their only form of contraception. In addition, IAVI recognizes the importance of condoms as the first line of defense against both HIV and pregnancy, strongly encourages condom use and emphasizes this as part of VCT at each center. Anatomical sterility in the male partner and abstinence may be considered

effective methods of contraception in certain settings, depending on the trial population.

To ensure the best possible family planning services for study volunteers, IAVI research partners should do the following:

- If providing family planning services through referral, ensure that off-site services in the community provide high-quality services with adequate supplies and staffing and, if necessary, provide support to improve off-site services
- If providing on-site services, offer a sufficient array of family planning methods to ensure adequate informed choice
- If a combination of on-site services and referral (e.g., for surgical methods) is used, both ensure the quality of the referral and offer a sufficient array of family planning methods
- Provide appropriate interactive counselling to help volunteers determine the most appropriate form of family planning according to individual needs

Follow-up procedures are specified in the protocols for women who become pregnant during clinical trials involving investigational agents.

At this time IAVI follows WHO recommendations on family planning methods and does not discourage the use of hormonal contraceptives in populations at risk for HIV. At a WHO meeting in 2012 (http://whqlibdoc.who.int/hq/2012/WHO_RHR_12.08_eng.pdf) experts reviewed existing evidence on the use of hormonal contraception in HIV-negative women who were at high risk of HIV. Studies that looked at the use of the oral contraceptive pills (combined oral contraceptive and progestogen-only pills) and injectable contraception (depot medroxyprogesterone acetate [DMPA] and norethisterone enantate [NET-EN]) were reviewed. Although some studies showed an association between oral contraceptives or injectable contraception with HIV acquisition, other studies did not show this association. These data were judged not to be strong or consistent enough to prompt policy change. Women using progestogen-only injectable contraception should be strongly advised to always use condoms, male or female, and other HIV preventive measures.

7. SEXUALLY TRANSMITTED INFECTIONS (STI) SCREENING AND TREATMENT

For clinical study populations considered at risk for STIs, IAVI follows national guidelines to provide screening and treatment for common STIs on a regular basis for both men and women. At a minimum, screening and treatment based on syndromic management is provided. Treatment for sexual partners will be available, if medically indicated. If treatment cannot be offered on site, referral for treatment will be made to an appropriate patient care facility.

8. COUNSELLING AND REFERRAL FOR HIV-INFECTED INDIVIDUALS

Qualified study counsellors will provide counselling to volunteers found to be HIV-infected at screening and volunteers who acquire HIV infection during a trial. The counselling process will assist the volunteer with the following issues:

- Psychological and social implications of HIV infection
- Disclosure and coping strategies
- Implications for sexual partners
- Implications for childbearing
- Prevention of transmission to others
- Implication for participation in the current study and any other research

Volunteers who are found to be HIV-infected at screening and volunteers who acquire HIV infection during a research study will receive referrals to a reputable HIV treatment centre or institution of his or her choice for a full discussion of treatment options, including antiretroviral therapy (ART) when medically indicated. Alternatively, research partners may provide a comprehensive package of HIV care, support, and treatment at the study centre. Referral systems will be pre-arranged, ideally in writing, with HIV and AIDS treatment centres, and IAVI and its research partners will work to facilitate effective referrals. See section 10 for elements of a strong referral system.

In addition to referrals for their own HIV-related care, HIV-infected pregnant women will also be referred to antenatal care and to a program for the prevention of mother-to-child transmission.

Access to long-term HIV and AIDS treatment for clinical trial volunteers must be a shared responsibility. IAVI is committed to working with its clinical trial partners, governments, and others to facilitate long-term access to HIV-related care, support, and treatment for all volunteers who become HIV-infected during an IAVI-sponsored trial. IAVI will provide free ART (as per national ART protocols) for clinical trial volunteers who seroconvert during a trial for up to five years after treatment is initiated, if not available from other sources free of charge. IAVI and its partners will actively seek collaborations with and commitments from other stakeholders to sustain long-term treatment and care.

9. REFERRAL FOR HEALTH SERVICES

Research partners should ensure robust referral mechanisms for family planning, ART services, STIs, and other health issues. Identifying appropriate referral sites is the responsibility of the research partner, although IAVI can offer technical assistance as needed. Some elements of a strong referral mechanism include:

- Identifying high-quality referral centres either by reputation or by direct assessment of services
- A pre-existing written agreement with the referral centre to define the terms of referral

- Identifying a point of contact at the referral centre
- Use of referral forms
- Mechanisms to follow up and document whether referrals were completed and to obtain clinical information as necessary

10. QUALITY ASSURANCE/QUALITY IMPROVEMENT FOR SERVICE DELIVERY

In addition to routine monitoring and audits for clinical research, IAVI encourages its research partners to institute participatory quality improvement approaches to assess, monitor, and continuously improve service delivery at research centres. VCT, counselling and education, informed consent, community outreach, medical care, and the overall service delivery environment are among the components that may benefit from quality improvement.

Continuous quality improvement approaches are used widely in health care service delivery. Rather than using an external approach to assessing quality, these methods involve research staff in identifying and solving problems and incorporate feedback from research volunteers. Participatory quality improvement is closely linked to supportive supervision approaches. IAVI has worked with research partners to adapt these approaches to the research setting and, in the process, has developed tools that can be readily adapted to the needs of different research partners.

11. LABORATORY MANAGEMENT

All clinical laboratory tests conducted at research centres for IAVI-affiliated studies are performed under a quality assurance certification program developed and implemented by IAVI to ensure the highest quality and consistency in clinical laboratory testing.

All clinical research laboratories collaborating with IAVI should operate according to existing health and safety legislation within their particular country. All clinic and laboratory staff should be trained in Universal Safety Precautions and able to recognise the risks associated with their research activities. An active Health and Safety Committee should be in operation with an identified Health and Safety Officer on site. IAVI has developed a Laboratory Health and Safety Resource Pack that research centres are encouraged to utilize.

12. VACCINE-INDUCED HIV ANTIBODIES

In all IAVI-sponsored AIDS vaccine trials, volunteers are advised during the informed consent process to avoid standard antibody-based HIV testing outside the vaccine clinical trial unit because vaccine-induced antibodies may lead to a mistaken diagnosis of HIV infection. Appropriate diagnostic follow-up testing during and after the study is available to volunteers for as long as there is potential for a false positive result.

The aim of this testing is to (1) ensure that the volunteer is not infected with HIV, (2) ensure that the volunteer and others, whom the volunteer identifies, understand that he or she is not HIV-infected, and (3) minimize the possibility of stigma and discrimination for volunteers who develop vaccine-induced HIV antibodies and test positive on a diagnostic HIV antibody test. In addition, investigators will have the option of offering the volunteer a card stating that they are participating in a research study. Volunteers can use this card to explain why they should not receive HIV testing outside the study centre.

13. TREATMENT AND COMPENSATION FOR PHYSICAL HARM

It is IAVI's policy that no volunteer should be financially burdened by medical expenses as a result of participation in an IAVI-sponsored clinical trial. It is not likely that any study volunteer will be injured as a result of participating in an IAVI-sponsored clinical trial. However, in case of such injury, the volunteer will receive diagnostic testing to determine whether an illness is related to participation in the study, as well as necessary treatment (including appropriate referral) for study-related injuries, including emergency treatment, without charge. However, there is no additional monetary compensation or other form of compensation provided by IAVI for an injury caused by taking part in an IAVI-sponsored trial.

14. POST-EXPOSURE PROPHYLAXIS (PEP) FOR STUDY STAFF

IAVI requires that collaborating research centres offer post-exposure prophylaxis (PEP) when medically indicated to staff working on IAVI-sponsored studies who are exposed to blood or body fluids of HIV-infected or potentially HIV-infected individuals during study-related duties. PEP should be provided in accordance with the research partner institution's standard operating procedures (SOP) for PEP. Research centres that do not have standard procedures for PEP should follow IAVI's SOP, which is based on recommendations of the WHO and the U.S. Centers for Disease Control and Prevention (CDC). IAVI also requires that centres provide appropriate training in occupational health and safety to all staff working at collaborating clinical research centre studies whose activities involve contact with blood or other body fluids.

15. SOCIAL IMPACT

Research partners should take into account the potential social impacts of participation in AIDS vaccine research. Participation in a study can result in social benefits to the volunteer, such as improved understanding of risk reduction, access to health care, and the sense of well-being and respect derived from acting altruistically.

But social harm may also result from study participation, particularly for vulnerable and stigmatised groups. For example, volunteers might be stigmatised if they are perceived as

HIV-infected due to their participation, or if they are identified as belonging to a stigmatised group. Participation in a clinical trial or study could exacerbate underlying stigma that these populations already experience. Research partners should anticipate the potential for stigma and discrimination and work to mitigate social harm and enhance social benefits, while ensuring that benefits are not so great as to constitute undue inducement to participate.

16. GENDER

Gender issues should also be taken into account in designing research processes. Different factors may influence men and women as they consider whether to participate in AIDS vaccine research. For example, in some places, it has been challenging to recruit sufficient numbers of women in trials. This may be due to limitations on women's autonomy in decision-making, concerns about future fertility, concerns about contraceptive requirements given social pressures to bear children, or logistical barriers due to child care, household responsibilities, and income earning. In other places, it has been more challenging to recruit men.

Gender can also affect how a volunteer experiences participation. Men and women may experience different social impacts of participation based on gender-related social norms. For example, women who participate in some studies may experience more stigma from families or communities based on assumptions about the type of people who enrol in HIV-related studies or trials, or may fear that participation will result in relationship problems that could threaten their social and economic well-being. Sexual or gender orientation may also determine social impact. Recruitment, retention, and other trial processes should address these gender issues to promote a positive experience and mitigate any potential negative social impact.

IAVI has developed gender training manuals for India and Africa that can be used to orient research staff, CABs, and others to key gender issues in the context of AIDS vaccine research. IAVI recommends that all trial staff be trained in gender-related issues in the context of clinical research.

17. POST-TRIAL ACCESS

IAVI is committed to developing a safe, effective, accessible vaccine to prevent HIV transmission. If an AIDS vaccine tested by IAVI is found to be safe and effective, IAVI will work with its partners, national regulatory authorities, and other national and international stakeholders to make the vaccine accessible to the volunteers who participated in that vaccine's clinical trial(s), as well as to the communities and countries that supported the trial. However, because access to vaccines is often controlled by national regulations, IAVI cannot guarantee post-trial access in all cases.

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IAVI gratefully acknowledges the generous support provided by the following major donors

Basque Autonomous Government (Spain) ■ Becton, Dickinson and Company (BD) ■ Bill & Melinda Gates Foundation ■ Bristol-Myers Squibb ■ Broadway Cares/Equity Fights AIDS ■ Canadian International Development Agency ■ The City of New York, Economic Development Corporation ■ Foundation for the National Institutes of Health ■ The Gilead Foundation ■ GlaxoSmithKline ■ Google Inc. ■ Government of Japan ■ The Hearst Foundations ■ Institut Mérieux ■ Irish Aid ■ James B. Pendleton Charitable Trust ■ Ministry of Foreign Affairs and Cooperation, Spain ■ Ministry of Foreign Affairs of Denmark ■ Ministry of Foreign Affairs of The Netherlands ■ Ministry of Science & Technology, Government of India ■ National Institute of Allergy and Infectious Diseases ■ Norwegian Royal Ministry of Foreign Affairs ■ The OPEC Fund for International Development ■ Pfizer Inc ■ The Starr Foundation ■ Swedish International Development Cooperation Agency ■ Thermo Fisher Scientific Inc. ■ U.K. Department for International Development ■ The U.S. President's Emergency Plan for AIDS Relief through the U.S. Agency for International Development ■ United Continental Airlines ■ The World Bank through its Development Grant Facility

And many other generous individuals from around the world

As of January 2012