Acquired immune deficiency syndrome vaccine trials: Managing ethical issues before, during and after the trials

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RATIONALE FOR CARRYING OUT ACQUIRED IMMUNE DEFICIENCY SYNDROME VACCINE TRIALS

Prevention of a disease is always cost-effective, particularly when transmission of the disease continues to occur over a long period of time during chronic phase of the disease, the treatment is complicated as well as expensive and there is no definitive cure. The focus of research on prevention of such diseases has to be always on development of a safe and effective vaccine. Although there are some promising leads, global efforts in acquired immune deficiency syndrome (AIDS) vaccine development of over two decades have not resulted in discovery of a safe and effective AIDS vaccine yet.[1,2]

In India, three phase I AIDS vaccine trials have been completed so far. The first trial conducted at National AIDS Research Institute (NARI) in Pune tested adeno-associated virus (AAV) based human immunodeficiency virus (HIV)-I subtype C vaccine candidate (AAV vaccine) and that conducted at Tuberculosis Research Center (TRC), (now renamed as National Institute for Research on Tuberculosis, NIRT) in Chennai tested Modified Vaccinia Ankara based HIV-1 subtype C vaccine (MVA vaccine). The results of these two phase I trials have been published.[3-6] The third Phase I AIDS vaccine trial was recently completed by the same two centers wherein a DNA-MVA prime-boost strategy was evaluated among 32 healthy volunteers for safety and immunogenicity endpoints (In Press: Accepted for publication in PLOS One).

Nearly three decades after initial reporting of HIV/AIDS epidemic in India the epidemic did not show an explosive spread as in Africa.[7] The adult (15-49 years) HIV prevalence in India is estimated at 0.32% in 2008 and 0.31% in 2009 with approximately 2.4 million people living with HIV.[8] Although some states are showing signs of stabilization, some districts and states are showing signs of emerging epidemic.[8] Hence, availability of a safe and effective AIDS vaccine can be an important prevention option, especially for use in core groups at high risk of HIV acquisition like female sex workers, men having sex with men and injecting drug users.

PROTECTING NATIONAL AND COMMUNITY INTERESTS

The HIV/AIDS vaccine development and testing initiative was charted under the tripartite agreement between National AIDS Control Organization representing Ministry of Health and Family Welfare, Indian Council of Medical Research (ICMR) and International AIDS Vaccine Initiative (IAVI).[9,10] ICMR established a National Advisory Board to steer the policy development process in this regard. Under this agreement, visits were made to vaccine manufacturing units in India and mechanisms of post-trial technology transfer enabling indigenous vaccine production following generation of evidence of a safe and effective vaccine were decided. The arrangements for sharing intellectual property rights (IPR) between the vaccine developers, study sponsors and trial partners
in India were also discussed. Plans for sample and data transfer, partner involvement, witness during the consent process and roles and responsibilities of all trial partners were finalized during trial partners’ meetings. The range of advocacy initiatives for AIDS vaccine trial included a meeting of the Parliamentarian’s from Asia and Africa to support AIDS vaccine, regional and state level sensitization meetings, workshop on AIDS vaccine for science writers of Indian print media and meetings of medical professionals, community-based and Non-Governmental Organizations (NGOs) and local Government representatives at the trial sites. Much of this effort focused on making the various faces of the community aware of the soon to be initiated AIDS vaccine trials in India.

PREPARATIONS TO ENSURE ETHICAL CONDUCT OF THE TRIAL

Appropriate clinical trial sites with adequate clinical, laboratory and data-management infrastructure and a competent team of researchers constitute the basic foundation for conduct of a high quality clinical trial. NARI had conducted background research through its internationally sponsored research projects like preparation for AIDS vaccine evaluation,[11] and HIV Prevention Trials Network.[12] Baseline data on incidence, prevalence and risk behavior among various high-risk populations were generated. The data on willingness and concerns of high-risk populations to participate in AIDS vaccine trials were also generated.[13]

With support from IAVI, vaccine trial clinics were established at NARI in Pune and TRC (now renamed as NIRT) in Chennai; both permanent institutes of ICMR located in the high HIV prevalence states of Maharashtra and Tamil Nadu respectively. The facilities created at both the trial sites at NARI and NIRT were world class.

The lead scientists from NARI visited two AIDS vaccine trial sites in Bangkok, Thailand for on-site exposure and training. All the investigators at the NARI and NIRT trial sites were trained in basics of bioethics (human subjects’ protection), good clinical practice (GCP), web-based course in HIV vaccine clinical trials, gender issues and protocol specific procedures.

REVIEWS AND APPROVALS

Conducting high-quality phase I trials on healthy adults in a GCP environment can be very challenging and many ethical issues have to be managed before, during and after the trials. It is the responsibility of the investigators on the research team to ensure that ethical issues are properly addressed in the research study protocol. Reviews and approvals of such protocols by competent bodies are of great significance because the review mechanisms are expected to ensure that dignity, safety and welfare of the participants of clinical trials are protected.

Significance of regulatory review
Regulatory review examines animal and laboratory data, clinical trial product (drug, vaccine, etc.) import, sample shipment and transfers, transfer of raw data, IPR issues, exchange of scientists or visitors, and the study budget. There is a special provision for regulatory reviews for genetically engineered products. Careful regulatory review results in answering some of the ethical concerns related to fitness of the product and protection of the intellectual property.

Relevance of scientific review
Justification for conducting the trial in the context of national priorities, scientific merits of the research project and feasibility of conducting the study, strengths of the study designs proposed (Inclusion-exclusion criteria, sample size, randomization/blinding procedures, outcome assessment, follow-up schedule, pharmacy plan, etc.,) and provisions for technology transfer and capacity building are reviewed. Scientifically well-planned clinical trials often have a strong ethical foundation.

Review by ethics committees
Ethics committees have a significant role in ensuring that research proposals of great scientific merit are supported and the rights, safety and welfare of the participants are duly protected. Ethics committees assess the competence of the researchers and the research team and review measures taken for protection of vulnerable populations, women and children like the appropriateness of the informed consent, informed consent procedure, reimbursements and compensation for study participation, study specific educational material, provisions for protecting confidentiality and non-discriminatory practices and care and referral services for the trial participants, especially those experiencing adverse events.

All the AIDS vaccine trials conducted in India went through the above-mentioned review processes.

COMMUNITY INFORMATION, ENGAGEMENT AND SUPPORT FOR CLINICAL TRIALS OF VACCINES

Significant efforts were taken to sensitize various faces of the community about the AIDS vaccine trials. The
main objectives of the community program were to educate the community about the vaccine trials and identify volunteers who could be recruited in the HIV vaccine trials. The education and sensitization programs in the community were organized and carried out by the outreach team implementing Community Involvement Plan of NARI in Pune. However, in Chennai, NIRT collaborated with Y. R. Gaitonde Care (YRG Care), a reputed NGO working in the area of HIV/AIDS in similar efforts. The individuals who participated in the community-level meetings and showed interest in getting more information on AIDS vaccine trials were invited to visit the institutes and participate in more focused and small meetings. Those who expressed continued interest were invited for discussion with their significant others and were provided extensive information. They were critically assessed for their motivation and willingness to participate in the vaccine trial. This approach helped to identify individuals who were truly keen to participate, had adequate motivation and who were more likely to pass through the screening evaluation for participation.

Some of the major concerns the community had were related to vaccine safety and care and management of vaccine-related side effects and medical problems. As most clinical trials would have a mechanism for providing care and support during the trial phase only, some of the potential participants were concerned about long-term side effects and their clinical management as well as the follow-up mechanisms. The community and individual meetings conducted by the investigators were specifically designed to address such concerns. Our goal was to ensure that the community in which the AIDS vaccine trials were being conducted was well-informed and hence well-prepared to participate and support the trials. Assuring the community that the research study had undergone a critical review process helped in building trust at the community level.

Both NARI as well as YRG Care have Community Advisory Boards (CAB) in Pune and Chennai respectively. Traditionally and conceptually CAB are gatekeepers to protect community’s interests in research. They also help researchers by acting as advisors and facilitators. The members of the CAB participated in special meetings arranged to discuss the steps in study implementation and recruitment strategies and also helped in reviewing translations and back-translations of consent forms, study-related material, etc., They helped in field testing of training modules and study instruments and also contributed in building relationships with NGOs and Community-Based Organizations as well as in advocacy.

MANAGING ETHICAL ISSUES AMONG PARTICIPANTS OF AIDS VACCINE TRIALS

Protecting participants’ interests
Potential participants had safety concerns about the immediate, short-term and long-term adverse effects due to study product administration. They had additional concerns about testing HIV positive as a result of AIDS vaccine trial participation and consequently, matters like immigration, blood donation or qualifying in pre-placement examinations. As per the recommendation of the ICMR Central Ethics Committee, certificates of participation were issued to volunteers explaining that their HIV positive test result could be due to vaccine trial participation. The study participants were given complete assurance of confidentiality and information about various measures taken to keep the study-related data unlinked from their names with access to only authorized personnel. It was repeatedly emphasized to the participants that specially developed study information material, volunteers’ information brochure and the consent forms were the excellent sources of information for most of the potential questions. The requirement of condom use to prevent pregnancy and the adverse effects on the fetus was also reported to be inconvenient by many participants. Patient education material was specially developed to address all such concerns. In all the three Phase I AIDS vaccine trials conducted in India, only literate individuals were enrolled with an expectation that literate participants would understand the study procedures and their role in the study readily. In the Indian socio-cultural context, we thought it desirable to involve the spouse, close family members or specifically identified significant others in the decision making on vaccine trial participation.

Informed consent procedure
Realizing the importance of informed consent in sensitive AIDS vaccine trials lot of efforts were taken in finalizing the informed consent documents using simple and clear language. The consent procedure involved two steps: Screening consent and enrollment consent. A comprehension questionnaire was also developed to ensure that the participants understood the consent well and the participants failing in the test twice were considered non-eligible for trial participation. The informed consents were developed in English and Marathi language through a consultative process. In pursuance with principles of GCP, informed consent forms were signed in duplicate and one signed form was offered to the volunteer for personal records.

Re-imbursement and compensation for participation in research studies
Deciding the right compensation for the trial participants for their time, daily wages lost and expenses incurred
for the clinic visit is important because appropriate re-imbursement is permissible but inducement is not. During the AIDS vaccine trials conducted by NARI, opinion of the members of the Ethics Committee and CAB were sought to decide appropriate compensation.

Care and treatment for trial related and unrelated events
In a national level consultative process guidelines for care and treatment of AIDS vaccine trial participants were developed. For trial related adverse events or disabilities, full treatment and support were expected to be provided by trial sponsors free of cost. Medical insurance was provided to the participants to cover the costs of vaccine unrelated medical events, including any costs for hospitalization for the duration of the trial. Both the study implementing institutions gave an assurance to trial participants that they would be able to provide clinical care to them in their clinical facilities even after completion of the vaccine trial and referral services would be provided as and when necessary. The clinic visit schedule for the clinical trial participants was fairly intense requiring nearly 10-12 visits during the 12-18 months of study participation. The clinical trial centers used flexible timings to accommodate requests for early morning or late evening visits by the study participants.

Mechanisms for hearing and addressing grievances of trial participants
The informed consent form clearly outlined the path to be followed if the participants had any grievances. They were encouraged to contact the principal investigator for any problems. If they were not satisfied, they could contact the Chairperson Ethics Committee for guidance. If it won't be possible to settle the matter at this level, the participant would be referred to an independent Arbitration Board consisting of a senior physician, a judge and a social scientist. ICMR Central Ethics Committee recommended involvement of participant's representative in the arbitration process.

Possibility and prevention of inter-current HIV infection
There have been reports of HIV infection among the AIDS vaccine trial participants. Such infections occur mainly due to false sense of security among the vaccine trial participants who tend to take undue risk and practice high-risk behavior, which might result in HIV infection. Hence the AIDS vaccine trial participants have to be counseled throughout the trial regarding experimental nature of the vaccine candidates being tested and the need for risk reduction behavior including condom use and the need to monitor the participants throughout the trial. The participants are informed that special immunological tests can differentiate between antibody positivity due to vaccination and natural HIV infection. However, for such cases, it becomes important to provide access to care, support and treatment, including anti-retroviral therapy as indicated by the national guidelines.

Safety monitoring of participants
The trial teams were vigilant about any medical events or laboratory abnormalities among study participants that could have safety concerns. An independent body like a Safety Review Board or Data Safety Monitoring Board reviews the adverse and serious adverse events recorded among the trial participants. In the AIDS vaccine trials in India, no significant safety concerns were noted by the independent Safety Review Board during the reviews conducted 2 weeks after each dose administration.

MEETING THE CHALLENGE
India is becoming a hub for clinical trials[8-10] and many clinical trials are likely to be taken up including vaccine trials. In the AIDS area, prevention trials on microbicides and vaccines are underway globally. Phase I, II, and III vaccine trials have their own challenges and it is important to gear up for them at all levels. It is necessary to build the capacity to conduct clinical trials conforming to ethical framework and on par with international standards.

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