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Challenges and impact of conducting vaccine trials in Asia and Africa

New Technologies in Emerging Markets, October 16th-18th 2012; World Vaccine Congress, Lyon

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Immunization is one of the most beneficial and cost-effective disease prevention measures. There are global efforts to develop new vaccines for disease control. The vaccine clinical trials must be conducted in the countries where they will be used. This has led to vaccine trials being conducted across Asia and Africa where there is a high burden of infectious diseases. The setup and successful conduct of International standard GCP vaccine trials across trial centers located in resource constrained settings are challenging. The challenges, ethical considerations and impact of the implementation of clinical trials in low-resource settings are highlighted here to help vaccine development programs successfully conduct such trials.

Introduction

The 13th World Vaccines Congress was held in Lyon, France on October 16th-18th 2012. The key focus areas of the congress included the following: government immunization priorities, international regulation, public-private partnerships to develop vaccines, vaccine formulations including adjuvants, multi-vaccine manufacturing, prophylactic and therapeutic vaccine evolution, vaccine safety and public acceptance, issues in performing epidemiological safety studies, the rapidly changing vaccine development landscape and designing the next generation of vaccines.

In the session on New Technologies in Emerging Markets, the Challenges and Impact of Conducting Vaccine Trials in Africa and Asia was discussed.

Climate for Clinical Trials Conduct in Developing Countries

The climate under which clinical trials are conducted in Developing Countries is often challenging. There is a hisotory of unethical research in some coutries leading to a mistrust for clinical trials, stigma associated with disease conditions like HIV/AIDS and TB, recruitment of volunteers is often difficult in the complex cultural context, there is a long approval process for clincial trials, significant bureaucracy and corruption in some of the coutries and a need to protect the rights and well-being of vulnerable populations (as there are often not preexisiting laws in place in the country).

The infrastructure in many developing countries is underdeveloped. Trial site capacity and country scientific capacity development is essential to conduct international trials and there is an important role of community and vaccine preparedness activities.[1] It is necessary to manage the expectations of the community, media, politicians and long-term commitment and support is required at all levels.

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Selection of a Country to Conduct Global Clinical Trials

The factors essential in the country include political stability, supportive regional leadership, general understanding of scientific research, public recognition of the need for the vaccine being tested and a strong regulatory and ethics infrastructure.

Research Center Selection

The factors for the research center selection include strong scientific leadership at the center, a high quality partnership with the principal investigator and research team, a team with experience in conducting international clinical research, Infrastructure for conducting global clinical trials, a developed disease surveillance systems and access to the relevant patient cohorts.[2]

Challenges for Conduct of Clinical Trials

Regulatory and ethical approval process. In the absence of independent strong regulatory and ethical oversight of clinical trials the safety of research subjects and the scientific integrity of clinical data cannot be ensured.[3] In developing countries, the Regulatory, Ethical Approvals are often lengthy or there is an ill-defined approval process, there is significant bureaucracy, lack of regulatory staff with expertise in reviewing CMC (Chemistry, Manufacturing, Control) and preclinical sections leading to the

referral of the dossiers to external committees for review. This considerably increases the review time. The regulatory authorities have limited experience with novel vaccines and are often reluctant to take responsibility for novel trials being conducted in the country. It is necessary to keep track of numerous regulatory evolutions. There are multiple Institutional Review Boards and Ethical Review Committees from institutional to national level leading to the need to ensure coordination of reviews. There might be language barriers that are encountered. The approval process varies from country to country and it is often required to prepare separate documents and dossiers for submission in the countries.

Lessons learnt. The sponsors should consult with in-country investigators in the protocol development and submission process. The Sponsors and Investigators should work with Regulatory and Ethical Review Committee members as collaborators. Open communication early in the clinical development program is useful. It is good to establish company-wide standards that can be applied across all African countries that are based on the most stringent existing regulatory requirements. The time required for the approvals and import and export licenses should be factored in. It is helpful to have a good understanding of local processes and submission requirements. Proactive provision of background and supporting documentation and explaining the complex science involved in developing vaccines to the National Scientific Experts and Regulatory and Ethics committees is useful in speeding up the review process.

Capacity building in research centers. The infrastructure required for international trials includes clinical centers set up to good clinical practice (GCP) standards, safety, immunology and virology GCLP laboratories, a pharmacy and a data management unit. The supporting services include trial monitoring, reliable medical treatment and referral systems[4-6] and depending on the trial, voluntary counseling and testing (VCT), risk-reduction counseling and family planning services.

Lessons learnt. There is a need to leave countries and communities better off in terms of infrastructure, personnel and technical capacity. Vaccine trial centers should be standardized across global centers in terms of equipment, extensive staff training, SOP's, validated assays and accreditation. External quality assurance and international audits are useful for ensuring quality.

Clinical research staff training. This includes training on good clinical practices (GCP), good clinical laboratory practices (GCLP), standard operating procedures (SOPs), data management, gender sensitization, crisis communications, media management, financial management, monitoring, team management, advocacy and community mobilization and Train the Trainers training to ensure quality local trainers. Ensuring the trial team participates and presents at workshops and conferences is useful for capacity building.

Lessons learnt. There is often lack of appropriate expertise in the staff initially, a high staff turnover needs to be anticipated for as the trained staff often leaves for better paying positions, it is useful to provide SOP examples and templates and conduct follow up assessment and refresher training.

Community engagement, mobilization. Community engagement can be ensured by measures which include the research centers building the capacity of community staff to educate and train others, a community center being set up to facilitate recruitment and ensuring an annual revised community engagement plan, community engagement and mobilization framework, doing stakeholder and community mapping, ensuring a recruitment and retention plan for the trial volunteers and a communication plan for the trial with the different stakeholders.

Community advisory boards (CABs) could be involved in protocol development, the informed consent review process and review of operating procedures. Country and regional training sessions are useful to ensure well-functioning CABs.

Consulting with Civil Society stakeholders can be considered by the trial team including non-governmental organizations, community based organizations, women's organizations, policy makers, doctors, research organizations, lawyers, activists and religious leaders.

Outreach to the partners, communities and media to disseminate information on the vaccine program and science of vaccines can be done through newsletters, websites, documents and media articles in easily comprehensive language, which can be translated into the regional/local languages.

Lessons learnt. Widespread dissemination of information on clinical research is necessary to build trust and support for trials, ensure transparency about trial conduct, reassure potential study volunteers, ensure the study procedures are culturally sensitive, manage expectations regarding study results and post-trial access to the vaccine if it is successful and ensure that the research is sustainable in the community. The community should be involved in the design and implementation of the research and trial results distribution.

Cultural differences issues. Awareness of use of local medical practices, especially traditional medicine in the community, is helpful. There might be a lack of translations for certain words, phrases or concepts in the local language and use of clinical trial language may not be easily understandable to the trial volunteers and community. It is important to understand how blood draws, sample collection and biopsies are viewed locally and to consider how to address issues particular to a community or country e.g., implementation of informed consent if there is a high prevalence of under-aged mothers or clarity on the need for assent from children (discussions with parents and community leaders might help them understand the need for assent).

Ethical Issues Encountered in Clinical Trials

Informed consent. Informed consent documents need to be culture and gender sensitive, ethically sound, easy to comprehend, standard reimbursement should be offered which does not serve as an inducement for the volunteer and measures must be put in place to ensure volunteers' confidentiality. The documents must be translated into the participants' regional language. The informed consent document template can be prepared with the help of an expert group or with the input of experienced

investigators and can be adapted for use by other clinical researchers in the country.

The volunteers understanding of the key features of the trial can be demonstrated with the help of a "test of understanding" with scores. This enables counselors to effectively assess whether volunteer are truly informed of the potential risks and benefits of trial participation.

It is necessary to emphasize to the trial team about the need to obtain informed consent from each individual subject, rather than exclusively from family members or community elders and the importance of confidentiality. The trial team should not discuss the volunteers' participation or health information with their spouses or family members without the volunteers consent.

Care and treatment guidelines. There is a need to protect the rights and well-being of trial volunteers if there are no pre-existing policies in the country.[7]

An example is of the first ever HIV vaccine trials in India where policy development was done with government partners to ensure that trial volunteers received the best possible care and treatment for disease condition during trial or for possible HIV infection due to their at risk behavior. Care and treatment guidelines for the volunteers were formulated through a national consultation, arbitration boards were set up, medical insurance was offered to the volunteers for the first time in the country for the duration of trial and the guidelines were implemented in trials in Africa and India.

Post-trial access. Vaccines tailored to the strains in regions of greatest need ensure that populations in which the product is tested will have access to the vaccine in a timely manner. There has to be a realistic prospect of rapid post trial access for the trial volunteers and community if the vaccine works.[8]

Volunteer protection from stigmatization. It is necessary to ensure that the volunteer's data are securely stored. In trials like AIDS vaccine trials, it is important to make laboratory methods available to distinguish between natural HIV infection and vaccine-induced seropositivity (a positive HIV test after receiving HIV vaccine, even though the volunteer is not truly infected with HIV or a false-positive HIV test). Volunteers who tested positive for antibodies to HIV because of the vaccine were offered special participation cards to protect them from being discriminated against for immigration, insurance, employment purposes.

Working with vulnerable communities. An example of working with vulnerable Communities at high risk for HIV infection is provided. Consultations were held with MSM (men who have sex with men) and Transgender communities to understand their concerns and access to VCT, health care and treatment services and gain acceptance by communities. Formative research was conducted in at risk communities (Transgender and MSM) to assess their social structures, understand their risk profile, identify health seeking patterns, quality of available services and identify potential barriers and opportunities for participating in future HIV vaccine research studies. VCT workshops were held for the MSM and transgender communities.

Lessons learnt. The vulnerable communities might expect the vaccines to be available in the immediate time-span and some disappointment might be encountered when their expectations are not met. The access and retention of these communities may be challenge for clinical research and large-scale trials.

Impact of Clinical Research

The impact of clinical research is significant in the developing countries where it is conducted and is seen at the level of the Research Centers, Volunteers, Communities and Country level.

Research centers. These benefit in terms of staff gaining experience in conducting global standard research and getting trained in ICH/GCP, clinical, laboratory, data management procedures, use of new equipment and vaccine safety assessment. There is development of standard operating procedures at the center that improves disease management for the community the center caters too. There is improved international quality infrastructure and equipment.

The research teams gain national and international exposure and there are better opportunities for future research funding at the center.

It is important to ensure that the scarce health personnel and facilities often found in developing countries are not utilized for the clinical trials at the detriment of local health care for the community.

Trial volunteers. The volunteers have the benefit of being protected if the vaccine is efficacious, prior to the vaccine incorporation into the national policy and its availability in the country (which can take a number of years post completion of the trial).

The effect of herd immunity is seen in the community especially when large scale trials are conducted on a large numbers of participants in a given community. There is increased awareness of the disease condition in the community. The establishment or strengthening of research facilities and training of health personnel at the research centers leads to strengthened delivery of and access to health services by the community. An example is the conduct of HIV vaccine trials in developing countries — apart from an increased awareness about HIV/AIDS, there is promotion of reproductive health in the community. Men are involved in HIV prevention, the clinical research encourages HIV testing in the trial volunteers and community and could lead to the empowerment of women through education and counseling.

Large-scale trials help to engage communities and support the establishment of community advisory boards.

There is a need to guard against community dependence on the research institute for health care needs. Otherwise, post completion of the clinical trials, the community might find that their health care needs are not being met.

Country. The impact of the clinical research on the country is to provide employment and professional development for the personnel involved in the research (which ranges from physicians, nurses, laboratory personnel, data entry staff to drivers, etc.). The research helps build medical research capabilities in geographical areas of need (this often includes rural areas). There is a development of regulatory bodies and ethical committees to higher standards if global clinical research is being done in the country. There is ideally a development of Disease Surveillance

Systems in the country. In case vaccines are found to be efficacious in trials conducted in a country, there should ideally be accelerated Vaccine introduction into the country's Vaccination Program. This would leads to reduced morbidity and mortality in the country. There is an opportunity for infrastructure development and capacity building (both at the clinical and laboratory level) in the country.

There should be resources shared within and across disease enterties and between trials. This ensures that when candidate products are unavailable there is retention of scare skills at the centers and helps to reduce brain drain from the country.

Conclusion

The key learning from conducting vaccine research in developing countries is the importance of working with local experts and investigators, being aware of cultural differences and sensitivities, dealing with the long approval process and significant bureaucracy often found in developing countries, discussing the development plans and dossiers with the regulatory agencies and scientific committees when possible[9,10] and understanding the local concerns and addressing them even if they are not thought to be scientifically valid. In developing standards of care for volunteers, it is important to try and balance scientific priorities, equity, contextual realities, community expectations and cost-effectiveness.[11] It is important to be aware that in spite of ICH/GCP, technical requirements and capacities vary tremendously between countries. Global regulatory dossiers are still not a reality and there is a need to prepare documents according to the local requirements.

In summary, there are several good reasons for conducting clinical trials of vaccines against infectious diseases in developing countries in Asia and Africa. The conduct of these clinical trials poses several challenges and is likely to have a considerable impact in the countries. These are worth considering by the investigators, manufacturers and sponsors for optimal execution of the trials.

Disclosure of Potential Conflicts of Interest

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