

Review: Impact, Challenges, and Future Projections of Vaccine Trials in Africa

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Abstract. Immunization remains the most cost effective method for the control of infectious diseases. Therefore, there is a global effort to deploy new vaccines for disease control and eradication. These new vaccines must be tested in the settings in which they will be used. This necessity has required the conduct of many vaccine trials in Africa, where several infectious diseases with significant public health impact are prevalent. However, these areas have peculiarities and are just beginning to gain expertise in the conduct of such trials. The vaccine developers and sponsors of these trials may also not be conversant with some issues unique to the trial site. The understanding gap from both partners can result in challenges if not addressed during the planning phase of the trial. This review seeks to highlight the issues surrounding the conduct of clinical trials in resource-constrained settings and suggests some ways of circumventing them.

INTRODUCTION

Immunization remains the most cost effective method of prevention of infectious diseases over the past few decades.¹ Immunization has also accounted for the eradication of small-pox² and elimination of polio in most countries. This success has led to an intensive effort to deploy the strategy of immunization in the control and eradication of infectious diseases. Consequently, the importance of clinical trials to test the safety, immunogenicity, tolerability, and appropriate dosing schedule for vaccines cannot be overestimated as more vaccines are being developed against various pathogens.

Because the major burden of infectious diseases occurs in resource-constrained countries, it is essential that these vaccines are tested in these regions. However, to obtain a license for the use of a vaccine within a certain region, the product needs to be well tolerated and proven to be effective in that particular setting. Thus, late stage clinical trials of relevant vaccines are increasingly being conducted in sub-Saharan Africa.^{3,4} Some developing economies are also beginning to conduct early stage clinical trials^{5,6} which will likely also pose a unique set of challenges. These trials create opportunities for collaboration between the pharmaceutical and biotech companies, academia, investigators, sponsors, clinical trial monitors, regulatory authorities, and the study communities.

Investigators often play a central role in bridging the gap between the sponsors and most of the partners involved in the evaluation of these investigational products. These investigators are also the link between sponsors and the community. These interactions are often quite complex, and several benefits and challenges come into play. This complexity could undermine the desired objectives when the major players in the partnership or collaboration have little understanding of the prevailing circumstances in the region. Understanding and discussing these factors may help with projections of financial, time and labor costs as well as the development of better working relationships between the key players. This report seeks to highlight some of the challenges and suggests possible solutions to these challenges in conducting late stage clinical research within Africa, with a view of stimulating interest

in this area and beginning the process of making the sub-Saharan region the future hub of clinical research.

IMPACT OF CLINICAL TRIALS ON THE COMMUNITY

Clinical trials in Africa can be perceived to have positive and negative effects on the community where research is conducted. These effects range from the direct benefit to the participant who encounters a new vaccine that he or she may not otherwise have come into contact with, to the provision of better health care for the study population, and to potential risks encountered especially where a vaccine has rare risks that have been missed in the pre-clinical and phase I stages.

Positive impact of clinical trials. *Potential protection against the disease.* A recipient of an investigational product during the clinical trial has the benefit of being protected if such a product happens to be efficacious. There is usually a lag time between the clinical trial, publication of trial results, its incorporation into national policy, and implementation of the policy. Persons vaccinated in clinical trials will have protective immunity well ahead of the community. In some instances, there is also the extended benefit to the community of the effect of herd immunity, especially when trials have been conducted on a large number of participants in a given community. Such an effect may have contributed to the decrease in all-cause mortality among infants after the pneumococcal vaccine trial in The Gambia.⁷ However, the lag period in the uptake of new interventions can be mitigated by earlier sensitization of the target stakeholders as the vaccine is being developed. This sensitization will enable cost-effectiveness analysis, health system preparation, resource mobilization, and human capacity development.

Accelerated vaccine introduction into the community. Communities who take part in vaccine trials usually have the benefit of having such vaccines introduced first or at least early into their vaccination program.^{8–10} There is usually an agreement between the sponsors and vaccine producers with the governments of countries where these clinical trials are conducted to provide these vaccines as soon as feasible at no or reduced cost for an agreed period of time. For instance, a large number of vaccine trials have been conducted in The Gambia, including hepatitis B, pneumococcal conjugate vaccines, and *Haemophilus influenzae* type B. After the efficacy of these vaccines was proven,

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they were incorporated into the country's Expanded Program on Immunization schedule. Consequently, The Gambia has one of the most robust and comprehensive childhood vaccine programs of all the countries within the west Africa subregion and Africa as a whole. It was one of the first countries in Africa to introduce the hepatitis B, *H. influenza* type B, and pneumococcal vaccines.¹¹ The protection against a larger number of pathogens through these vaccines will certainly impact positively on the entire populace by reducing morbidity and mortality.

Health care and capacity building for the community. Conduct of clinical trials often comes with establishment or strengthening of research facilities in a given region. This conduct is usually also associated with the deployment of trained health personnel. For instance, there have been clinical trials with a team of two or more clinicians taking place in a health center with no resident doctor. Such doctors provide skilled services to the center, in addition to their working on the clinical trial. The benefit is that the study community has a greater chance to now encounter highly trained health care professionals able to attend to the health care needs of the population. There is usually also the direct benefit of free health care from the clinical team for the participant and their immediate relatives. The interaction with the clinical trial clinicians also results in better training of local health care personnel with resultant improvement of care to the local population.¹² In some settings, the tendency of locally available trained staff preferring to take up jobs in the urban often better paying government setting is now being reversed. More young professionals now move to rural research sites for the purposes of training and exposure to other highly trained professionals.

Health awareness in the community. The presence of research teams and activities in the community helps to create increased awareness of public health needs in general. This awareness may be in the form of health talks in the pre-vaccination clinics, information contained in information sheets for specific trials, or through specific interventions. For instance, in a recent trial to test the safety and immunogenicity of a conjugate vaccine, it was noted in the course of the follow-up period that children enrolled in the study soon after birth tended to develop malnutrition around the age of one year, most likely as a result of problems in either the weaning style or food, an activity that occurs commonly at this period. The Data Safety Monitoring Board then recommended an intervention, including health education and demonstrations of how to use locally available food items, to prepare healthy weaning meals. Subsequently, the prevalence of malnutrition among this cohort of study participants decreased, which was a good lesson for subsequent implementation. The improved access to health care results in improved child survival and reduced childhood mortality in intervention studies compared with the rest of the community. This finding is more evident in malaria studies in which the close follow-up results in disappearance of severe disease, making it difficult to be studied as an outcome measure.¹³

Infrastructure development and capacity building. Most clinical trials require the use of equipment that may not otherwise be available in the community/research institute, especially in settings that were not initially designed for clinical trials.⁶ For instance the pneumococcal vaccine trial in The Gambia and RTS,S vaccine trial in seven countries in Africa (Mozambique, Malawi, Kenya, Tanzania, Ghana, Gabon, Burkina Faso) required the acquisition of a good quality digital radiography

machine, and a good microbiology laboratory to enable the trials to be conducted to the required standards. Along with such upgrade in facilities often come staff training on the use and maintenance of new equipment, and thus capacity building for that community. Such an upgrade in infrastructure and staff capacity strengthens the research institutes. This upgrade makes them better contenders for future research funding. This result is especially true because such facilities will need to meet Good Clinical Practice and Good Clinical Laboratory Practice standards. However, there may remain issues with initial calibration of such equipment, availability of spare parts, and the expertise for repair of such equipment when they break down.

Furthermore, some new clinical trials require erecting new buildings or renovating existing ones, including sanitary facilities. These buildings and state-of-the-art equipment and laboratories are often taken over by the research centers or the government after completion of the trial, thus contributing to infrastructure development and improvement of standard of health care within the community.

Provision of employment opportunities. The regulatory authorities require clinical trials to be conducted to the highest standard and for the quality of results to be robust and trustworthy. Therefore, clinical trials are rigorous and require a large team of staff for the various tasks involved. In resource-constrained sub-Saharan Africa, which has high unemployment rates, vaccine trials provide opportunities for employment for the community at various levels such as doctors, nurses, field workers, data clerks, administrative assistants, drivers, cleaners, and other support staff.

The conduct of clinical trials in the region has greatly contributed to capacity development of the regulatory authority as they oversee these trials. The conduct of pivotal trials in the region has seen frequent inspection of the sites by U.S. Food and Drug Administration and the European Medicines Agency, and this has increased the interaction between these two leading regulatory authorities and the local regulatory authorities.

Challenges of clinical trials. Several challenges are encountered in the conduct of clinical trials in sub-Saharan Africa. Some of these challenges are caused by unique peculiarities of the region and others are more generic. These challenges if not well managed, may affect the credibility of clinical trial data obtained in the region. Several issues have been overcome on many trials sites, including the maintenance of cold chain for vaccines, and provision of continuous power supply for sample storage. This section seeks to highlight some pressing but often neglected challenges as a possible starting point to developing a coordinated approach to dealing with some of these problems.

Community dependence. One of the major drawbacks of clinical research in general, and vaccine research in particular, is the tendency for the communities to begin to rely on the research institute or project for their health care needs. This drawback is more so when such research is conducted in largely donor driven economies. The tendency is for the community to see the research institute as another donor agency, which is there to meet a certain need. The situation also tends to be worse in less literate communities in which understanding of the difference between research and development projects is limited. As a result, the time-bound nature of studies may not be clearly understood by the community, who then expect ongoing care long after funds for the study are no longer

available. The health facilities and government also begin to rely on such services and may fail to plan for appropriate staff and adequate drug, laboratory reagent, and other consumable stocks. The result of this failure is a rapid decrease in the key performance indicators of health facilities that were doing well during the active phase of a clinical trial. Because patients are unlikely to know about such a change in quality of care, an increase in the morbidity and mortality might occur.

Brain drain/circulation. Vaccine research, especially when funded by large pharmaceutical or international agencies, often pays better than other available local sources of employment. Although this leads to transient increase in income and standard of living for the involved employees, it could in certain countries lead to a brain drain from government and other private establishments to these centers. This drain can result in significant friction between the government and the research centers, especially where these centers are not government owned. It is therefore necessary to devise means of mitigating such effects. In some situations, there are policies in which anyone who has held government employment in a certain time frame is not eligible for a job interview at the research establishment unless there is permission from the government. However, there is a need to balance such policies because they may end up becoming discriminatory toward staff or prove to be detrimental to the usual capacity building/strengthening associated with working with such establishments.

However, in other settings, beneficial effects of such movements of staff have been noted. Staff involved in clinical trials are more willing to work in rural areas where many research sites are located because of better incentives. In these situations, there is more of brain circulation than a drain, and this may result in skilled care being better available where it is needed. Governments where feasible, may need to make efforts to match these incentives, especially for their staff in rural areas.

Budget. The area of clinical trials might be new in a specific region. As a result, experience is often limited and investigators seem to have a tendency to overlook or under budget for the needs that will arise. Some funding bodies do not want a miscellaneous budget line for incidentals in the budget. In addition, there is often a time lag between the time of budgeting and the actual initiation of the studies because of the period required to get regulatory approvals and import licenses. In most of the resource-constrained countries, the local currency is unstable and depreciation in value tends to put a stress on the budget.

Sometimes the budget is already finalized before details of the protocol are in place. It is necessary that the study team has all details of a project at the point of budgeting, such as duration of follow-up, frequencies of home and clinic visits, and frequency of blood sample collection. The team also needs all the information about their study area mapped out so that they can accommodate the necessary costs when negotiating for a project. Having in place a health and demographic surveillance system enables the investigators to know the number and location of potential study participants. Costs to maintain this surveillance system also need to be factored into the study budgets. Unless these drivers of budget lines are known and well articulated, they can result in unprecedented challenges. These challenges place a responsibility on the overall principal investigator of the study to ensure that adequate provision and planning is made for such trials, which may involve employment of expertise outside what is usual for the team, such as financial experts.

These issues are further complicated by the fact that some funders are unwilling to either review or supplement the budget once agreements have been finalized. Taken together, there are several anticipated and unanticipated factors that could increase the cost of clinical trials in developing countries, and should be considered when preparing the budget. In addition, a degree of flexibility over budgets or addition of a reasonable proportion of the budget as incidentals would be useful, otherwise the quality and standards of the trial might be compromised. This problem may also require legal and project management support for the study team to ensure their part of the agreement is well taken care of for optimal and seamless conduct of the study.

Consent process. The Informed Consent Forms (ICFs) and information sheet from sponsors of clinical trial are often long, could range from 10 to 20 pages, and contain a mixture of technical and legal language.^{14,15} Although there are some good reasons for the content of these lengthy ICFs and subject information sheets, this content poses a significant challenge in executing trials in developing countries. Such a lengthy information sheet will take a lot of time to explain to an illiterate person, and is also not likely to be comprehended to any reasonable degree. Moreover, to have such a rigorous consenting process for a study that requires a large number of participants recruited per day will require a large staff. Inability to provide adequate staffing will lead to either a poor consenting process or huge waste of participants' time, which discourages further participation. This aspect is often neglected and many sponsors insist on lengthy information sheets without a commensurate budget for the staff required to administer them appropriately.¹⁶

The language of the subject information sheet is often a challenge because most of the major local languages are spoken and do not have any known written form.¹⁷ Where written forms of these languages exist, they are not easily read even by literate persons. Thus, consent forms in many of these regions are currently accepted in English. This acceptance poses a wide range of challenges because most of the rural population in which illiteracy rates are high is also unable to read English. This problem also means that a study in such an environment will require extra capacity to explain in detail the contents of these forms to each person. This difficulty can be resolved when the consent process continues during the study and at every visit an attempt is made to assess the understanding and more explanation is provided. To obviate variation in explanation if the local language is not written or even where it is written but there is high illiteracy, the study team can prepare a video/audio tape of the consent process so that every person gets consistent information. The potential participants watch or listen to the tape in the presence of a study team member who is competent to answer the questions. Depending on the nature of the trial, the tape could be watched or listened to by a group. This policy is especially important because > 38% of adults in sub-Saharan Africa lack the literacy and numeracy skills required for everyday life, and the situation is worse in women and in rural areas. Illiteracy rates are as high as 90% in some settings.¹⁸

Also important during the consenting process is the need in many settings in Africa for community consenting. This consent is required because of the communal nature of most communities in Africa where a community leader needs to have a say in what is allowed into his or her community.

If not well managed, this policy could lead to abuse of authority and coercion of potential study participants. Conversely, getting sponsors to see the need for this process may be difficult in the absence of a clear understanding of the culture and tradition of a particular community. The same policy applies to spousal consent because in some communities, it is not sufficient to have only one parent provide consent; the other parent, usually the husband, may be required to give consent as well. In some cases, the decision is taken by an uncle or grandfather, and there may be significant variation in what is acceptable even within the same community.

Another peculiarity in the consenting process in many resource-constrained settings is the high prevalence of underage mothers. It is not uncommon to have mothers who are less than 18 years of age in these settings. Whether such a mother can provide consent for herself and her child to participate in a vaccine trial is of considerable debate.¹⁹ This situation in most settings in Africa is accepted in studies and the participant is allowed to consent as a mature or emancipated minor. However, some sponsors have issues with this definition.

Also worth mentioning is the issue of the legal guardian. In many parts of Africa, it is customary for young children to be left in the care of relatives to be weaned off breastfeeding or to enable their parents to seek employment elsewhere within or outside the country.²⁰ These relatives often do not hold any legal document stating their relationship, but may be fully responsible for the child's care. Whether such a foster parent without a legal document for his or her ward can give consent to have this child enrolled in a study is also debatable. This problem can raise issues because some studies have shown that non-parents are more likely to consent to have children participate in trials than parents.²¹ What should be obtained in such situations is not yet clearly defined in many settings, leaving a gray area that needs to be explored further. Sponsors are encouraged to accept what is culturally acceptable to the community, and the local study team has to put mechanisms in place to ensure that the rights of the children are not infringed.

In illiterate populations, there is often a need to appoint an impartial witness who is educated and understands the ICF and information sheet to act as a witness to the consent process for the illiterate person who cannot read these documents. This situation often poses another challenge to consenting because men who are often the educated members of communities often delegate the responsibility of health care to the women and may thus be unwilling to come along to clinic visits with their wives or may be too busy providing for their families. This problem has in some instances led to study teams delegating a few educated members of communities to serve as impartial witnesses. How impartial this process is may then become an issue, especially where these persons serve as witnesses over the long term.

Some African cultures require that inheritance is through the mother lineage, not the father's. Thus, maternal uncles are responsible for the children of a woman. In this context, it would be required that this maternal uncle and not the father give consent for study participation. Communicating this to external sponsors may pose a challenge, especially when there is some cultural transition within the community as occurs in much of the developing world, and some persons opt to have fathers give consent.

Another issue is the lack of clarity on the age at which consent should be obtained from study participants. For instance,

in a multisite study involving three countries in West Africa, age of assent was defined as 12–17, 13–17, and 15–17 years of age in three countries.²² Although most countries will accept the teenage age group, this acceptance may not resonate with a sponsor from another country, such as the United States, where the legal age of assent is seven or eight years. These matters call for tolerance and letting local population requirements prevail. Despite these age limits in rural settings, the demand for consent from children may be perceived as eroding the parental autonomy. This problem requires a well-guided and negotiated discussion with community leaders to help them understand the need for consent and avoid a negative perception of the research requirements.

Diary cards. The use of diary cards that are completed by the study participants in their homes is generally not feasible in vaccine trials in developing countries because most participants are illiterate. An additional complement of staff trained to perform this task will be required to visit participants' homes to complete the diary cards. This necessity will increase costs. In other instances, involvement of the entire household is required to enable a literate family member to complete the card for the mother.

Culture and belief systems. The belief system within a community may pose significant challenges to the conduct of clinical trials.¹² In some instances, it is difficult to recruit participants with a clear understanding of trial related procedures.⁶ For instance, certain communities believe that blood is sacred and that young children become ill after venous blood samples have been collected from them.²⁰ At best, most mothers know only about obtaining blood samples through pin pricks on the fingers. Such mothers become worried when venous blood samples are collected in clinical trials, and this issue leads to their withdrawing their children from the study. This problem is often heightened when a study requires the collection of samples into several tubes, which can be met with significant resistance because of the perception that this implies that more blood is being collected.²³ A clear explanation of what blood samples in different tubes are to be used for is usually helpful in allaying anxiety. In other regions, there is the belief that if a child received oral polio vaccines, the child could become sterile and may be infected with human immunodeficiency virus. Such beliefs would affect acceptance of clinical trials in a given community.²⁴ As a result, the need for education and re-education and the involvement of key community leaders cannot be overemphasized. As a result, sponsors need to be flexible in the planning phases, allow for long windows for each visit, and calculate a significant dropout rate into the original sample size estimations. The presence of community advisory boards is crucial in this regard to help the study team navigate through wrong perceptions from the community and also widely held beliefs that are counterproductive to research outcomes.

Monitoring and communication. Until the mid 1990s, most clinical trials were conducted in Europe, the United States, and Japan. Today, 10% of all clinical trials occur in Africa.⁴ The conduct of these trials requires the strictest standards as they involve human subjects. The International Conference on Harmonization/Good Clinical Practice guideline is often applied to such research.²⁵ There are certain procedures, such as reporting serious adverse effects, that require fast means of communication to the sponsors by telephone or e-mail, which are, unfortunately, either expensive, dysfunctional, or non-existent in rural trial centers. Sponsors need also to be aware

of these needs and to anticipate them. In addition, clear monitoring and communication plans need to be communicated and agreed upon before budgets are finalized and signed. This problem poses a challenge to local institutions to ensure training of research managers and auditors so that required personnel are available thus making clinical trial monitoring cheaper and more effective in the long run.

Disposal of waste. Waste materials could be produced by clinical trials. These materials need to be disposed of appropriately because much of these substances may be biologically hazardous. However, in resource-constrained settings with weak regulation or vigilance, there may be a tendency not to adhere to universal precautions in a bid to cut costs. This policy puts at risk the person responsible for disposing this waste and possibly others in the community. This risk may not have been encountered in the absence of clinical trial activity in that setting.

Transportation system. In most parts of Africa as with the rest of the developing world, transport systems are still underdeveloped. This problem may lead to study participants arriving late or not at the required times, and also creates difficulty in transporting persons with adverse events and serious adverse events for appropriate care. Circumventing this problem will entail alternatives that are likely more expensive, and poses a significant burden on the budget. In addition, the difficult terrain and seasonal poor condition of the roads may deny some participants access to care.

Investigator professional development. Scientific publication is a major parameter for assessment of investigators, but publication is unfortunately limited for clinical trials despite the huge investment of time and labor. Investigators often do not believe that they are getting commensurate scientific output for their intensive input into these trials. In some instances, samples are processed in laboratories overseas and with little provision for technology transfer and capacity building in country.⁶ To be more cost effective, some investigators develop interlocking studies that are feasible within the main vaccine trials. Such studies may entail collecting extra but safe volumes of blood and/or swabs for additional analysis at the same time the participants are sampled for the primary trial.

Surprisingly, this process is often resisted by some trial sponsors, although such additional studies may not interfere with the parent study. It is hoped that local investigators would be allowed to benefit from the clinical trials by either technology transfer, undertaking ancillary studies, or funded for relevant higher degrees. These processes will help to place the investigators in a better position to continue to attract funding. This situation is currently changing as some sponsors accept investigator-initiated ancillary studies and provide resources. There is a need for technology transfer to the centers in Africa so that more of the centralized laboratory support can be present in the region, but this process requires proper planning and co-investment by the local institutions in infrastructure development for the future.

FUTURE PROJECTIONS

As more trials are conducted in Africa and capacity is built, it will become necessary to develop the capacity not only for vaccine testing, but for vaccine development and conducting early phase vaccine trials. Most of this capacity is currently being implemented in more developed settings, although the Indian subcontinent is fast gaining ground in this regard. This

advancement will ultimately decrease the cost of interventions, especially those for use in the region and will create employment opportunities in the region. It should also encourage research and intervention that is relevant and acceptable. This issue is being addressed with three phase I facilities supported by the INDEPTH-Network that have been set up in Bagamoyo, Tanzania, Nairobi, Kenya, and Kintampo, Ghana. The initiative will be supported by the newly launched African-controlled human malaria infection studies platform involving seven research centers in Africa and several northern partners. This initiative has the prospect of developing capacity in early clinical product development in the region.

The need for clinical trials to be conducted in settings to which diseases are endemic is as obvious as the challenges highlighted. Many funding agencies have begun to recognize these challenges and have included capacity building, networking, and infrastructural upgrading as integral parts of the required outcome of the projects. Communities and some governments are beginning to reciprocate by contributing to capacity building and improvement in infrastructure. More cooperation of stake holders, including vaccine developers, sponsors, governments, and the communities, is needed. It is most likely that sustained interest and activities will with time yield the desired dividends. However, some issues, such as local culture and belief system, may never change and there is a need to work with understanding within a given context.

The drive to achieve greater collaboration taking into account the local context and increasing government participation needs to be intensified. Along with this collaboration and participation is the need for local study teams to continue to put measures in place to ensure that data collected are credible and participants remain protected from harm.

In summary, there are several good reasons for conducting clinical trials of investigational products against infectious diseases in developing countries. The conduct of these clinical trials pose challenges, as well as peculiarities that are worth considering by the investigators, manufacturers, funders, and sponsors for optimal execution of the trials. It is envisaged that with coordinated, targeted, and sustained attention to resolving these challenges, the future health care delivery system will be greatly improved.

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