

Vaccine trials in Africa: Impact and challenges

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1. INTRODUCTION

Immunization remains the most cost effective method of prevention of infectious diseases over the past few decades (Duclos, Okwo-Bele, Gacic-Dobo, & Cherian, 2009). Immunization has also accounted for the eradication of smallpox (Birn, 2011), and elimination of polio in most countries. This 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, efficacy, tolerability, appropriate dosing schedule and effectiveness for vaccines cannot be over emphasised as more vaccines are being developed against various pathogens.

As the major burden of infectious diseases occurs in the resource constrained countries, it is essential that these vaccines are tested in these regions with the same rigor as anywhere else. To obtain a licence for the use of a vaccine within a certain region however, 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 (Craddock, 2012; Rehnquist, 2001). Recent increases in the number of early phase clinical trials being conducted in developing countries have brought a set of additional factors that pose considerable challenges to planning and implementation of clinical trials in these settings (Beurret, Hamidi, & Kreeftenberg, 2012; Louisa, Takeuchi, Setiabudy, & Nafrialdi, 2012). These trials create opportunities for collaboration between the pharmaceutical and biotech companies, investigators, sponsors, clinical trial monitors, regulatory authorities and the study communities. Investigators often play a central role in filling the gap between the sponsors and most of the partners involved in the evaluation of these investigational products including the community. These interactions are often quite complex, with several benefits and challenges coming 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 sub region. Understanding and discussing these factors may help with projections of financial, time and labour costs as well as the development of better working relationships between the key players. This chapter seeks to highlight the impact and some of the challenges and innovative ways of conducting early and late stage clinical research within Africa, with a view of stimulating interest in this area and charting the process of making the sub-Saharan Africa region a future hub of clinical trials.

2. IMPACT OF VACCINE TRIALS ON THE COMMUNITY

Vaccine trials in Africa can be perceived to have varying effects on the community where research is carried out. These range from the direct benefit to the participant who encounters a new vaccine which he/she may not otherwise have come into contact with, to the provision of better health care for the study population to potential risks that can be encountered especially where a vaccine has not been well evaluated in the pre-clinical and phase I stages (Idoko, Kochhar, Agbenyega, Ogutu, & Ota, 2013).

Box 1: Impact of Vaccine Trials:

- Potential for protection against disease
- Accelerated vaccine introduction into the community
- Health care and capacity building
- Health awareness
- Infrastructure development
- Employment opportunities
- Community engagement

2.1 Positive Impact of Vaccine Trials:

2.1.1 Potential Protection Against Disease:

A recipient of an investigational product during the vaccine trial has the benefit of being protected if such a product is found to be efficacious. Since there is usually a lag time between the clinical development and ultimate registration of a product leading to its roll out through a national policy and program, such an individual 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 large scale trials (phase IIIB or phase IV) have been conducted on large numbers of participants in a given community. This may have contributed to the decline in all cause mortality among infants following the large Pneumococcal Vaccine trial in The Gambia (Cutts et al., 2005), and insecticide treated bed nets (ITNs) trial in Kenya (Snow et al., 1999). However, the lag period in the uptake of new interventions can be mitigated by earlier sensitization of the target stakeholders during the product development phase. This will allow for cost effectiveness analysis, health system preparation, resource mobilization and human capacity development ensuring health system optimization ahead of time.

The reverse is however also true as if the vaccine is found to have significant deleterious effects or not protective; the study community bears the brunt. For instance, the use of thalidomide as an antiemetic in pregnant women in the 1960s led to teratogenic effects in hundreds of children as this drug had not been well researched for this indication (Miller & Stromland, 2011). A recent drug trial in France also left 1 man dead and several others with neurologic disability after they received increasing doses of a drug aimed at treating anxiety and motor disorders associated with Parkinson's disease, and chronic pain in people with cancer and other conditions (Butler & Callaway, 2016). The same would apply for poorly evaluated vaccines in the early stages of development. There have also been a number of vaccine trials that have shown no protective effect despite being safe such as SPf 66 (Nosten et al., 1996) MSP1 and ME-TRAP (Bejon et al., 2006; Ogutu et al., 2009). However, these trials for vaccines which proved ineffective in protecting against the diseases for which they were designed have been major learning steps in vaccine development in resource constrained settings.

2.1.2 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 programme ("Ethical issues facing medical research in developing countries. Gambia Government/Medical Research Council Joint Ethical Committee," 1998; Kremer, 2001; Shapiro HT, 2001). There is often an agreement between the

sponsors and vaccine producers and the government 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*. Following the proven efficacy of these vaccines, they were incorporated into the country's Expanded Programme of Immunization (EPI) schedule. Consequently, The Gambia has one of the most robust and comprehensive childhood vaccine programmes of all the countries within the West African sub-region and Africa as a whole (UNICEF/WHO, 2011). The protection against a larger number of pathogens through these vaccines will certainly impact positively on the entire populace reducing morbidity and mortality.

2.1.3 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 is usually also associated with the deployment of trained health personnel. For instance, there have been clinical trials with a team of clinicians taking place in health centres with no resident doctor. Such doctors provide some skilled services to the centre in addition to their working on the clinical trial. The benefit is that the study community has a greater chance to 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 improved care to the local population (Arenas-Lopez et al., 2011; Ogutu, Baiden, Diallo, Smith, & Binka, 2010; Tinto et al., 2014). In some settings the tendency of locally available trained staff preferring to take up jobs in the urban often better paying government settings is now being reversed. More professionals than previously now move to often rural research sites for the purposes of training and exposure to other highly trained trial professionals (Tinto et al., 2014).

2.1.4 Health Awareness in the Community:

The presence of research teams and activities in the community help to create increased awareness of public health needs in general. This 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 during the course of follow up of the children enrolled in the study from soon after birth that they tended to develop malnutrition around the age of one year. This was likely as a result of defects in the weaning style or

feeds, an activity that occurs commonly at this period. This led to the intervention of the Data Safety Monitoring Board which 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 declined, which was a good lesson for subsequent implementation. The improved access to health care results in improved child survival with reduced childhood mortality in intervention studies compared to the rest of the community. This particular intervention had a spill over effect to the community as other caregivers not involved in the main study routinely participated in these education and demonstration sessions. This is more evident in malaria studies where the close follow up results in disappearance of severe disease making it difficult for such disease to be studied as an outcome measure (Steketee & Campbell, 2010).

2.1.5 Infrastructure Development and Capacity Building:

Most trials require the use of equipment which may not otherwise be available in the community/research institute especially in settings that were not initially designed for clinical trials (Kilama, Chilengi, & Wanga, 2007; Louisa et al., 2012). For instance the pneumococcal vaccine trial in a province in The Gambia required the acquisition of a high quality digital X-Ray machine, and a microbiology laboratory to enable the trials to be conducted to the required standards. Along with such upgrades 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, which makes them better contenders for future research funding. This is especially so as such facilities will need to meet Good Clinical Practice (GCP) and Good Clinical Laboratory Practice (GCLP) standards. This has been also the case of RTS,S malaria vaccine trials where all the centres involved acquired digital X-ray machines and bacteriology laboratories (Tinto et al., 2014).

Furthermore, some new clinical trials require erecting new buildings or renovating existing ones including construction of sanitary facilities. These buildings plus the state of the art equipment and laboratories remain within the research centres or the government health facilities on completion of the trial, thus contributing to infrastructure development and improvement of the standard of health care and research capacity within the community.

2.1.6 Provision of Employment Opportunities:

Regulatory authorities require clinical trials to be conducted to the highest standard and for the quality of results to be robust and trust worthy. Therefore clinical trials are rigorous and require a large team of staff for the various tasks

involved. In resource-constrained sub-Saharan Africa with high unemployment rates vaccine trials provide opportunities for employment for the community at various levels such as doctors, nurses, field workers, data clerks, administrators, financial managers, logisticians, drivers, cleaners and other support staff. However, the sustenance and retention of these skilled workers is not easy in circumstances where the trials are not conducted in settings with the framework of continuity after the specific studies are over. This is key for development of the region as a hub for clinical trials in the future as there is need for ready platforms that can initiate and execute studies on short notice with minimal lag period. This calls for a concerted effort by all partners involved in clinical trials to nurture the varied clinical research careers that are critical for product development.

2.1.7 Community Engagement:

The presence of research institutes in the community often leads to engagement with the community which may go beyond the direct impact or benefit from individual research projects. This leads to a generally more enlightened populace as it relates to issues of health. Schools and other institutions are likely to engage in field trips to these institutions resulting in more interest in the sciences that allow the institution to be effectively run. A number of institutes offer foundation degrees or training courses which create educational opportunities where there may previously have been none including platforms for MSc, PhD and post doctoral projects. All these may ultimately lead to better community engagement with the sciences and overall capacity development within the community.



Figure 1: Community engagement: a crucial part of vaccine trials.

Photo courtesy Abdoulie Cham MRC Unit, The Gambia.

2.2 Challenges of Vaccine Trials

As in every operation, several challenges are encountered in the conduct of clinical trials in sub-Saharan Africa. Some of these are due to the unique peculiarities of the region while others are more generic. These challenges if not well managed, may affect the credibility of clinical trial data obtained in such regions (Idoko et al., 2013). This section seeks to highlight some pressing and often neglected challenges as a possible starting point to developing a co-ordinated approach to dealing with some of these problems.

Box 2: Challenges of Vaccine Trials:

- Community dependence
- Brain drain/circulation
- Waste disposal
- Budget constrains
- Obtaining informed consent
- Follow-up and protocol adherence
- Stringent enrolment criteria
- Use of diary cards
- Culture and belief systems
- Monitoring and communication
- Institutional understanding of trial needs
- Use of electronic data collection methods
- Vaccine/sample storage/transport conditions
- Absence of local reference values
- Supplementary EPI campaigns
- Use of prophylactic or post vaccination antipyretics
- Infant weight faltering
- Investigator professional development.

2.2.1 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 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 there to meet a certain need (Idoko et al., 2013). The situation tends to be exacerbated by low

literacy levels and lack community understanding of the difference between research and development projects. As a result, the time-bound nature of studies may not be clearly understood by the community, who then expect continued 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 consumable stocks. The result of this is a rapid decline in the key performance indicators of health facilities that were doing well during the active phase of a clinical trial. As patients are unlikely to know about such a change in quality of care, an increase in the morbidity and mortality might occur. Clear communication which starts prior to study enrolment and continues throughout the course of a trial is crucial. Such timelines and budget limitations need to also be emphasized at community meetings and other community engagement activities. Trial teams need to also ensure that where feasible they strengthen the capacity of local health teams to continue to provide optimal care beyond the life span of the trials.

2.2.2 Disposal of Waste:

A lot of waste could be produced by some clinical trials. These need to be disposed of appropriately as a lot of these substances may be biologically hazardous. However, in resource-constrained settings with weak regulation or vigilance, there is a tendency not to adhere to the rules and universal precautions in a bid to cut cost. For instance in one trial it was noted that study staff chose not to adhere to colour coding required for biohazard waste disposal bags as they temporarily run out of these (personal communication). This puts at risk the individual 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. This is worsened by the high cost of establishing an optimal waste disposal system that can often not be borne by a single clinical trial however large. Research sites need to follow international and local regulations as available in the course of waste disposal and training and re-training on these issues is essential. This calls for a concerted effort by the governments, communities and researchers to put up waste disposal facilities for the safety of the society.

2.2.3 Brain Drain/Circulation:

Vaccine research especially when funded by pharmaceutical or biotech companies, public-private partnerships 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 local private establishments to these centres. This can result in significant disharmony

between the government and such research centres especially where these centres are not government owned. It is therefore necessary to devise means of mitigating such effects. Ensuring that the human resource involved in research activities also support the clinical care of the community through an agreed framework that supports the greater good of the community but not compromising standards. In some situations for instance, there are policies requiring that anyone who has held government employment within a certain time frame is not eligible for a job interview at the research establishment unless there is permission from the government. There is however a need to balance such policies as they may become discriminatory toward staff or prove to be detrimental to the usual capacity building/strengthening associated with working with such establishments.

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

2.2.4 Budget:

The area of clinical trials is still quite new in the region. As a result experience is often limited and investigators seem to have a tendency to overlook or under budget for the subtle needs which can arise during the trial. 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 due to the period required to get regulatory approvals, import licences, review of product development milestones among others. In most of the resource constrained countries the local currency is unstable and depreciation in value tends to put stress on the budget. This is worsened by the fact that almost all consumables used in clinical trials are imported from the global North to resource constrained countries. This makes the cost of these commodities prohibitive due to transportation cost, taxes and lag time in delivery (particularly important where items are perishable) and limited numbers of vendors deal in them. The foregoing makes them highly sensitive to currency fluctuations.

These uncertainties need to be factored in when budgets are drawn up, and calls for the recruitment of competent finance managers to work with the study teams on the planning and execution of the study. These should be financial managers with a good understanding of product development logistics which are also difficult competencies to come by in resource constrained settings.

Sometimes the budget is already finalised before details of the protocol are agreed on. For instance the sponsor at initial contact with the site could suggest that a study will require 500 participants recruited over 6 months and each participant will be followed up for another 6 months. The cost of these will certainly differ if participants are visited in their homes every two weeks for the 6 months and need blood samples collected for laboratory investigations compared to a less vigorous follow-up scheme. The latter with intensive home and clinic activities would require more staff and resources than the former, but this might not be considered if the intensity of activities are either not disclosed or anticipated at inception and planning of the budget. Moreover, a simple procedure such as visiting study participants in their homes could turn out to be more expensive than anticipated as the lack of addresses could make a team waste considerable time and resources in the process of accessing such participants. Therefore, the study team should have all the information about their study area mapped out such when negotiating for a project so they can justify their costs with respect to the requirements of the study. Having in place a health and demographic surveillance system enables the investigators to accurately estimate the number of potential study participants and where these participants may be located. 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. In circumstances when budgets are 'per patient' based, it calls for ingenuity in budgeting to cover all the cost areas antecedent to the study without setting up the study for cost overruns that may create study partnership fallout. A number of studies may also depend on climatic seasons and any slip in the timelines can have significant cost implications.

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. Therefore, good legal and project management support for the study team is needed to ensure their part of the agreement is well addressed for optimal and seamless conduct of the study. These all come at additional cost and need to be built in over time through a holistic partnership approach.

2.2.5 Consent Process:

The Informed Consent documents (ICD's) and information sheet from sponsors of clinical trial are often very long, and could range from 10 to 20 pages containing a mixture of very technical and legal language (D, 2012; Preziosi et al.,

1997). Although there are some valid reasons for the contents of these lengthy ICF and subject information sheet, this poses a significant challenge when it comes to execution in resource constrained settings. Such lengthy information sheets will take a lot of time to explain to a participant with limited education, and will also not likely be comprehended to any reasonable degree. Moreover, having such a rigorous consenting process for a study that requires a large number of participants recruited per day will require more personnel. 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 with many sponsors insisting on lengthy information sheets without a commensurate budget for the staff required to administer them appropriately (Lang, 2011).

The language of the subject information sheet is also often a challenge as most of the major local languages are spoken and do not have any known written form (Fairhead, Leach, & Small, 2006). Where written forms of these languages exist, they are not easily read even by the literate. Thus consent forms in many of these regions are currently accepted in English. This poses a wide range of challenges, as most of the rural population where illiteracy rates are high are unable to read English as well. This also means a study in such an environment will require extra capacity to explain in detail the contents of these forms to each participant. This can be resolved where the consent process continues during the study and at every visit an attempt is made to assess the understanding and more explanation 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 so that every individual gets consistent information. The potential participants watch/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 can be watched/listened to as a group. In addition, a multimedia informed consent tool has been developed in Gambian local languages to deliver study information to low literacy participants (Afolabi et al., 2014). This has also been used with good outcome in Western Kenya (*personal communication*).

Another peculiarity in the consenting process in many resource constrained settings is the high prevalence of under-aged 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 for her child to participate in a vaccine trial is of considerable debate (Erulkar & Muthengi, 2009). This in most African settings is accepted and the participant allowed to give consent as a mature/emancipated minors. Some sponsors however have issues with this definition for legal reasons and may thus result in discrimination of this segment of the population.

Another issue is that of the use of the term 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 allow their parents to seek employment elsewhere within or outside the country (Ota, Idoko, Ogundare, & Afolabi, 2012). A number of orphaned children are also taken in by the relatives. 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/her ward can give consent to have this child enrolled in a study is also debatable? This can raise issues as some studies have shown that non-parents are more likely to consent to have children participate in trials than parents (Nunez-Wallace, Gill, Harrison, Taylor, & Charles, 2010). What should obtain in such situations is not yet clearly defined in many settings leaving a gray area that needs to be explored further. This can be a grave issue when dealing with a disease such as HIV where a number of children may be orphaned and in the strict sense may not participate in studies due lack of a legal guardian. Sponsors are encouraged to accept what is culturally acceptable to the community and the local study team need to put mechanisms in place to ensure the rights of the children are not infringed and regulatory authorities accept the agreed practice.

In populations with limited access to education there is often a need to appoint an impartial witness who is educated and understands the ICF and information sheet, to act as witness to the consent process for the participant who cannot read these documents. This often poses another challenge to consenting as 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 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 individuals serve as witnesses over the long term. Study teams need to set up checks that help to keep this process as impartial as possible for instance setting limits to the number of participants an impartial witness may attest for.

Some African cultures require that inheritance is through the mother and not the father's lineage. 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 subjects opt to have fathers give consent.

Another issue is the lack of clarity on the age that assent should be obtained from study participants. For instance in a multisite study involving 3

West African countries, age of assent was defined as 12 to 17, 13 to 17 and 15 to 17 years in three countries (Sow et al., 2011). While most countries will accept the teenage age group, this may not resonate with a sponsor from another country where the legal age of assent is 7 or 8 years like the USA. These call for tolerance and letting the local population requirements prevail. Despite this age limits in rural settings the requirement for assent from children may be perceived as eroding parental autonomy and this requires a well guided negotiated discussion with community leaders to help them understand the need for assent and avoid a negative perception of the research requirements.

An area that has not received much attention and will likely become an area of intense debate is the evaluation of new products in persons who are mentally challenged. They are often left out in most of the early product development in the context of cultural beliefs and practices in reference to this segment of the population. However as more products enter the development pipeline,, this will likely become a topic requiring attention.

The area of the consenting process will remain an evolving area in clinical trials over time and legalities surrounding it should take into context cultural practices of the different communities. This is because individual autonomy operates in harmony with the wider community practices impacted by rapidly changing cultural practices due to technologically driven globalization.

2.2.6 Follow-up and Adherence to Protocol:

Adherence to the protocol is essential for the success of vaccine trials. This needs to be ensured among the participants and investigators alike, and failure to do this may impact significantly on research findings. Reasons for non-adherence vary from migration out of the study area to ill health, death, refusal to continue with the study, adverse events and dissatisfaction with the trial procedures or perceived benefits. In many communities within Africa populations are becoming increasingly mobile. It is not uncommon for school age or young children to move from rural to urban areas in pursuit of education. Another common scenario is that of the expectant mother moving to stay with relatives for a period and returning when her child is a few weeks or months old. In other cases, the population moves around for family events which may in some instances require weeks or months away from homes. Where such mobile populations are enrolled into clinical trials there may be difficulty in adhering to the follow up period and the protocol. Such issues need to be taken into account when planning studies and attempts made to either avoid mobile populations where feasible and where it has no impact on generalizability, or factor in attrition rates that take this into account. The mobility of populations is critical where infectious disease studies are concerned as transmission pattern variations can be significant within a short distance. In addition, clear communication lines

including the use of mobile phones which are now common place in most communities ensure that the team can remain in close contact with participants and plan study visits around engagements which were unforeseen or undisclosed at the last face to face contact. Setting reasonable visit windows also helps to mitigate this risk such that participants have a reasonable window within which a visit can be planned. For instance a Day 28 visit could be planned to occur anytime between day 21 and day 35.

2.2.7 Stringent Enrolment Criteria:

Some trials require that stringent inclusion/exclusion criteria be met prior to clinical trial participation. A common one is the requirement to have received routine infant vaccines within a specified time period often as specified in the immunization schedule. This is often a challenge in many parts of the developing world as even in countries where immunization coverage is high, the schedule is often not well adhered to. Thus there may be several months as opposed to 4 weeks between vaccine doses. In such instances early planning for the trial may involve following up potential participants from birth or even prior to this, to ensure that the schedule is adhered to. This definitely comes with a cost and where not possible needs to be taken into account in the study design.

2.2.8 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 as in many cases the majority of participants are illiterate. An additional complement of staff trained to do this will be required who can visit participants homes to fill the diary cards. This will increase the cost. In other instances, the involvement of the entire household is required such that the literate member can complete the card for the mother. Another challenge may arise in this regard when it comes to interpretation of trial data as there are likely to be key differences in data collected by a primary caregiver such as the mother and that collected by a field worker/assistant. For instance mothers may be more likely to report irritability in their child than a field assistant would. Additionally as mothers are usually resident with their young infants it is easier to take temperatures when the child appears warm leading to higher reporting of fever than in the instance where a field assistant visits at a certain point in the day when such may not be the case.

2.2.9 Culture/Belief Systems:

The belief system within a community may pose significant challenges to the conduct of clinical trials (Arenas-Lopez et al., 2011). In some instances it is difficult to recruit participants with a clear understanding of trial related procedures (Louisa et al., 2012). For instance, certain communities believe that

blood is sacred and that young children become ill after venous blood samples have been collected from them (Ota et al., 2012). At best, most mothers know only about obtaining blood samples through pin-pricks. These mothers may become worried when venous blood samples are collected in clinical trials leading to their withdrawing their children from the study, as their initial understanding of blood sampling is different from their experience. This is often heightened when a study requires the collection of samples into several tubes, which can be met with significant resistance due to the perception that this implies that more blood is being collected (Howie, 2011). A clear explanation of what is to be done with blood samples in different tubes 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 HIV. Such beliefs would definitely affect the acceptance of clinical trials in that given community (Kaufmann & Feldbaum, 2009). As a result, the need for education and re-education and the involvement of key community leaders cannot be overemphasised. Sponsors as a result need to be flexible in the planning phases allowing for long windows for each visit and factoring a significant drop out rate into the original sample size estimations.

The impact of beliefs is not only in those who are uneducated but cuts across the board at times and for the educated it gets compounded by the information freely available on the internet which can create significant concern in reference to certain procedures, research, vaccines and drugs.

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 the research outcomes. This can also be allayed by members of the community being investigators which calls for capacity building and retention of local expertise in the team for long term involvement by the community. There need to be innovate ways to ensure the boards remain impartial of the study teams and that they are truly in touch with the community perceptions, beliefs, aspirations and changing trends.

2.2.10 Monitoring and Communication:

Until the mid 1990's most clinical trials were conducted in Europe, the United States and Japan. Today 10% of all clinical trials occur in Africa (Rehnquist, 2001). These trials require conduct to the strictest standards as they involve human subjects. The International Conference on Harmonization/ Good Clinical Practise (ICH/GCP) guideline is often applied to such research (Englev & Petersen, 2003). There are certain procedures, such as reporting serious adverse effects etc. that require fast means of communication to the sponsors by either telephone or email, which at times unfortunately are either very expensive,

dysfunctional or non-existent in rural trial centres. 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 has been previously addressed by use of VISATs in a number of research centres and as mobile telephone penetration increases in the region it is becoming a major tool for data collection, participant follow up and study team communication. This is not without concerns especially as it relates to confidentiality.

Another challenge is that of readily available monitoring teams often sourced from Contract Research Organizations (CROs). In many parts of Africa however, there is a paucity of such organizations with the few available often overwhelmed. This poses a challenge to local institutions to ensure training of research managers and auditors so that required personnel is available thus making clinical trial monitoring cheaper and more effective in the long run. The other challenge is the development of local CROs that understand the regional research and cultural dynamics for sustainable capacity development.

2.2.11 Institutional Understanding of Trial Needs:

As clinical trials are relatively new in certain areas there is often a tendency to underestimate the needs of the trial. This may be due to the institutions previous experience with basic science and non-interventional clinical research which may not have come with the rigors of clinical trials. This can lead to significant strain on staff involved in these trials or strain on the budget which has not taken all these factors into account. An example is the extent of documentation and internal and external quality control needs for clinical trials which has serious impact on personnel and infrastructure requirements.

2.2.12 Use of Electronic Data Collection (EDC) Methods:

In many parts of Africa internet facilities are often slow and erratic. Data collection is however increasingly based on electronic methods. Where electronic case report forms or diaries are used in vaccine trials, this may pose challenges for the trials teams when connection speed makes data entry or upload difficult or impossible to achieve. In some instances trial sites and indeed the entire country have gone without internet access for extended periods of time making it impossible to access data real time. In the African context it therefore seems pertinent to have in place back-up systems which can be used should the electronic systems fail or be temporarily unavailable. The other challenge with EDC systems creates a situation where the research centre remains with no data copy for their own capacity development once the study is over as the data

management has all been done remotely offsite. Study sites need to have clear data and material transfer agreements prior to study start.

2.2.13 Vaccine/Sample Storage and Transport:

Power supply in many parts of Africa remains erratic and unreliable. Vaccine trials however require that vaccines can be stored at the required temperatures at all times. This often requires a significant investment in vaccine fridges with a constant source of power and vaccine carriers as appropriate. The need for a stand-by generator which itself has an effective back-up system cannot be overemphasised in such situations. Certain study vaccines especially in early phase clinical trials require transportation at $\leq 20^{\circ}\text{C}$ or below to the trial site, which may not be located at the same site as the storage facility. Unfortunately, dry ice is in limited supply in most developing countries. For instance, only one company produces dry ice in commercial quantity in The Gambia and this supply is often unreliable. Attempts to produce dry ice and liquid nitrogen within host institutions are currently not widely available. This suggests the need for development of a sustainable “in-house” dry ice and liquid nitrogen production in research institutions in developing countries. We also recommend development of cold-chain free vaccines where feasible for resource-constrained settings.

Vaccine trials often collect significant quantities of biological samples which require storage at specified temperatures until sample analysis is done, or the samples are transported to sister laboratories for analysis. Maintaining the required temperature for these samples also stresses the need for stand-by generators with back-up systems.

The exploration of solar power as alternative or main source of power with the erratic grid power being a back up is important and may be the source of power for the future. Sunshine is always available in most parts of sub-Saharan Africa and the cost solar power installation has come down remarkably. Strathmore University in Nairobi, Kenya has installed solar systems for all its power requirements.

2.2.14 Local Haematology and Biochemical Reference Values:

In certain parts of Africa there are no local reference values for haematology and biochemical parameters for the paediatric age group. Haematological and biochemical references are however essential indices used in establishing safety parameters, especially in early phase intervention trials (Afolabi et al., 2014). The accuracy and appropriateness of these laboratory parameters are thus critical to understanding the results from such trials. This implies the need to use reference values validated from elsewhere. In view of differences in environmental, genetic, and nutritional factors that may influence these laboratory indices (Dhingra & Mishra, 2011; Kumwenda et al., 2012), there

is a need to ensure the development of local reference values. These values need to be developed outside the specific clinical trials to avoid bias. This therefore requires specific financial support as part of the holistic development of the clinical trial and optimal clinical care framework.

2.2.15 Use of Supplementary EPI Vaccines:

To ensure adherence to international recommendations aimed at facilitating eradication/elimination of childhood vaccine preventable diseases, many African countries organize periodic house-to-house campaigns to immunize infants under 5 years of age. This is done irrespective of their previous receipt of the Expanded Program on Immunization (EPI) vaccines. Notable among such campaigns are the polio and measles vaccine campaigns. Among infants participating in vaccine trials, these additional immunizations could potentially act as confounding variables because of variations in age at vaccination and batches of vaccines administered. More important, these variations may distort findings about interference of the EPI and study vaccines. Studies involving children within age ranges involved in such campaigns need to work with EPI teams to devise methods of avoiding such scenarios. This may involve placing informative stickers/cards on the child's immunization record (Afolabi et al., 2014) and engaging public health officers and nurses involved in these vaccination campaigns to recognise these stickers/cards. The study team would then need to ensure all such infants receive all recommended EPI vaccines according to local immunization schedules. To further minimize potential disruptions in clinical trial schedules, we suggest that the clinical trial team should work with the local EPI team to plan and identify favourable dates for the supplementary immunizations. In situations where it is impossible to avoid study participants or where some of them slip through and get these additional vaccines, this needs to be clearly documented and accounted for at the point of data analysis.

2.2.16 Analgesics for Post-vaccination Fever:

A common adverse event following infant vaccinations is fever. Studies have shown the efficacy of acetaminophen prophylaxis after whole cell pertussis vaccination and also in treating febrile episodes after routine immunizations (Dhingra & Mishra, 2011). Some studies have however reported that prophylactic or therapeutic use of acetaminophen may reduce immunogenicity to vaccines (Prymula et al., 2009; Rose et al., 2013). As such is often encouraged that such antipyretics not be used or that use be well documented. In our experience however, although mothers reported fever in vaccinated and non-vaccinated infants following vaccination, the temperature records taken by trained field staff did not support the episodes of reported fever. This observation suggests a need

for rational use of acetaminophen after infant vaccinations (Afolabi et al., 2014) and may require innovative communication strategies especially in societies where such use is generally the norm.

2.2.17 Infants' Weight Faltering During Follow-up:

It is common in the developing world for growth to falter characterized when complementary feeds are introduced to growing infants (Shields, Wacogne, & Wright, 2012). The mothers of infants enrolled in vaccine trials in these regions are often educated to use locally available food items as complementary diets. However, this does not always result in a change in practice and may require intervention of the teams to provide the requisite nutrition or monitor the feeding of the child. Sustainability of such interventions may be a major financial challenge if not factored into the clinical trial budgets. We suggest that clinical trials conducted on children in low-income countries make appropriate budgetary provisions for malnutrition-related events that commonly occur in this age group (Afolabi et al., 2014). This has recently become a major budget line item in a number of clinical trials despite not being foreseen.

2.2.18 Investigator Professional Development:

Scientific publication is a major parameter for the assessment of investigators, but this is unfortunately limited from clinical trials despite the huge investment of time and labour. Investigators often do not feel that they are getting commiserate scientific output for their intensive input into these trials. In some cases the samples are processed in laboratories overseas and with little provision for technology transfer and capacity building in country (Louisa et al., 2012). To be more cost effective, some investigators opt to develop nested studies where feasible within the remit of the main vaccine trials. Such studies may entail collecting some extra but safe volumes of blood and/or swabs for additional analysis at the same time the subjects are sampled for the primary trial. Surprisingly, this is often resisted by some trial sponsors no matter how benign such an additional study may be to the parent study. We advocate that local investigators are allowed to benefit from the clinical trials by technology transfer, undertaking nested studies, or funding for relevant higher degrees. These will help to place the investigators in a better position to continue to attract funding.

This is currently changing with some sponsors accepting investigator initiated ancillary studies and even providing resources, however, this is an exception rather than a norm. There is a need for technology transfer to the African centres so that more of the centralised laboratory support can be done in the region but this requires proper planning and co-investment by the local institutions and their governments in infrastructure development.

The support of established investigators to enhance their career and in the process mentor upcoming investigators is integral to the future of clinical trials in sub-Saharan Africa and requires a formidable partnership between research centres, academic institutions, regulatory authorities and relevant government departments.

2.2.19: Changing Dogma on the Need for Accelerated Vaccine Development:

The development of a vaccine against a particular disease is usually driven by potential profits that could be derived from such huge financial investments. Very little commercial incentive exists for the pharmaceutical industry to commit resources into vaccine development against certain infectious diseases and this has contributed to festering of diseases that erupt sporadically in some of the poorest parts of Africa. The largest and worst outbreak of Ebola in West Africa represents a paradigm shift from this dogma and has dramatically changed perceptions about the need for an Ebola vaccine for the affected populations (Levine, Tapia, Hill, & Sow, 2014).

The weak healthcare infrastructure of the affected countries occasioned by years of civil wars and political/economic instabilities contributed to the spread of the massive outbreak in poor urban slums and remote villages leading to nearly 11,000 deaths and 28,000 cases (WHO, 14th January 2016). Healthcare workers constituted approximately 10% of the deaths. Consequently, fear for their lives and concern for their families led healthcare workers in some settings to stay away from their duty posts, while others refused to care for Ebola patients. This presented an emergency crisis with multiple dimensions, since Ebola has no known cure and no licensed vaccines were available but the patients required intensive medical care from clinical staff needed to administer this with strict adherence to isolation and infection control techniques (Levine et al., 2014).

The ravaging outbreak showed that Ebola is capable of spreading more easily than expected in certain high density impoverished populations. The high morbidity and mortality among healthcare workers also revealed a new highly focused target population requiring urgent protection from the disease. A well tolerated, highly effective Ebola vaccine that can rapidly elicit protection following the administration of a single dose would constitute an important public health tool (Hoenen, Groseth, & Feldmann, 2012), at the least to protect healthcare workers and avoid interruptions in medical care (Kerstiens & Matthys, 1999). Subsequently, a vaccine regimen with more durable protection can be developed after providing initial prophylactic vaccine for frontline workers who are dealing with a dangerous, fast moving virus in remote areas with weak health infrastructure (Levine et al., 2014).

2.2.20 Ethical and Safety Review Process:

The ethical review process varies from country to country on the continent. Given this diversity, there is likely to be significant variation in decisions reached following review of the same protocol. The same applies to data safety monitoring boards (DSMB) now known as data monitoring committees (DMC) which are an essential requirement for vaccine trials. This is particularly pertinent when considering multicentre studies which are becoming more and more common, and suggests a need for some harmonization of standards in this regard. This can be achieved through engagement of various stakeholders to ensure complementary rather than duplicative roles for the various committees. There is also an urgent need to build capacity among members of ethics committees ensuring that they are knowledgeable on relevant national and international guidelines for vaccine and other clinical research. The AMANET network has made an effort to promote health research needs in Africa, by taking a holistic approach in addressing human, financial and infrastructural needs at research centres. A sub-grant from this group was used by a research institute in Tanzania to start a two-way community engagement programme to convey information regarding health research ethics to communities. This enhanced researchers' understanding of community concerns and perceptions of their research (Mwangoka et al., 2013). In addition, The European and Developing Countries Clinical Trial Partnership (EDCTP) through Mapping of ethics review and trial regulatory capacity in sub-Saharan Africa (MARC project) supports strengthening of the existing ethical review capacity throughout Africa (Mwangoka et al., 2013).

3. CONCLUSION

In summary, there are several important reasons for conducting clinical trials of investigation products against infectious diseases in developing countries. The conduct of these clinical trials has great benefits, poses challenges, as well as peculiarities that are worth considering by the investigators, manufacturers, funders and sponsors for optimal execution of the trials. Clinical trials in the region will have varied costs across the different countries and may cost more. This extra cost is however part of the investment for development of the clinical trials platform in Africa which has so many facets dictated by rapidly changing requirements with the acquisition of new innovations and development of new regulations globally.

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