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The Ethics of End-of-Trial Obligations in a Pediatric Malaria Vaccine Trial: The Perspectives of Stakeholders From Ghana and Tanzania

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Abstract

This study explores stakeholder experiences and perspectives on end-of-trial obligations at the close of a phase II/III Pediatric Malaria Vaccine Trial (PMVT) [GSK/PATH-MVI RTS, S) (NCT00866619]. We conducted 52 key informant interviews with major stakeholders of an international multicentre PMVT in Ghana and Tanzania. The responses fell into four main themes: (a) Communicating End-of-Trial, (b) Maintaining Health Care Services, (c) Dissemination of Results, and (d) Post-Trial Access. Interviewee responses shared important practical experiences and insights that complement current thinking in the literature on research ethics guidance: (a) accompany end-of-trial communication with information on personal and family health care responsibilities, (b) establish public health indicators to measure the impact of research on a health care system, (c) design a gradual exit strategy with opportunities to address unplanned events, (d) endorse a principled approach of continuity of care when designing a health care service handover, and (e) devise an actionable post-trial treatment access pathway with diverse stakeholder representatives.

Keywords

ethics, vaccines, end of trial, equality, equity

Introduction

The global health community ranks immunizations against infectious diseases among the most cost-effective public health interventions for reducing global child morbidity and mortality.(Ozawa et al., 2016; Saul & O'Brien, 2017) A natural consequence of this drive for new childhood vaccines is the need to test them in more pediatric populations in various disease transmission settings. These trials are essential so that any vaccine introduced into a population is shown to be safe, effective, and well tolerated. Pediatric vaccine trials generate new knowledge about vital life-saving preventive measures to protect children below 5 against disease. This empirical ethics project adds to the current literature on what makes research in vulnerable populations ethical. In particular, the focus of this article is on end-of-trial obligations. The study is based on the perspectives of stakeholders involved with a pediatric malaria vaccine trial (PMVT) conducted in Ghana and Tanzania (Tinto et al., 2015).

The (now replaced) 2008 version of the Declaration of Helsinki specified that research participants are entitled to share in the benefits that result from the studies in which they participate, including access to interventions identified as beneficial in the study or to "other appropriate care or benefits" (World Medical Association, [WMA], 2008). This provision, which broadened the range of feasible research benefits, was added as an update to earlier versions of the Declaration, accounting for the fact that many trials conducted in low-resource settings fail to provide any benefit to trial participants in those countries. In seemingly stark contrast, the (current) 2013 updated version of the Declaration omits reference to "other appropriate care or benefits" (WMA, 2013). It rather reframes the scope of possible benefits to "interventions identified as beneficial in the trial"(Hurst, 2017). On a narrow reading, this change appears to restrict the end-of-trial responsibility of research programs and no longer addresses

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the fact that, by the very nature of health research, many trials do not result in any effective intervention for participants and the local populations (Dal-Ré, Ndebele, Higgs, Sewankambo, & Wendler, 2014). Moreover, as Weigmann (2015) articulates,

> making important new treatments available in low-middle-income countries should be considered a health priority, but this might take years or even decades. For participants in clinical trials, it will, therefore, be important to help them bridge the gap between the end of the trial and the time the intervention becomes available in their country (p. 569).

Given the increasing number of studies being conducted across low-resource settings, in particular within countries of Africa, it is vitally important to define the ethical responsibilities linked to research activities, including end-of-trial obligations. Critically, it is important to evaluate and address the public health impact that conducting research, such as a PMVT, may have had on a health care setting; both to mitigate against any negative impact and to sustain any positive gains of system-strengthening.

At present, there are only a few examples of empirical work addressing the topic of end-of-trial obligations and benefits (Bege & Kris, 2015; Lairumbi, Parker, Fitzpatrick, & Mike, 2011; Lutge, Slack, & Wassenaar, 2017; S. Molyneux, Mulupi, Mbaabu, & Marsh, 2012; Munung, 2016; Zvonareva et al., 2015). This study adds new empirical evidence and presents unique insight into the views of partners across a multi-center PMVT from two countries, Ghana and Tanzania and the wider international partners. The study presents what responsibilities are owed toward participants and their communities at the end of a PMVT from the perspective of key stakeholders. The results aim to inform ethical planning at the end of a PMVT and guide the conduct of international collaborative research partnerships operating in low-resource settings.

Method

A semistructured interview method was selected for this study. All respondents were involved in the conduct of an international malaria vaccine candidate phase II/III trial carried out in 11 research centers of seven African countries between March 2009 and January 2014 (GSK/MVI, RTS, S; Abdulla et al., 2013; Leach et al., 2011; Tinto et al., 2015). The conclusion of the vaccine-trial data collection in January 2014, for the purpose of this article, is defined as the end-of-trial. Two countries, Ghana and Tanzania, were included for this ethics project along with the international partners (sponsor-investigators). The results reported in this article are part of a larger research project entitled Good Collaborative Practice and International Health Research Partnerships. The results in this article have not been published before. The same respondent set (n = 52) has been included with other published papers on different topics elsewhere: Defining *Health Research for Development* (Ward et al., 2017); and *The Ethics of Health Care Delivery in Research* and *The Journal of Empirical Research on Human Research Ethics* (JERHRE; Ward et al., 2017). These earlier papers provide extensive detail on the methodology used in the interviews. In this current article, we have analyzed the data-set responses to the interview questions on end-of-trial responsibilities. All the interviews for this article were conducted across a 10-month period between November 2014 and September 2015.

Face-to-face interviews were conducted with all stakeholders based in Ghana and Tanzania. The interviews with the wider international partners were completed via a mixture of face-to-face, phone and Skype communication, depending on the respondents' location.

Results

Respondent Disposition

Figures 1 and 2 below describe the disposition of respondents. In total, there were 52 key stakeholder interviews. Figure 1 presents respondents' stakeholder roles in relation to the PMVT. Figure 2 describes the respondents by their country location.

There were four main result themes: (a) Communicating End-of-Trial, (b) Maintaining Health care Services, (c) Dissemination of Results, and (d) Post-Trial Access.

Qualitative Results

Communicating end-of-trial. One important consideration for the research team was to inform all stakeholders that the trial is coming to an end. The senior researchers, in particular, noted that the end of the trial brought changes for participants regarding both their connection with the research team and their access to health care services.

> For the field, it was very critical for us to get in touch with our fieldworkers, so we would be able to share that the study is coming to an end. They are virtually community members and so they are extending the end of study communication with the community. (Snr Researcher, Epidemiologist, GH/B/27)

The fieldworkers and fieldwork managers stated that although the participants knew the project was time-limited, the change in access to health care created anxiety and feelings of abandonment in the community. The participants were disappointed to see the trial and the associated health care advantages end.

> We started informing them [participants] that the project is coming to an end and that the benefits are going to end . . . Oh, you can imagine, they [participants] never liked it. They wanted us [the research] to continue. (Research Manager, GH/A/16)

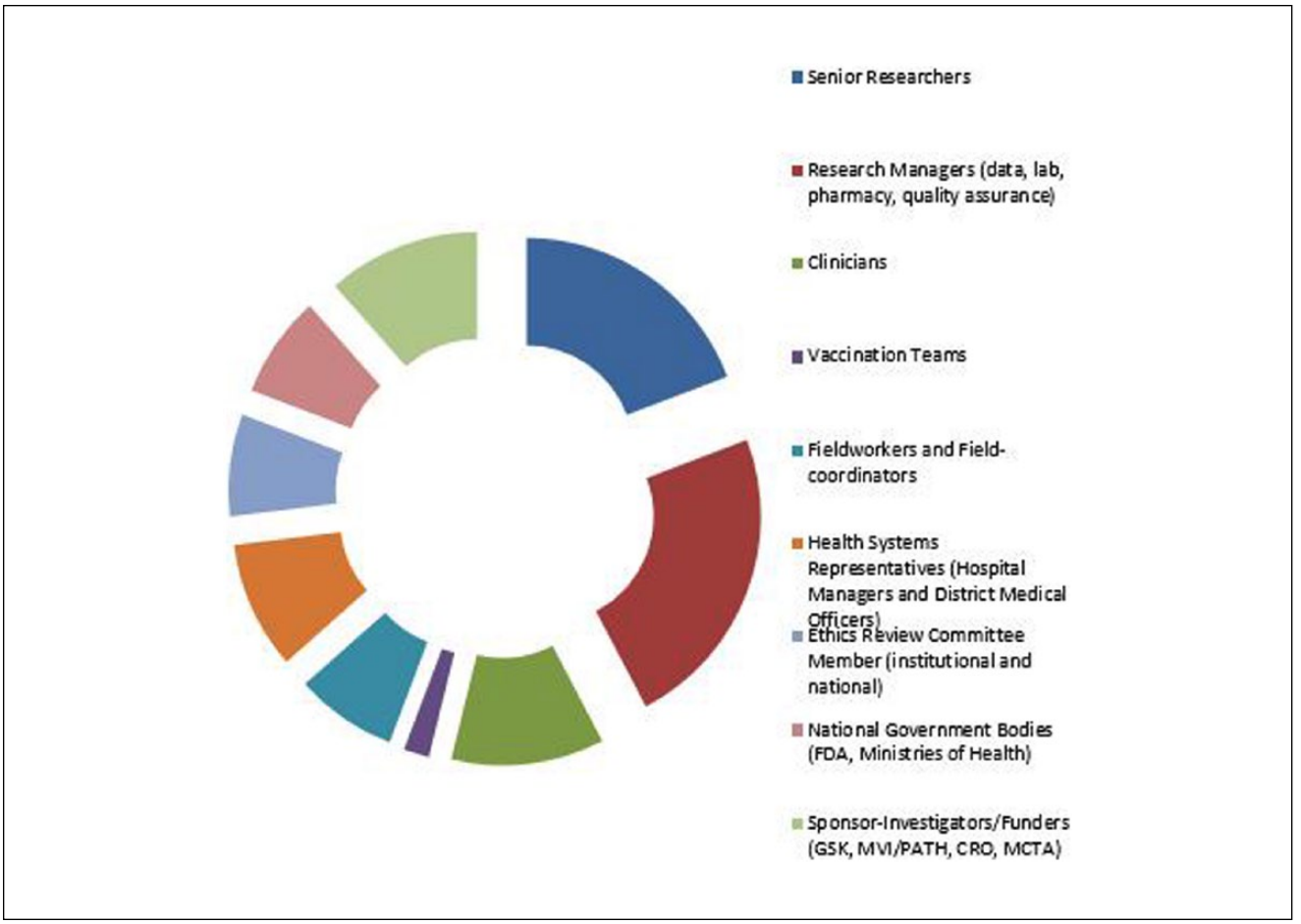

Figure 1. Doughnut chart presenting number of respondents by stakeholder roles in the pediatric malaria vaccine trial ($N = 52$).
Note. FDA = food and drug administration; GSK = GlaxoSmithKline (pharmaceutical company); MVI = Malaria Vaccine Initiative; PATH = Program for Appropriate Technology in Health (global health organisation); CRO = Clinical Research Organisation; MCTA = Malaria Clinical Trial Alliance.

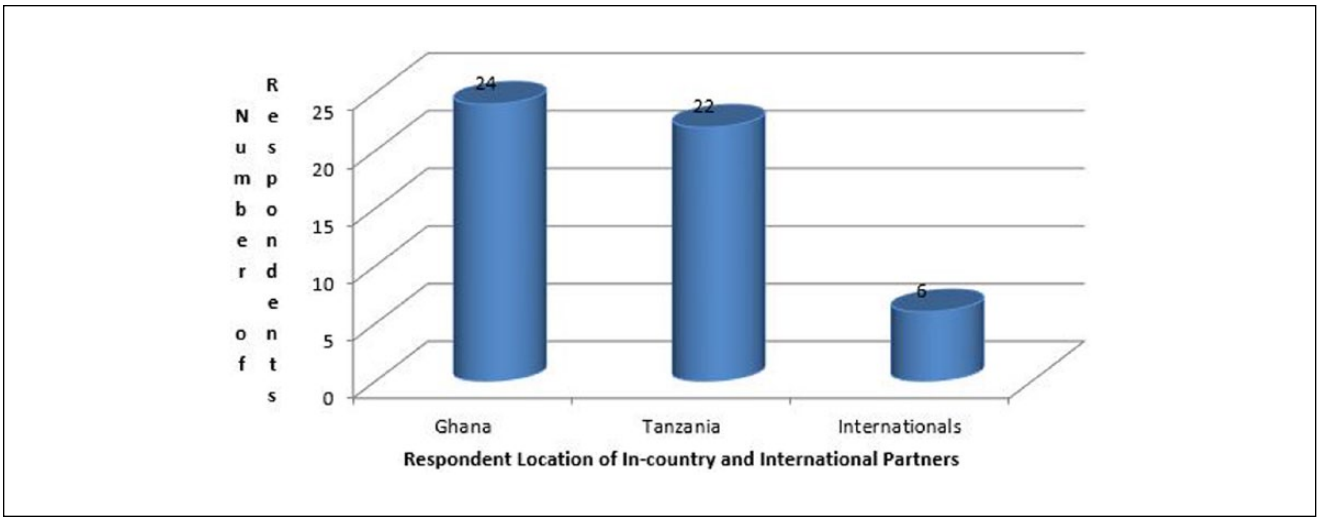

Figure 2. Bar graph presenting country locations of respondents.

The fieldworker team explained that mothers were not only concerned with the short-term health advantages ending but also had concerns in respect of longer-term safety issues.

> To be very frank we have a problem with the project coming to an end. First, when the project ended, there were mothers complaining that since you left us, up to now, we have not heard anything about you again. Maybe vaccine has a side effect that maybe will take four or five years before you will experience it. (Fieldworker, GH/A/33)

Expressing appreciation and thanking participants and communities for their involvement with research was an important aspect of respectful disengagement at the end of the trial and vital for maintaining trust.

> We gave them certificates that the study has ended, so that every group that was graduating from the study was given these certificates—"thank you for participation." The village leadership was also notified when the study ended and, of course, the district [district health office] was also notified. (Snr Researcher, Epidemiologist, TZ/A/52)

Many of the medical doctors spoke of the importance of encouraging participants to continue to use the health care services even after the research program ended. There were differing opinions among respondents on whether health gains resulting from the research study and positive health-seeking behavior could be sustained in the community once the PMVT had ended.

> Something that is a bit depressing is that some, members of the study, when the study was over, they immediately stopped coming [to the hospital]. Some of the families just did not manage the transition from being so proactively looked after in the study and then taking full responsibility again to come on their own. (Clinical, Physician, GH/A/10)

> Because we educated them [participants and communities], the education sticks in their mind even though the project has ended but the education in the mind is still there so they keep the environment clean . . . Even though we do not offer free transport, but in case their child is sick, they try their best to find some money so that they can get her or him to the health facility. (Research Manager, TZ/B/49)

Maintaining health care services. The topic of maintaining improved health care services and infrastructure after the end of the PMVT was raised by most stakeholder representatives. A tension exists between respondents wishing that the level of care established by the PMVT could be continued and the cost of financing the improved standard of health services.

> Because, I mean, it doesn't sound ethically right. I mean it is like, zooming in, collecting what you want, and zooming out, Kangaroo Research. It is frowned upon. You should leave the people with something. (Ethics Review Committee Member, GH/B/19)

> We saw that challenge coming, and somehow we did not want it to be that way. Like ok when we leave, everything collapses. So there are a lot of discussions on how to manage that situation. But honestly after the study ended that was the end of all these supplies and stuff, but they [the community] benefitted from having the structures. In terms of human resources, yeah, we, like, the government cannot support so many people working, so they had to go back to how it used to be. (Snr Researcher, Epidemiologist, TZ/B/17)

The research centers reported that the infrastructure and equipment remained with the hospitals and available to communities. However, respondents raised concerns over the continued maintenance cost to ensure the equipment functioned and was an available resource for the hospital.

> We handed back the paediatric Ward with all the facilities which were bought by the project, this was handed back to them [to the local health authorities]. We did not pull out anything, so all the things were left. We handed back the clinic which we built at the hospital and at the satellite dispensaries. The digital x-ray is housed within the hospital and it is used routinely by other people . . . The problem I see is the maintenance. . .because the government cannot afford it. (Snr Researcher, Epidemiologist, TZ/A/41)

> Since then, there is a, I think, a basic care that is supported by the government, so what we did was increase the quality of that but that increase has a cost, and at the moment there is nobody bridging the gap, so at the moment some of the services we still maintain, some of the services we don't maintain. (Snr Researcher, Epidemiologist, TZ/A/44)

On the whole, the general view across the respondents was that at the end of the PMVT the level of care in the health care facilities was difficult to maintain.

> The nurses have been here most of the time, have the training and can care for the children with severe malaria, but long term sustainability of the good quality healthcare system in this part of the world is very difficult because there are no resources. (Clinical, Physician, TZ/B/51)

Conducting the PMVT in a health care setting offered various learning opportunities. One medical doctor described how the PMVT had discovered the extent of anemia in their community and employed a nutritionist in the pediatric ward to support families; a service which was later taken over by the hospital. Another respondent described how he had worked with the district health officers to establish ambulance transport services in the region. A number of respondents described the improved staffing expertise.

> Yeah, there are no longer any specialist clinicians but my impression is that during this interaction [the PMVT conducted

> in the hospital setting] which lasted for about five years, I want to believe that it changed the juniors who are now in the hospital, and they are now practicing much better than before. (Snr Researcher, Epidemiologist, TZ/A/43)

Communicating the end-of-trial also focused on negotiating means to sustain positive changes to service provision.

> At one time we invited the Member of Parliament, the district executive, director and district health managers to discuss the challenge; ok the project is coming to an end. We had this number for staff, if the Government could absorb some of the staff to work in and to be employed as permanent government staff, then we are sure that we have sustainability of these skilled medical personnel. (Snr Researcher, Epidemiologist, TZ/B/36)

> Well the sustainability, I can say it is going on, but it has not gone as well as we wanted it to be, and the main thing is the funding. Though it was clearly known by the government that you know come 2014, that this project would end, but it looks like it [the Government] wasn't well prepared to ensure that all the activities that we were implementing were incorporated into the government budget and strategy. (Vaccine Developer, PATH TZ/A/13)

The government representatives also explained the challenges they face with external projects bringing additional resources into the health care system.

> I think it is always very good to have international organizations feeding into building capacity for research. Again that has to be guided so that they do not introduce structures and systems resource requirements that we cannot meet, when they [a programme of research] pull out; this is our weakness. . . We need to start a dialogue with the national level as early as possible, and make sure that all these programmes are part of our annual programmes. (Government Official, GH/A/11)

One research team explained that they provided health insurance to participants for a 5-year period so that they could continue to access health care services.

> You know the way we treated them [participants] was like we have over pampered them. We did everything for them. Now if you leave them to pay out of their pockets it will create a very big gap. So to help them, is to give them the health insurance . . . Not just to say we are finished and we thank you all for taking part, bye bye. No we finish, we thank you all for taking part and this is your health insurance card. (Clinical Physician, GH/A/07)

Dissemination of results. Disseminating results was identified by all the stakeholders in the PMVT as a necessary and important step. Designing a broad outreach strategy was widely advocated.

> The key consideration of this communication strategy is to ensure that first, it reaches all the key people that it is intended to. It is not only maybe ending in urban areas, but it is communicated even to the rural areas. It also aims to be communicated to the highest stakeholders. (Vaccine Developer, PATH GH/A/05)

There was agreement among stakeholder responses that dissemination of results should not be reserved only for the end of the study. It required a strategy that continually informed regional stakeholders and the health care system over the course of the PMVT.

> The research team together with our sponsors, we thought that to make integration of this vaccine into the routine health services smooth, the stakeholders have to understand the issues involved: the progress over time, the challenges over time, so that you don't go back to them with your research when they don't understand anything that has gone on. So involving them [country/local stakeholders] from the word go in the progress of the work. (Snr Researcher, Epidemiologist, GH/B/24)

The need to inform participants of the results was also raised by respondents. This was both respectful and helped maintain trust among the research center, hospital, and patients.

> Once in a while they also organised a stakeholder forum, where they communicated the stakeholders involved and how far they have come with their research, and the efficacy aspects, they tended to give more highlight on that. Saying that the vaccine is capable of protecting this number of children, out of this number of children who received the vaccine, but more research is needed to be done. They involved the community leaders, other leaders like the churches and mosques. (Vaccination Nurse, GH/A/23)

> We call durbars [community meetings] and that is very fun with this centre. They organise opinion leaders like chiefs and elders of a community, so that is another level of representation, and then they come and you have a debate, bring it [the trial findings] down to that level of people's understanding. (Snr Researcher, Epidemiologist, GH/B/21)

> You create the communication strategy documents which are written in the language that is clearly understood, even in the very rural areas. You may not need physically to go there, but if the document is written in the clearly understood language, it can be sent to the health facilities, health centres and dispensaries. (Vaccine Developer, PATH, GH/A/05)

Post-trial availability. The issue of post-trial availability was mainly discussed among ethics committee members. This is a requirement commonly set out in research ethics guidelines that any successfully developed, effective intervention (e.g., the malaria vaccine candidate), will be made available to the participants and the communities that were involved with the trial. Whether this is achieved in practice remains a topic of discussion.

> I mean there is direct dialogue with the investigators about this [post-trial access]. First of all we find out from the investigators what they plan to do. If it is something they have given consideration to, they [the investigators] go think it over, they come back, sometimes they will be happy to take it on, and at

> times they will take it to a limited level or sometimes they will say the cost contribution is such that we cannot go ahead, and then a compromise has to be reached. (Ethics Review Committee Member, GH/B/19)

> The other thing that the ethics committee would usually be asking the investigators of the study, what happens to those who are in the control arms? When you are testing a vaccine, so I mean some are getting the vaccine and some are not getting it. At the end of the study, if the vaccine is ok, what will they do with those who did not get a vaccine? The bigger question is what happens to the community at large. A lot of dialoguing. I mean ethics boards have not insisted that mandatorily it should be done, but many times they urge the investigators to give it serious consideration. (Ethics Review Committee Member, TZ/B/37)

It was mentioned by a few respondents that the logistics, organization, and planning of post-trial availability requires many different stakeholders to work together and, it is not only a responsibility of the research team. However, most respondents explained that the negotiation of post-trial access remained between the ethics committee and the research teams.

> Many times they [the research team] will already have the World Health Organisation involved in the vaccine that they are going to try, and updating them on the progress. Eventually when the vaccine is thought to be good, it gets some certificates from the WHO. WHO links up with, it could be GAVI, which is interested in vaccines for kids and then they will try and solicit funds to commence roll-out. Because many times, the countries in which it is happening do not even have the money anyway. Then of course they will prioritise the places where it was tried to make sure that they are part of the roll out district. So ethics, you will find, will be constantly pushing to maximise what will come to the community and the researchers will not be enthusiastic but will be looking at the bills, and figuring out what does it mean financially to them to do that. (Ethics Review Committee Member, GH/B/15)

Establishing a mechanism for post trial access therefore should be established through a comprehensive network of appropriate stakeholders that support country preparedness to facilitate rollout of a novel product.

> What we had learned collectively is that it is not just about finance mechanisms, which are key, when it comes to the roll out of these products, but there were so many other things. You would find that, you know there was country preparedness and national governance preparedness, for them to be able to sort of swiftly roll out the up-take, and scale up with these products. (Snr Researcher, Epidemiologist, TZ/A/44)

The concept of having to make post-trial commitments a requirement was also challenged in the context of a PMVT because a single trial does not lead directly to an intervention that can be implemented in a population. To bring a vaccine to market requires further testing and extensive regulatory review before receiving approval to be licensed and permissible for general access.

> Like a vaccine trial, you cannot go and provide them, like these are now the best for you, because they have to go into policy and so forth. So it is just that you provide the feedback, at the community level, at the different levels, according to the ethic committees. (Snr Researcher, Epidemiologist, TZ/A/39)

Although post-trial access is arguably a long-term consideration, a need for early planning with appropriate stakeholders was identified as a requirement of ethical research.

> I think the ethics of post-trial access even today, are very challenging and I think that is where we have failed miserably in the past . . . The hope is that they have seen from previous products, the lessons, and they saw the need to engage the national governments very early in the process. Not just as researchers or research science, but also be able to work with different partners. You will need a stakeholder from the ministry of health, from the ministry of finance, the ministry of women and children, from research institutions, from academia. You need like a mixture of policy experts who need to sit and look at the decision-making framework. (Ethics Review Committee Member, TZ/B/43)

Discussion

The study presents the views of stakeholders in an international health research partnership at the end of a Phase II/III vaccine trial conducted in Ghana and Tanzania. In this discussion, we explore the responses of participants and relate them to current thinking in the literature and research ethics guidance on end-of-trial obligations.

Communicating the End-of-Trial

Clear communication throughout a research study and especially at the end of a trial is necessary for local trial populations to benefit from knowledge generated by the research (negative or positive results), and to support local health care provision, even after the resources provided by a study program have stopped. The end of a trial can present hardship or cause for concern for the communities involved in a research program and the health care setting more generally. Sensitive communication and attention to these issues are respectful and necessary to support the allocation of resources, staff, and health care responsibilities. This is crucial both for the promotion of public health, and the prevention of harm in local populations where health research is conducted. Moreover, a carefully structured exit strategy ought to maintain and instill trust in health care services and encourage future research partnerships. Importantly, if

participants or the wider population feel abandoned or exploited by a research program, they are likely to reject and distrust not only research teams but also public health services as a whole. Such a break in trust can be detrimental to an individual's health, or health of their children, should they fall ill, and no longer have confidence in seeking professional help. Furthermore, a break in professional trust can threaten public health more generally (particularly in a context of infectious disease prevention, reporting, and control).

A number of interview responses, in particular from clinicians and fieldworkers, suggested that participants of the PMVT felt disappointed with the study ending and had concerns about their future health. Vulnerabilities and anxieties of this nature must be appropriately addressed with reassurance and sufficient guidance to transition participants back into available public health services where possible. Moreover, the interview responses highlighted that much of the complex day-to-day ethical decision making is managed by the fieldworker-teams on behalf of the research institute. Institutional support is needed to assist fieldworkers in this role with sufficient training in value-based decision making that best promotes patient safety and supports local health systems. A number of the senior researchers stated that a respectful process of disengagement needed meticulous planning across gradual stages, as was implemented in the PMVT. For example, it was mentioned in the interviews that over the course of the year leading up to the end of the vaccine trial, the participants (mothers of infants) were informed on different occasions that the trial was coming to an end. A method also described by Kamuya et al. (2013).

There can be significant public health benefits from integrating a culture of research into a health care setting and supporting sustained conditions of improved health in a population. There was a divergence of opinion as to whether this benefit could in practice be sustained. On one hand, the health education of the trial remains with community members and thereby improves health-seeking behaviors in the local population. On the other hand, one senior researcher described the participants as having been "over-pampered" and not able to cope with the transition from the controlled research setting to managing their own (and their children's) health needs. Novel approaches are required to safely support the transition of health care responsibilities of participants (in this case, mothers and infants) and secure beneficial health-seeking behavior accrued during the study. On the whole, it appeared that the end of the trial in the health care settings was managed between researchers and local health care facilities with little, or no, direct input from the sponsor–investigators. As a result, the management of local health needs at the end of the study varied, with no unified agreement on the responsibilities of the research team toward the health of local populations, or how the transition should be handled. This is in contrast to the trial set-up and conduct of the PMVT, which had been highly scrutinized to ensure uniformity across the research centers. For example, one research center took a decision to support local community health by funding health insurance for participants at the end of the trial to reduce disruption to access for health service provision. This was not provided by all research centers or coordinated by the sponsor investigators. Although each group needs to establish contextually relevant approaches, the divergence in management at the end of the trial calls into question whether the health needs of all participants were adequately and consistently addressed by the research program. Moreover, ethically, what are the sponsor–investigator responsibilities toward health care provision when a trial ends? The design of the exit strategy must be appropriately tailored with and for the local setting. Researchers and sponsors must remain committed to supporting the public health goals of the local populations. To a greater extent, the PMVT achieved this through improving local research, clinical and laboratory skills, supporting local health education, and promoting good health-seeking behavior in the community. Establishing the barriers and enablers of sustainability for each of these system strengthening components would help inform end-of-trial responsibilities and further support long-term improvements in local conditions of health.

Maintaining Health Care Services

All respondents agreed that over the course of the PMVT, there had been substantial positive changes in health facilities—improved infrastructure, staff and care standards. This service improvement ensured participants received adequate standards of care as set out by international and national standards (International Council for Harmonization-GCP, 2017; WMA, 2013). Maintaining these beneficial changes beyond the end of the study was a challenge recognized across the different stakeholder groups. These concerns aligned with recent literature calling for more empirical work to fully understand the consequences and benefits of international collaborative health research operating in weak health care settings (Angwenyi et al., 2015). We recommend that future programs of health research and the local health care services design a range of indicators to assess the impact on the health care setting. Involving a capacity developer partner could help with this aspect. For example, the PMVT involved the INDEPTH Network Malaria Clinical Trial Alliance as capacity-developers (Ogutu, Baiden, Diallo, Smith, & Binka, 2010). An alternative option would be to involve an organization such as Council on Health Research for Development (COHRED, 2015), which offers helpful monitoring tools, such as the Research Fairness Initiative (RFI). Health research impact data help inform shared system learning, co-ordinate capacity building efforts and increase the overall social value of a

collaborative partnership. Measuring the system impact of a study will identify the positive achievements of integrating a program of research into a health care setting. This impact data can thereby inform and provide an impetus to find new mechanisms for system strengthening, providing quality care services and improving local conditions of health.

Across the interviews, a number of responses from medical professionals stated that the end of the PMVT would result in reduced standards of care, decreased treatment availability and constrained health access. Questions were raised over the issue of whether future maintenance costs for equipment and additional staff could continue. Such fluctuations in services were raised as a concern because of the destabilizing effects this has on the local health system. This system impact at the end of a trial, as previously reported, has the potential to disrupt care and to demoralize hospital staff (Merritt, Katz, Mojtabai, & West, 2016). By contrast, it was also mentioned in a number of interviews that the skills and education training attained by local research teams and health professionals were considered sustainable because these skills had the potential to be passed on between colleagues leading to overall strengthened hospital standards.

The objective of health research and partnership is to improve health and, this needs to be a guiding principle in both the conduct and outcome of the process. An earlier study by Angwenyi et al. (2015) suggested "developing a staggered strategy of exit and hand-over of responsibilities and equipment to MoH (Ministry of Health) or other key local actors. A negotiation process also needs to be in place to handle unmet expectations" (p. 16). Aiming to protect the continuity of care and care standards should be a guiding objective of any handover process. This is an area of further research which would be well served by more research partnerships sharing their experiences, as presented here in respect of this PMVT. Although there is extensive literature and ethics guidance on community engagement at the start of a study, there is very limited guidance on community debriefing at the end of a research study.

Dissemination of Results

The interview responses show that dissemination of results must reach a broad cross-section of society. A clear understanding of the political and cultural setting will inform which institutions, authorities, community representatives, and opinion leaders are to be included and notified of the results. For example, one interview respondent mentioned that it was important to involve the local church and mosque in that particular setting. Identification of the appropriate opinion leaders needs to be supported by community liaison teams, participant advisory groups, health authorities and sociologists (M. Molyneux, 2017; Schulz-Baldes, 2006). Time and careful assessment are needed to understand who represents a community and in what capacity. Moreover, it is important to avoid endorsing inequitable structures in a region, for example, partisan politics, gender inequalities, local rivalries, or discrimination (Alvarez-Castillo & Feinholz, 2006). A further aspect to consider is the order in which you approach different members of a community. Guidance on local hierarchies and social customs are important to maximize the social value of results and the acceptance of findings among local and national health authorities; a vital step for policy change and improved health care practices (Wenner, 2017). The dissemination strategy needs to be directed and appropriately structured to facilitate the translation of results with tailored dissemination tools (accounting for education, training, and background context) and clear research messages.

The content of results is also important. Beyond providing information on the test product, there is often other relevant health-related information that can be shared, such as measurements of quality assurance, standards of care, epidemiology, and public health indicators. Notably, a point that was mentioned in many of the interviews is that a dissemination strategy is an ongoing process extending from community engagement at the start of a trial and continued through system strengthening and sharing in the final results at the end of the trial.

Post-Trial Availability

The central message from the interviews on the topic of post-trial access was that there is a lack of clarity around the methods of implementation. The inability to define an actionable approach for post-trial access to effective proven interventions has become a major barrier to fulfilling the ethical requirement and, benefiting trial populations. In the interviews, one ethics committee member explained that committing to post-trial provisions in an ethics review application form is routine for research groups, but implementation of this benefit in practice is rare. Further meaningful discussion and better guidance is required to support post-trial access and the translation of research into improved local conditions of health (Cook, Snyder, & Calvert, 2015; Haire & Jordens, 2015; Hurst, 2017). Notably, post-trial availability was almost exclusively only mentioned by the ethics committee members; reaffirming the point that it is ethically undisputed but practically challenging. One senior researcher made the point that the posttrial-access concept had no practical application in the context of vaccine research because of the time delay between the trial results and the licensing of a successful product. A single trial conducted in the community will not lead to a product that can immediately be administered to the participants or their wider community. Further steps are needed along the development pipeline before an intervention can and should be made available (London & Kimmelman, 2008). As such, clinical trials and other health interventions will rarely lead

directly to post-trial access. It is argued by some commentators that it is important to identify this time-lag in a research proposal and offer other forms of compensation in lieu (Largent, 2017). Others argue that although post-trial availability is not the only condition of ethical acceptability, it is still a "salient" condition of international research in low-resource settings (Haire, 2016). A similar point was made by respondents in the interviews that, on one hand, post-trial availability alone does not ethically justify the conduct of health research. Yet, on the other hand, not considering an actionable post-trial access treatment pathway is unethical. This is especially true in poorer countries where state finances and policy structures are not readily in place to deliver on proven-effective interventions. From a public health perspective, the obligation ensures that the research is driven to improve local conditions of health. Furthermore, extending this principle, Haire and Jordens (2015) argue that "failure to implement research findings, when viewed through a quality improvement lens, is a breach of the social contract made by researchers and policymakers with the communities that participate" (p. 16). In the interviews, it was stated that although post-trial access may be a benefit that is only awarded in the long term, it does need early planning and commitment from a wide range of global and local representatives. As such, this places an onus on countries to strengthen overall administrative and operational systems in preparation to be able to benefit from a preferential rollout strategy (Romore et al., 2016).

A few of the researchers stated that arranging country preparedness falls outside the remit of their responsibilities. The duty of facilitating post-trial availability is therefore argued to be incorrectly levied against the program of research. Commentators have shared this concern before (Nuffield Council on Bioethics, 2002). The main arguments stated in the literature are that the research team does not control the drug approval process in any given country, has limited research funds which are often restricted for defined activities of research and moreover a research team would be conflicted if they attempted to influence the political processes that define government spending decisions (London, 2005). We argue that these are organizational issues, but not sufficient grounds or ethical justification for denying participants and communities benefit for the risks that they are undertaking in research. The latest updates of both the Declaration of Helsinki (2013) and Council for International Organizations of Medical Sciences (CIOMS, 2016). Ethical Guidelines state post-trial access is an ethical requirement that ought to be addressed with a wide range of stakeholders sharing in that responsibility, including for instance "sponsors, researchers and host country governments and other relevant parties" to deliver on this commitment (CIOMS, 2016; WMA, 2013). A major advantage reported by interviewees in the functioning of the PMVT was the early involvement of the national food and drug authority (Food and Drug Administration [FDA]) and governmental officials, so that any positive trial findings could be efficiently scaled to the national level. Further monitoring of this novel partnership model as the vaccine moves through later development and regulatory stages would provide additional helpful insight on the role and responsibilities of collaborative research and post-trial access (World Medical Association, 2013).

A possible alternative is to establish, alongside a study trial, a specific board dedicated to implementing post-trial availability; constituting such a board could become a requirement for ethical research approval. This board may be chaired directly by an ethics committee or an independent mediator and would involve all necessary stakeholders for the rollout of an intervention. At present, researchers seem unprepared and poorly placed to find practical, feasible and legally plausible mechanisms to deliver on post-trial access. This creates a barrier, but the ethical principle is still valid (Cook et al., 2015; Grady, 2013).

Limitations

The stakeholder recruitment for the project adopted the organizational structure of the PMVT. One limitation of this approach is that although the total number of interviews ($N = 52$) was substantial, the number of respondents in each stakeholder group varied between a single representative and up to 15 representatives (see Figure 1). The objective of the project methodology was to represent the various perspectives of stakeholders in a collaborative partnership and capture the group dynamics between partners, such as decision making processes around shared experiences. The ability to compare and contrast across stakeholders also acts to triangulate findings and, provides robustness to the final conclusions. However, in this study, the variation of respondent numbers in stakeholder groups weakened the integrity of this process to some extent. As the vaccine trial was ending a number of stakeholder representatives had already disbanded, which is a project finding in itself. This issue, in respect of the provision of health care is addressed under the results and discussion sections entitled "Maintaining Healthcare Services." The need to sustain local research systems for public health is also further discussed in linked paper entitled "Defining Health Research for Development" (Ward et al., 2017).

The main limitation of this study is that the four themes broached by respondents are extremely dense and complex on their own terms. Further research and exploration of the topics across different research programs would help in sharing practical experience and substantiating recommendations of best practice. It cannot be excluded that a number of the experiences and findings were specific to this research program and settings. Other programs of health research may present different issues, questions, and novel solutions. In the spirit of mutual learning for change, we strongly urge

stakeholders in international health research to be alert to these issues, account for them at the formation of a collaborative partnership, and diligently record and share on these experiences.

Conclusion

The interview responses reinforced the strong ethical and public health arguments for ensuring appropriate planning for the end-of-trial commitments with participants, communities and local systems of health. Respondents of the PMVT emphasized the importance of constructing an effective and gradual end-of-trial communication strategy that informs participants and communities that the research trial is coming to an end. This process should be respectful to community health matters and aim to defend against any possible harm caused by foreseeable service disruptions. Discussions at the end-of-trial around service responsibilities with hospitals and government officials should not be based solely on a spreadsheet of who owns what. By principle, the process needs to be premised on upholding the continuity of care and sustaining positive changes in the health care setting for local populations.

Although widely accepted as a condition of ethical acceptability for health research, the practical implementation of post-trial availability (for interventions proven effective) is challenged by operational barriers. The PMVT was commended for their novel approach in engaging early with a wide stakeholder group to address and facilitate post-trial access. The establishment of such a decentralized post-trial treatment access pathway is important for public health. A considered, health-orientated approach to managing end-of-trial obligations is important for pro-actively embedding collaborative research in a wider global justice framework.

Best Practice

Communication

a. Employ effective end-of-trial communication to support community access to health services for personal and family health matters.
b. Deliver a message expressing sincere gratitude to participants and communities with adequate information and support for safeguarding future health needs.
c. Report on effective health care management and facilitate hand-over planning meetings with health system representatives.

Dissemination of Results

a. Disseminate results to support public health needs and optimize the social value of international partnerships.
b. Methodically identify relevant community stakeholders and representative leadership.
c. Design an appropriate format for reporting results across various audience-bases.

Maintaining Health Care Services

a. Use creative mechanisms, dialogue and active engagement with diverse local stakeholders to sustain continuity of care as a benefit at the end of a program of research.

Post Trial

a. Plan the post-trial access schemes early and engage with a wide range of global and local representatives.
b. Constitute a post-trial availability board to devise a functioning access treatment pathway for intervention rollout; chaired by an ethics committee or an independent mediator.

Educational Implications

a. Support the social value of research with effective end-of-trial communication and results dissemination.
b. Establish practical guidance to implement recent changes in major ethics guidelines; this is a shared responsibility between sponsors, researchers, host country governments, and wider relevant partners.
c. Define and fund a capacity development component to work between a program of research and local health systems. Consider working with a specific capacity development organization.

Research Agenda

a. Capture and evaluate the views and opinions of participating mothers and community members at the end of a trial.
b. Report and analyze standardized impact data on health research conducted in low resource health care settings, across various programs of research.
c. Evaluate the considerations and challenges of providing health care insurance as a post-trial benefit.
d. Analyze the role of post-trial access schemes in the context of addressing a global health agenda.

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