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The Ethics of Health Care Delivery in a Pediatric Malaria Vaccine Trial: The Perspectives of Stakeholders From Ghana and Tanzania

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Abstract

This study explores ethical issues raised in providing medical care to participants and communities of low-resource settings involved in a Phase II/III pediatric malaria vaccine trial (PMVT). We conducted 52 key informant interviews with major stakeholders of an international multi-center PMVT (GSK/PATH-MVI RTS,S) (NCT00866619) in Ghana and Tanzania. Based on their stakeholder experiences, the responses fell into three main themes: (a) undue inducement, (b) community disparities, and (c) broad therapeutic misconceptions. The study identified the critical ethical aspects, from the perspectives of stakeholders, of delivering health care during a PMVT. The study showed that integrating research into health care services needs to be addressed in a manner that upholds the favorable risk–benefit ratio of research and attends to the health needs of local populations. The implementation of research should aim to improve local standards of care through building a collaborative agenda with local institutions and systems of health.

Keywords

ethics, vaccines, therapeutic misconception, undue inducement, disparity

Introduction

The World Health Organization (WHO), World Malaria Report of 2016, stated that although malaria mortality rates have fallen worldwide, in 2015 the disease still killed globally an estimated 303,000 infants below 5 years of age . Of these recorded deaths, 292,000 (96%) were in the African region (WHO, 2016). As a result, scientists seek to find a malaria vaccine suitable for African children to complement existing control measures (Tinto et al., 2015). To evaluate the safety, efficacy, and protectiveness of a possible pediatric malaria vaccine candidate, it is necessary to carry out randomized control trials (RCTs) in the relevant target population: children below 5 years of age living in varying disease transmission settings in Africa. A cautious approach must be taken with enrolling children into research, in any setting, because of their vulnerability, inability to give informed consent, and increased propensity to adverse reactions (Olson, 2014; WHO/Initiative for Vaccine Research [IVR], 2002). Moreover, the regions where malaria vaccine research takes place are in general low-resource settings, characterized by weak health care systems, underfunded public health facilities, drug shortages, and unmet population health care needs (Angwenyi et al., 2015; Lang & Kokwaro, 2008; Mwangoka et al., 2013). Health research in low-resource settings gives rise to challenging decisions and ethical questions. This article focuses on one ethics issue in particular, health care delivery in the context of a pediatric malaria vaccine trial (PMVT).

Ethical Guidance on Providing Health Care in Research

Ethical guidelines for conducting research in international settings—in particular the Declaration of Helsinki (DOH) by the World Medical Association (WMA; 2013) and the International Ethical Guidelines for Health-Related Research Involving Humans by the Council for International Organizations of Medical Sciences (CIOMS; 2016)—clearly state that there is a duty for research teams to provide health care over the course of a trial. The requirement of researchers to provide adequate health care is advocated

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for on four broadly accepted premises: "the welfare principle, rule of rescue, justice, and entrustment" (Georgetown, 2008; Richardson & Belsky, 2004). A positive obligation to provide comprehensive care for participants and local communities over the course of research is necessary for safety and to defend against possible risks of exploiting deprived populations, even when, as in the case of a malaria vaccine trial, the cause is admirable (Weigmann, 2015; Wertheimer, 2008). The extent of the health care obligation is defined in relation to the longevity and proximity of the research to the health care system, the expertise of the research team, and the urgency to act (Hyder & Merritt, 2009; Merritt, Taylor, & Mullany, 2010; Richardson & Belsky, 2004).

Research and Systems of Health

The positive impact that can be made by integrating research into health and social systems is widely documented (Denburg, Rodriguez-Galindo, & Joffe, 2016; Massawe, Lusingu, & Manongi, 2014; Mwangoka et al., 2013; Tinto et al., 2014). The health system improvements forged by research programs create community access to reliable, trustworthy, and efficient health care for at least the period of a trial. Long-term benefits have also been reported regarding strengthened physical infrastructure, better-trained staff, and improved community health-seeking behaviors (Angwenyi et al., 2015). While few would argue with the goal of providing necessary health care in the course of a community-based PMVT, the implications, complexity, and sensitive nature of the responsibility require scrutiny (Asante, Jones, Sirima, & Molyneux, 2016). Providing extensive health care in the course of a research program does not remove all practical and ethical concerns, but rather raises new ones.

This is not an exhaustive list, but the following points define the main concerns in current academic literature in respect of health care provided in low-resource setting research. First, there is the issue of exacerbating disparity. Improving access to health care for one part of the population but not another can increase regional and community inequalities, especially in impoverished settings. As a result, the presence of a research program may inadvertently lead to eroding trust in routine public health services (Tinto et al., 2014). Even to improve one section of a hospital but not the rest can create social tensions (Angwenyi et al., 2015; Asante et al., 2016). Second, when access to health care becomes the main incentive for parents to enroll their child in a trial, then the appropriateness of this inducement needs to be carefully considered and may amount to undue inducement (Njue, Kombe, Mwalukore, Molyneux, & Marsh, 2014). For example, is a participant who has no access to health care able to weigh up the risks of entering into a trial? Worthy of note, Emanuel (2004) state that the term "undue inducement" has no practical function in ethical deliberation and should be abolished. This is argued on the premise that inducements can never be "undue" when research is scientifically sound, the collected data has social value, participants are selected fairly, and the overall risk–benefit ratio is favorable (Emanuel, 2005; Emanuel, Currie, Herman, & Project Phidisa, 2005). In practice, most research ethical guidelines and the standard operating procedures of ethics review committees continue to consider the term, "undue inducement," as a frame of ethical enquiry when assessing research protocols (CIOMS, 2016; Krubiner, Syed, & Merritt, 2015).

Third, another concern specific to providing health care during a vaccine research, such as the PMVT, relates to how the standard of care should be defined (e.g., prevention measures, treatment options, and broader non–trial-related treatment, referred to as ancillary care). Ensuring adequate health care requires that a program of research provides a level of care that defends against the possible exploitation of populations—"avoidable harm, disrespect or injustice" (Resnik, 2003). Historically, the debate has focused on whether high-resourced programs of international research should be required to raise the standard of care in low-resource settings, where local health care services are otherwise limited (Angell, 1997; Lurie & Wolfe, 1997). Yet, there is a further consideration, when the health care package provided in the frame of a Phase II/III clinical trial is significantly improved (but different) compared with the "real-world" setting, this may reduce the effect size of a modestly efficacious intervention (Padian, Buve, Balkus, Serwadda, & Cates, 2008). For example, in the PMVT, because the care provided to all trial participants was optimal, this "might have limited the ability of the trial to detect an effect on mortality or other severe outcomes" (Tinto et al., 2015). This challenge defines the difficult balance that needs to be struck between protecting the rights of individual research participants and the needs of society; the common good of obtaining data for scientific advancement (Weigmann, 2015).

Fourth, the standard of care problem in vaccine research is arguably heightened specifically in relation to the level of preventive measures offered to participants and local populations. A vaccine intervention can only be assessed when new infections have the opportunity to occur in the trial population. For example, when testing a malaria vaccine, it must be tested in a region where a population is affected by the target disease, malaria. Given such a setting, the question becomes, to what extent is a research team obliged to provide preventive measures, for example, bed nets, environmental controls, and improved health education? On the one hand, for the vaccine trial to function effectively, a difference must be detected between the incidences of infection in the control and vaccinated arms of the study; establishing an altered disease prevention model, using protective measures other

than the vaccine candidate, may compromise this objective (Georgetown, 2008). Yet, failing to prevent disease and illness, where there are known proven effective interventions, is ethically contentious. On the other hand, research into novel interventions is necessary because the background interventions that constitute the standard of prevention are themselves suboptimal in real-world settings. The current methods that make up the standard of prevention have modest effectiveness but are not "good enough"—hence the need to find an effective vaccine and conduct randomized controlled trials, such as the PMVT. This ethical debate over the "standard of prevention" has met particular scrutiny in the literature in relation to HIV prevention trials, where contracting HIV leads to chronic, debilitating, and often fatal outcomes (Guenter, Esparza, & Macklin, 2000; Haire & Jordens, 2013). Comparably, severe malaria is categorized as a life-threatening but treatable disease (WHO, 2016). The characteristic of the disease profile and the consequential risks to life and livelihood play an important role in the determination of the ethical standard of prevention and treatment in the course of research (Guenter et al., 2000; Joint United Nations Programme on HIV/AIDS, 2012).

Underlying all of the above issues is the inherent conflict in objectives between providing health care and conducting health research. The defining goal of health research is the generation of generalizable knowledge and not the promotion of individual patients' health ("best interest"; Belsky & Richardson, 2004; Katz, 1993) As Pinxten, Ravinetto, & Buve (2016, p. 18) state, "there is an ethical rationale to separate research from routine care where possible. Routine care and clinical research each have their own agenda." The two activities have different obligations, objectives, and outcomes, and maintaining a distinction is vital for trust, safety, and research integrity (Henderson et al., 2007; Miller & Brody, 2003). However, what is ethical becomes more nuanced and convoluted when conducting a PMVT in resource-limited settings. For the two activities to work entirely independently would result in research studies neglecting individual participants and community health needs. Numerous commentators have argued that researchers in developing countries should address possible health inequalities as a requirement of global justice when setting up health research in low-resource settings (Benatar & Singer, 2010; Macklin, 2007; Tarantola et al., 2007). In particular, where the international research collaboration has the expertise, proximity, and finances to respond to unmet health care needs, this arguably gives rise to a general duty of rescue (Belsky & Richardson, 2004). That said, for the two activities to become inextricably interlinked can lead to participants' misconception on the role, objectives, and limits of health research (Belsky & Richardson, 2004; Pinxten et al., 2016).

Empirical Study Objectives

The objective of this article is to address the ethical issues raised by the provision of health care during the conduct of a long-standing PMVT in resource constrained settings. The results and discussion present the challenges and responsibilities associated with the special contract of trust that forms among the research teams, health care systems, individual participants, and local communities.

This empirical study moves the debate from the theoretical to the practical to assist in understanding what types of decisions are being faced by researchers providing health care and what ethical dilemmas arise, along with insight into how such questions are being addressed in practice.

This project is based on the perspectives of stakeholders from a large, long-standing PMVT Phase II/III efficacy and safety trial (RTS,S) (NCT00866619) that involved 15,459 infants at 11 sites in seven sub-Saharan African countries (Tinto et al., 2015). The trial was funded and developed by GlaxoSmithKline Biologicals SA (GSK) and the PATH Malaria Vaccine Initiative (PATH/MVI) in partnership with Malaria Clinical Trials Alliance (MCTA). Our study presents the responses of stakeholders from Ghana and Tanzania (two research centers per country) involved in the international malaria vaccine candidate trial from 2009 to 2014.

Method

A key informant, semi-structured interview method was selected to understand stakeholder perspectives on the practical considerations and ethical challenges of health care delivery in the course of a PMVT.

Study Population

All respondents were stakeholders of the PMVT in Ghana and Tanzania. The two specific countries of Ghana and Tanzania were selected through dialogue with local partners following initial assistance and introductions through the Swiss Tropical and Public Health Institute (Swiss TPH). The interview respondents comprised clinical and research team members from four separate research centers as follows:

Ghana: (a) Malaria Research Centre, Agogo Presbyterian Hospital, Agogo, Ashanti (administered by the School of Medical Sciences, Kwame Nkrumah University of Science and Technology, Kumasi); (b) Kintampo Health Research Centre, Ghana Health Service, Kintampo.

Tanzania: (c) Ifakara Health Institute, Bagamoyo; (d) Tanga Research Centre, Korogwe, National Institute for Medical Research (NIMR).

In addition, the wider partners of the PMVT were also included as respondents: respective government bodies, ethics review committees, health care system representatives, and international partners.

The study sample was defined and agreed upon following consultation with local partners at all the research centers during a preliminary scoping visit. A scoping visit by the authors C.L.W. and E.A-S. to Ghana and Tanzania was carried out in January 2014. The study method was further designed through a participatory process and the advice of local partner institutions. The data collection activities of conducting the interviews were carried out by author C.L.W. Local country partners and institutional contacts facilitated the recruitment of eligible interview respondents. Invitations with additional study information were sent out to all potential interview respondents.

Sample

Individual semistructured interviews were employed for the majority of stakeholders (n = 50) except for two group interviews (n = 2). Group interviews were conducted with the vaccination nurses and fieldworker teams (four individuals per group). Fieldworkers are members of the local community employed in community liaison roles to inform, support, and communicate with participants (mothers and infants) and the research teams (Molyneux et al., 2013). The individual interviews included senior researchers, research managers (data, lab, pharmacy, and quality assurance), clinicians, field coordinators, and health system representatives (hospital managers, district medical officers), ethics committee member (institutional and national), national government bodies (FDA and ministries of health), sponsor-investigators/funders (GSK, MVI/PATH, CRO, MCTA); see Table 1 and Figure 1.

The specific job titles of respondents and their associated research center have been withheld to protect the anonymity of the interviewees.

Study Instrument

A semi-structured interview guide (see appendix) was developed following a review of the current literature and collaboration with a range of experts working in the field of global health research and empirical ethics. The interview guide covered a variety of topics relevant to the conduct of international health research in resource constrained settings. This article is based on a section of the interview guide relating to standard of care and health care services (see the appendix).

The interview guide was developed with the support of a qualitative methods advisory group consisting of the article's authors, qualitative research methodologists, and country experts from Ghana and Tanzania. The interview guide was then piloted with medical researchers based at the Swiss TPH who have extensive experience of conducting clinical trials in resource-limited regions (in particular in Tanzania) and two research ethics committee members in Ghana. This aided in testing and revising the semi-structured interview guide for optimal functionality and coherence. Pilot interviews (N = 5) were not included in the final interview data set of 52 interviews (N = 52).

Table 1. Number of Respondents Presented as a Total, per Country and Institution (N = 52).

Group	Number of respondents
Total	52
Ghana	
Research Center A, GH	11
Research Center B, GH	6
Ethics review committees	2
Health system	3
Government	2
Tanzania	
Research Center A, TZ	7
Research Center B, TZ	9
Ethics review committees	2
Health system	2
Government	2
International partners	
GlaxoSmithKline (GSK)	2
Contract Research Organization (CRO)	1
Malaria Vaccine Initiative/PATH	2
Malaria Clinical Trials Alliance (MCTA)	1

Ethical Approval

Permission to proceed with this study was provided by the GSK/PATH MVI Ancillary Studies Review Committee on July 18, 2014, along with signed agreements from all the requested health research centers. The study protocol, informed consent forms, and interview guide were reviewed and approved by the University of Basel in Switzerland by the Ethikkommission Nordwest- und Zentralschweiz (EKNZ). The study was also approved in each country, Ghana: Ghana Health Service Ethical Review Committee; Kintampo Health Research Centre Institutional Review Board (IRB); Committee on Human Research Publication and Ethics, School of Medical Sciences, Kwame Nkrumah University of Science and Technology; and Tanzania: National Health Research Ethics Review Committee for NIMR; Ifakara Health Institute IRB; Tanzania Commission for Science and Technology (COSTECH).

Informed Consent

The corresponding author conducted all 52 interviews in English between November 2014 and September 2015. All respondents were notified that the interview would be audio recorded. Written and oral informed consent was

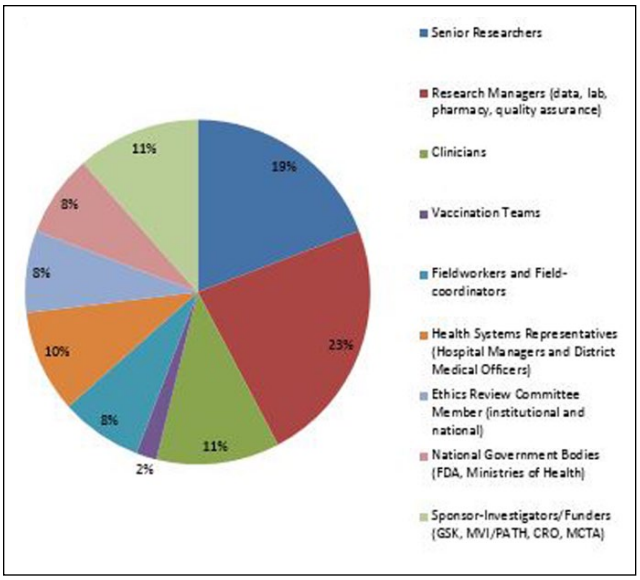

Figure 1. Pie chart presentation of respondents by stakeholder roles in the pediatric malaria vaccine trial ($N = 52$).
Note. GSK = GlaxoSmithKline; MVI = Malaria Vaccine Initiative; CRO = Contract Research Organization; MCTA = Malaria Clinical Trials Alliance.

obtained at the start of all interviews. The informed consent process informed respondents that interviews would be saved under a nonidentifiable code anonymously, and confidentiality would be protected. In addition, respondents could end the interview at any time, or refuse to answer any specific question(s).

Interviews and Transcriptions

Interviews lasted between 35 min and 2 hr (50 min on average). This article presents results on one aspect of these interviews—the standard of care and the relationship between the PMVT and the health care services. Author C.L.W. transcribed 40 interviews in full, and 12 interviews were transcribed by two departmental assistants, and then reviewed for accuracy by author C.L.W. Departmental assistants were subject to the same terms of project confidentiality.

Data Analysis

The interview transcripts formed the basis of raw data for this research. The transcripts were read multiple times by C.L.W. and D.S. ahead of coding. Author C.L.W. carried out thematic coding with all the transcripts using qualitative research software MAXQDA. Repeated ideas were identified across the transcripts and constituted into subthemes. The subthemes were then grouped, and this led to the establishment of themes and the development of theme narratives (Auerbach, 2003). To minimize researcher bias, author D.S. consolidated the coding by reviewing all codes and subthemes to ensure agreement and consistency in theme definitions and groupings.

Results

Respondent Disposition

In total, 52 interviews ($N = 52$) were conducted; see Table 1 for a summary of the respondents presented by country and institutions, and see Figure 1 presenting respondents by stakeholder roles.

Qualitative Results

The interviews ($N = 52$) were analyzed using thematic coding. Three major themes emerged (a) undue inducement, (b) community disparity, and (c) therapeutic misconception. The results are presented under these thematic headings.

Undue inducement. To protect against any possible research harm, senior researchers emphasized the need to explain the risks of research as well as the benefits of health care during the trial. In particular, it was noted that where the health care benefits are advantageous to the participant, and superior to normal health care services, this may distort an individual's ability to reflect on the risks of the study and influence their decision to take part—the concept of undue inducement. There were mixed views among respondents on whether health care provision during a research project simply encouraged or unduly induced community members to participate.

> **Research Manager (GH/A/16):** Because here, you know, poverty rate here, so as soon as the person hears of the benefits, even if he is not interested, all he knows is that he is going to get some benefits from it [the research]. That would coerce the person to take part in the study.

There was a consensus among all the stakeholder groups regarding the importance of improving pediatric care for the whole community and not only for the research study participants. Different reasons were provided for why this was important across the interviews. One reason given was to equalize local health care services for the local population, whether within or outside the PMVT. This then limits any possible undue influence on participants that may be created by the added attraction of improved services. It further enables local communities to collectively take advantage of the benefit provided by an international research program.

> **Senior Researcher, Epidemiologist (TZ/A/44):** We already knew that they [participants] will get better care with the level of personnel that we [the research team] have and the standard procedures that we would implement. So to remove that aspect,

we had to provide all services to everyone coming to the hospital for the paediatric services.

The resource constrained context remains a relevant factor with regard to the possibility of undue inducement. Most senior researchers, research mangers, and medical teams recognized that background inequalities made participants more susceptible to the attraction of health care benefits. However, the frontline staff did not perceive the provision of health services per se as a concern. The vaccination nurses still recalled a few mothers who refused to enroll their infants into the PMVT. This illustrates that (certainly in some cases) participants weighed up the risks of the research and decided freely not to enroll their infants.

Vaccination Nurse (GH/A/22): Some mothers refused to be recruited because they were scared they thought maybe this vaccine could harm, unsettle the children or something.

Fieldworker (GH/A/34): You see concerning malaria, they [the community] really know how dangerous malaria is, and the way that the little ones are dying because of Malaria . . . and so they say "oh if our kids are being killed by malaria deaths and these people are doing something about it, why don't we involve ourselves" . . . The mothers, I should say they were more interested in the welfare of the children than when the vaccine out comes. So that motivated them to be part of the study.

The predominant view of respondents is that the PMVT had a hugely constructive impact on the whole health system and safeguarded against possible research harms and poor health.

Clinical, Physician (TZ/B/51): [Before the PMVT started] . . . there were seven kids who were being cared for by only one nurse. Children were dying, but when we [PMVT] went there [Paediatric Ward], we started to avert most of the deaths, regardless of whether the child was from the project or not.

Community disparity. Respondents offered differing opinions on whether health care delivery with the research created apparent, or even perceived, community disparities. Most respondents drew attention to positive changes generally made by the PMVT in the local health system and to the improved local standards of care, for example, additional resources, equipment, skills, and medical services.

Vaccine Developer, GSK (BE/A/52): There is the benefit in the level of training perhaps and, quality in the delivery of medical and nursing care that is provided [over the course of PMVT], without saying "so I haven't sufficient resources" to do that. We don't aim actually to do that, to improve beyond the local standard of care. It is one of our principles that our trials are conducted according to the local standard of care.

The topic of disparity, and the impact on health, was brought up most often by the frontline staff—medical team members, fieldworkers, and vaccination nurses. All the doctors stated that they treated participants and non-participants the same, but were in agreement that the logistics for study participants were improved, and all barriers to access, in particular transport and costs, were removed.

Clinical, Physician (GH/A/07): Someone comes to the hospital, and you say "why did you not come to the hospital yesterday, your child has a fever, you should have come yesterday." "I did not have money for transport." The study subjects had no reason to stay home. They just needed to send a message to us, my child is sick, and then a car would go and pick them up.

A few examples were provided by respondents where community disparities led to some community tension, disruption in the wider health care services, and distrust between the community and the research program.

Clinical, Physician (GH/A/10): At a point, you see people consulting us: "how can my child also get into this study?" We say "no, we have recruited them already. We are following them for four years, so we can't enrol your child now." And they say "ok when you next do something, invite us."

Senior Researcher, Epidemiologist (GH/B/27): Some of them [participant's mothers] were comparing the health status of their children, their current children to previous ones and making comments like "this child of mine who didn't take part in this programme has been very sick as compared to the one who was part of the programme."

Senior Researcher, Epidemiologist (TZ/B/30): Even when we wanted to share the workload, the community would prefer to come and see the physician who is employed by the project [the PMVT]. So that was a bit of a challenge.

An important aspect in addressing factors which unfairly promote community disparity is to address what level of health care provision is fair within local communities and also equitable across international partners conducting the research.

Vaccine Developer, GSK (BE/A/19): The key criteria that we thought was most important for a vaccine clinical study, was the ability to provide good care at the hospital, and having the impression that the local infrastructure and staff and leadership understood the importance of that.

The vaccine developer described health care provision as a key criterion. However, the response below also shows that the extent of health care provided by a program of research required discussion across partners.The local team had to negotiate with the sponsor to obtain additional health care services to defend against community disparity.

Senior Researcher, Epidemiologist (TZ/A/41): Now when we discussed with the sponsor, this [community disparity] was one of the main issues of contention in the sense that, from the perspective of the sponsor, our costs were more than what somebody would think is needed just to implement the study. We are not talking about just implementing a study just independent of what else is happening in the place, we were talking about implementing a study, in the context, and so these are additional costs of just making sure that good service is available to everyone . . . Ok, so now the costs of doing the studies in Africa is becoming close to what it costs to implement a study in Europe or somewhere else and we said yes it is close, but the costs are different. The structures of the costs in Africa are maintaining routine services that are not being provided routinely to everyone. The cost of Europe and US is the high cost of personnel.

The above quote presents a clear argument that conducting health research in low-resource settings must be intended to improve health rather than to reduce costs. The costs are reflective of the context of the local population and their health needs, be it covering cost of personnel or reducing community disparity. All the senior researchers emphasized the importance of using the process of research to improve services for the local health care setting. For example, in the instance of the PMVT, better laboratory diagnostic facilities were provided and standardized approaches to record-keeping were introduced.

Senior Researcher, Epidemiologist (TZ/B/29): You cannot put the machines there and you say this machine will only be used by my research participants. That again ethically is wrong, because we also know the setup of our health facilities and especially for us, we are poor. So if you are here, you have the facilities, they should benefit everyone.

Community engagement and involvement was identified in the interviews as central to the setup of the PMVT and vital for protecting against issues of community disparity. A number of respondents talked about different ways they connected with the community. In particular, the fieldworkers and medical doctors described the communication strategy, transport, and education services that were provided for local populations.

Clinical, Physician, (GH/A/14): We went once to a village, and on our way, we saw another child sitting somewhere, just shivering. There was no way we could allow this child to be buried so we just carried them to our car, came to hospital, and treated them.

The centrality of community to the study design was emphasized as highly important for the conduct of responsible research and should be recognized as an ethical requirement.

Ethics Review Committee (TZ/A/43): Community becomes as a partner in the research. Because that is how research works, research does not leave the community aside, so they engage them as partners, and that dialogue with community and researchers resulted into various community healthcare mechanisms.

However, a few senior researchers raised concerns that the improved health care can lead to results which do not replicate real-world settings. Yet, it was also recognised that the setup of the research in local health systems demonstrated locally what service improvements and levels of personnel are required to offer comprehensive and effective standards of care.

Senior Researcher, Epidemiologist (TZ/B/49): Even in all our published findings, we commented on that, that the overall care was good across all the sites and that was reflected by the low mortality rate compared to the overall mortality in the same paediatric population. It is hard to replicate, I mean this was under research conditions, but we have demonstrated that it can be done.

Therapeutic misconceptions. The relationship that is fostered among the research enterprise, community, and the health care system over the course of a long-standing PMVT is important for building trust. A careful consideration of the approach is required to avoid harmful therapeutic misconceptions. Moreover, the health ministers and district health officers raised concerns that time-limited supplements to health care services can create artificial health care conditions and unsustainable system dependencies. This concern was also acknowledged as a practical concern by frontline teams. One senior researcher recollected system dependencies that can be created by the research structures and have the potential to be dangerous, mentioning in particular one tragically fatal incident.

Senior Researcher, Epidemiologist (TZ/B/11): I remember there was one study where a child died because they [the participant's family] were calling one of the research assistants whose phone was off and then by that time the child was really bad. That was a huge mistake from the fieldworker because we told them their phone should be on, all the time. So that was a typical example of, what happens if you do not have access on time.

The important role of communication to defend against medical misconception was identified in a number of interviews. Representatives of the health services stated that an open and active dialogue between the research program and the hospital was an important mechanism to stabilize care for participants and communities.

Healthcare System Representative (GH/B/48): If the hospital member knows much, they will transmit information

to the dispensaries, to the health centres, about the issues . . . So if now, maybe RTS,S [the paediatric malaria vaccine trial], and the district health officer, and executive director, and the district medical officer, if they sit together and say "our budget would be this, we are doing this and this, how about your health department?"

Maintaining a clear distinction between the research team and health care services was regarded as necessary to manage the expectations of mothers and infants in the PMVT, and so as not to disrupt local health care services.

Vaccination Nurse (GH/A/23): Sometimes we went for home visits, and, they [mothers] were confusing the research team with the CWC [Child Welfare Clinics]. So with the research mothers, we had to inform the fieldworkers, and then they go to talk to the mothers.

Some of the medical doctors also emphasized that a PMVT recruits healthy children. If the participants do not understand that this is a test candidate vaccine, the participants may stop rigorously using other malaria preventive measures. This risk is further heightened in a context where the mothers are of the view that by enrolling their children in the PMVT, this will improve a child's health.

Discussion

The results from this study present the practical experiences of a PMVT providing care in resource constrained settings. Importantly, the multistakeholder perspectives reveal the different views of various respondents across an international collaborative health research partnership. This article offers a unique opportunity to learn from the experiences of a long-standing PMVT operating in resource-constrained settings. The main themes that arose were concerning undue inducement, community disparity, and therapeutic misconceptions.

Undue Inducement

Undue inducement is addressed in ethics guidelines and literature as an incentive that persuades participants to volunteer against their better judgment or deeply held beliefs to accept the risk of research (Emanuel, Currie, & Allen, 2005; van Delden & van der Graaf, 2017). Responses in the interviews showed that research managers and senior researchers addressed this ethical challenge by taking active steps to prevent mothers enrolling their infants only for the reason of better care and ensuring effective communication to convey all the possible risks. The medical teams and staff working closest with the community, including the fieldworkers and vaccinations nurses, were of the view that the additional health care provided was of great benefit to local population health and highly appreciated by participants and their communities.

The debate in the literature has argued that a context of resource constraints does not, per se, make the offer of health care undue inducement, if the research risk has been minimized, and there is an overall favorable risk–benefit ratio (Emanuel et al., 2005). Under such circumstances, the offer of health care is advantageous, responsive to local health needs, and participants are free to enroll in research to promote their own health (Mfutso-Bengo et al., 2008). Importantly, it remains the responsibility of sponsors, ethics committees, research teams, and governments to ensure that basic health care is not used as an unethical recruitment tool for risky research, and especially so in contexts of poverty. Moreover, even where a research program is ethical and approved by an independent ethics committee, any trial product may trigger an idiosyncratic reaction which can negatively impact on a participant's health. This nuance is complex, and the risk needs to be fully discussed with participants. The inducement of health care provision can ultimately place a child's health at risk and potentially lead to harm. It is crucial that the research participants are genuinely able to comprehend and assess the risks of research and continue to be informed throughout a study. For example, in the results of this study, community fieldworkers explained that a central part of their role was communicating with, and advising, the community on the risks of research, as well as undertaking the informed consent process during the PMVT. In part, this equates with the conclusions drawn by Emanuel et al. (2005), in that the assessment of any research needs to focus on minimizing risks and not merely the presence of inducement factors, such as the incentive of better health care. Therefore, under these circumstances, concern over incentives that encourage and facilitate improved conditions of health are "misplaced" and do not amount to an inducement that is undue (London, Borasky, Bhan, & for the Ethics Working Group of the HIV Prevention Trials Network, 2012). However, it does not necessarily follow that the term "undue inducement" is redundant, as Emanuel et al. argue, but rather that the presence of inducement factors, health care, or otherwise reinforces the need to scrutinize social value, scientific validity, and fair participant selection with a context-informed approach. For example, it may be concluded in some instances that further safeguards are required beyond the conventional informed consent form due to the particular inducement factors in a given setting. For instance, it may be required that guidance on risks is delivered by impartial teams who have no interest in the study recruitment numbers (CIOMS, 2016). Technology can also support the understanding of risks and the informed consent process. A mobile phone platform survey could assist in educating and objectively assessing

mothers' comprehension of the risks of research. The appropriate strategy has to be determined by the community context to appropriately defend against risks of undue inducement. This is essential for the conduct of safe and ethical studies.

The interview responses showed that access to health care remains the main reason for mothers to enroll their infants in the PMVT, in line with recent literature (Angwenyi et al., 2015; Angwenyi et al., 2014; Asante et al., 2013; Febir et al., 2013; Jaffar et al., 2008; Kamuya et al., 2014; Liheluka, Lusingu, & Manongi, 2013; Massawe et al., 2014; Ravinetto et al., 2015). Moreover, the care and clinic visits provided for participants are a necessary component of the research, and especially important for building a trusting rapport with participants in the community. Although the provision of health care may not amount to undue inducement, the participants' voluntariness may be restricted due to background inequalities. This makes participants vulnerable because participating in health research should not be a pre-requisite for obtaining access to health care (Homedes & Ugalde, 2015; Kalabuanga et al., 2015; Pinxten et al., 2016). However, in the absence of sociopolitical and structural change on the ground, researchers and fieldworkers must responsibly navigate this ethical challenge (Kingori, 2015); where the provision of care in a context of suffering is at odds with freedom of choice, then this needs to be recognized as a vulnerability, but not a barrier (Kingori, 2015). The research must be responsive to the local context and introduced to the community with caution (Lang et al., 2012; Lusingu et al., 2010; WMA, 2013). To do so requires not only supplementing local services but also seeking to make any improvements to the standard of care more broadly available through partnership with local systems. In the example of the PMVT, the distribution of mosquito nets and malaria education were organized through local malaria prevention schemes and supply chains. Equally, hospital staff and research staff were trained with new techniques on upgraded laboratory equipment to benefit the whole population using the hospital. This approach requires careful involvement and engagement with the appropriate local structures: ethical, legal, political (including local leadership and opinion makers), and clinical.

In addition, factors contributing to undue inducement must be addressed by reporting on situations of ethical concern between stakeholders. This will encourage necessary deliberation between the research and health care teams to assess issues that arise from the complex interplay between background inequalities, benefits, and risks. This process will also contribute to strengthening the collaborative partnership between programmes of research and local systems of health care.

Disparity

A concern raised by supplementing a weak health care system with the resources from a program of research is that doing so may increase community disparities. In this respect, the standard of care selected for a trial is critical to addressing concerns of disparity while also ensuring participants are not put at risk of harm from the research that could have been foreseeable and preventable with adequate care (London, 2000; Tarantola et al., 2007; Wendler, Emanuel, & Lie, 2004). The international partners and medical teams explained that the standard of care provided by the PMVT was, as a matter of fairness, set in accordance with official national guidelines; the local *de jure* standard of care (London, 2000). It was noted by respondents that on the ground, this still required the PMVT to upgrade from the *de facto* standard of care, otherwise under-resourced public district hospitals to meet the set national guideline standards (London, 2000). The clinicians involved in the PMVT emphasized that they treated all patients equally: The same treatments and procedures were provided at the pediatric ward. However, it was acknowledged that access to the available services was not equal between participants and non-participants. For participants, access to services was streamlined with the provision of transport, specifically allocated doctors, access to all necessary medication, and organized referrals to more specialized hospitals where needed. These services were not available to nonparticipants. In addition, all direct and indirect costs of health care were removed for participants. The vaccination nurses stated that giving free medical care is in effect putting money in the pockets of those participants. Moreover, a sense of being treated differently by care providers can lead to community distrust not only in the research program but also in the public health facilities (Angwenyi et al., 2015; Mfutso-Bengo, Manda-Taylor, & Masiye, 2015; Ravinetto et al., 2013). As a cautionary point, unequal access to treatment may further push those not profiting from formal health care services to seek alternative treatment elsewhere, for example, using unregulated drug stores or traditional healers. This outcome could further exacerbate poor health outcomes. In a case study by Vallely et al. (2009), the health care provision was established with collaborative agreements in local systems and funding secured through government and external funders. This approach enabled both health care provisions for the wider community and sustained improvements to the standard of care beyond the end of the study. The operation of international research should support and complement the wider goals of global health to reduce health inequalities and improve local standards of care. Shapiro and Benatar (2005) referred to this concept as the aim to "ratchet up" standards of care for the most impoverished and vulnerable populations.

Poorly planned medical components of research projects can leave participants feeling used and with the view that the health care system is uncommitted (Aellah, Chantler, & Geissier, 2016; Angwenyi et al., 2015). The challenge is to retain the independence of the research program from the health services and yet support a functioning partnership with the community (Jaffar et al., 2008). One example presented by Pratt et al. (2013) defines a situation where a research unit in a region with no health care joined with a medical NGO into a single organization, to fulfill the moral obligations of providing care for a wider population, while gathering research data. It is vital to devise the appropriate medical care plan for the setting regarding the nature, coverage, and time frame of the care to be given (WHO/IVR, 2002).

Practical and ethical issues will also arise unplanned in the course of research, and a mechanism needs to be in place to account for these. In some circumstances, especially when there is a disparity, researchers may be best placed to provide urgently needed help. The duty to rescue will at times expand the researchers' responsibilities to provide care (Richardson & Belsky, 2004). This can be hugely beneficial to the communities and health care settings, both for providing additional health resources and as a mechanism to evaluate, inform, and strengthen local health care procedures. The respondents of this study and the literature seem to emphasize, and be in agreement, that a research team shouldnot undermine or absolve the public health service of their responsibilities and funding commitments (Emanuel et al., 2005; Georgetown, 2008; Kamuya et al., 2014). To maximize the learning opportunity between the research and the health care system, all unplanned health care provision events should result in a joint case review between the research and hospital setting to identify where gaps or oversights may exist in routine care.

The final concern with the additional provision of health care during a PMVT is that a disparity exists between the research health care setting and the real-world setting. This occurs where the standard of care provided in the PMVT is higher than what is generally experienced within resource constrained health facilities in the wider population. This improved health care experience in the PMVT could potentially bias the results of the trial. In the main, providing optimal health services does not affect the ability to isolate the efficacy and safety results of the intervention though it may complicate a secondary endpoint of delayed disease progression (Tarantola et al., 2007). These known effects must be accounted for, and stated in, the study design and post-licensure surveillance strategy to deliver quality data, assure compliance with ethics, limit harm, and retain community trust in research. Worthy of note is that an RCT is not an implementation study. A Phase II/III malaria vaccine trial designed in the format of an RCT does not aim to replicate the "real world" and will routinely optimize various conditions to remove biases, such as enrolling participants who are in optimal health. Importantly, researchers remain responsible for the well-being of their participants which is paramount over other goals and scientific objectives. Therefore, once the risks of a new intervention have been understood in the context of good health care access, implementation research can be established to look at the effectiveness of the innovation closer to real-world settings, as is common in Phase IV testing.

Therapeutic Misconception

The precise definition of therapeutic misconception is debated in the literature, but by way of summary, it is understood as a participant failing to understand the intent of research and equating the activity of research to the provision of routine health care (Henderson et al., 2007). A few of the interview responses remarked that the integration of the PMVT and supplementation of health care services had the potential to give rise to a therapeutic misconception because the two services were closely interlinked. The shared components of the clinical trial with the health care facility—staff, infrastructure, procedures, and clinical language—were often indistinguishable, both for the PMVT participants and in some instances also for the staff themselves. The close relationship between the community and the research was articulated by fieldworkers who stated that the community members referred to them as "family." Equally a recent paper by Angwenyi et al (2015) defined the function of the PMVT in a local health system as a "short term complex health service delivery intervention." This very close relationship may pose a risk because communities become dependent on the research teams for access to health care which may not be adopted into routine district health care services. Creating a dependency ethically fosters therapeutic misconceptions and practically can create system instability. For example, in the eventual absence of the study, local services might suffer a loss of popular and political support, leading to further service depletion (Merritt, Katz, Mojtabai, & West, 2016).

Another factor fueling a possible therapeutic misconception is that communities' previous knowledge of health research will have been limited or nonexistent, whereas experience with hospitals is more common place. Therefore, as the fieldworkers stated, the natural association from the community perspective is that the health care providers, or those who are providing health care, are acting to directly benefit their health (Lema, 2009). The roles, responsibilities, and objectives of the two enterprises become conflated. Clearly defining and introducing the goals and interests of research into an existing health care setting is, therefore, a challenge for research activity. The nature of the relationship and activity can lead to confusion and misunderstanding.

The results from this study also show that the conflation between research and service provision can operate to create wider public health misconceptions. One concern that a respondent pointed out is that participants' mothers would confuse the research appointments (vaccination days and follow-up) with visits to the routine child welfare clinic. This is an example of where the presence of research could disrupt and cause confusion with vital public health services. This also signals a misunderstanding as to the intent and nature of the research clinics. An inability to distinguish between research activity and routine health care undermines informed consent processes and the participants autonomy; such confusion can then also place healthy infants' well-being at risk (Horng & Grady, 2003). This further emphasizes the importance of designing and establishing a context-relevant education strategy in association with any program of research. Information provided to participants must communicate the objective of the health research and the relationship of the research with the health care system, and crucially distinguish the differences between the two activities. For example, the consent process should present the key aspects of research in comparison with the function of health care. This would also be supported by using appropiate tools, for example clear illustrative posters to display at research clinic visits (Breault & Miceli, 2016; Henderson et al., 2007). Moreover, in respect of medical misconception, if a participant contracts the disease (e.g., malaria) under the belief that the trial vaccine would offer protection, then this may also damage trust in other proven effective vaccines and health services. Should participants reject other proven childhood vaccines after being disappointed by a trial vaccine, this could be very disruptive to established programs of public health. Notably, it was clear that the PMVT study took extensive steps to prevent risky behavior through education and the distribution of bed nets to mothers and children. This also helped reinforce a clear message that there was no guarantee of protective effect from the candidate vaccine. Therefore, the provision of best practice standard of prevention works against the therapeutic misconception, by emphasizing that there is no assurance that the trial intervention will have a protective effect. The results have shown that managing the realities and expectations of the study participants is challenging, especially because the concepts of a trial are technical (randomization, placebo, protectiveness), programs highly resourced, and mothers' expectations tend to be that a PMVT will directly benefit their child. Literature has further suggested that not enough is being done to combat therapeutic misconception and rather complacency allows it to be exploited as a recruitment tool (Lema, 2009). Issues of therapeutic misconception must be explicitly identified and addressed in the research protocol and critically scrutinized by ethics review processes. In the continuing contexts of underresourced health systems, high disease burden, and systemic poverty, ethical debate on the health responsibilities of research teams will repeatedly arise as a topic of discussion. Scientific, medical, local, and global communities will continue to face tough challenges between facilitating necessary health research and addressing the immediate needs of disadvantaged populations and weak health care systems (Benatar & Singer, 2010; Pratt et al., 2013; Shapiro & Benatar, 2005). Underlying the responses of this project was a broad message emphasizing the importance of communication between international, national, and local stakeholders in the planning, implementation, and management of health care provision during the course of a trial. Well-designed, locally inclusive, collaborative partnerships support appropriate and sufficient health care delivery and the operation of vital health research.

Limitations

The main limitation was the timing of the interviews. The PMVT study had just completed the final data collection and participant follow-ups. As a result, many of the vaccination nurses and fieldworkers had dispersed. In addition, the project did not interview the research participants (in this instance, mothers of infants). This decision was taken due to the study focus on the system level and the collaborative partnership dynamic. One disadvantage of this approach was that not including the research participants meant that our project did not fully capture the experience of the local community, which ultimately defines the impact of collaborative research. However, the stakeholder groups that we did meet were able to reflect on the conduct of the PMVT having worked closely with participants and local populations across the lifespan of the study, giving in-depth, information-rich responses with illustrative examples.

Conclusion

This study identified the critical ethical aspects raised by stakeholders on designing and implementing health care delivery in a PMVT. There were three major areas of concern: undue inducement, community disparity, and therapeutic misconception.

The inducement or benefit of health care per se is not problematic where the study risk–benefit ratio is favorable because under these conditions the addition of health care is adding a further health benefit to an already ethically sound and socially valuable study. However, it remains necessary to protect participants' decision-making capacity. Careful planning of the standard of care and implementation need to account for background inequalities and possible sources of community disparity. The challenge is to retain the independence of the research program from local health services, and yet sustain a functioning partnership that continuously informs and communicates with the community. In part, this is achieved by explicitly defining the roles and responsibilities of the research

and health care teams both between the teams and with the participants and their communities. Nonetheless, unplanned emergency health care situations will arise where the PMVT may have to step in and play a wider health care role. The close relationship between the PMVT and health services can create broad therapeutic misconceptions which, if not carefully managed, may disrupt routine care and breach community trust (both in public health vaccine programs and local health care services). The process of devising a medical care plan must account for these ethical concerns and should involve all stakeholders in an active discussion, with built-in mechanisms for communication and case reviews throughout a research programme. Successfully integrating global health research into local health systems can strengthen partner dialogue, create a culture of research in health care, and ultimately promote sustained regional health improvements.

Best Practices

Protecting against *undue inducement*:

1. Employ culturally relevant and context-appropriate tools to actively explain risks and evaluate participants' comprehension.
2. Require a favorable risk–benefit ratio. This is ensured by locally responsive research with minimized risk that has undergone appropriate scientific, ethical, legal, cultural, and political reviews.
3. Establish a shared reporting system with the health care setting to record,evaluate and resolve, clinical and ethical issues.

Protecting against community *disparity*:

1. Engage with the local health care system and come to a joint agreement on the standard of care, nature, coverage, and time frame of supplementary support.
2. Retain the independence of the research program from the health services and sustain a functioning partnership with the community.
3. All unplanned health care provision events should result in a joint case review between the research and hospital setting to identify where gaps or oversights may exist in routine care.
4. Acknowledge and address the effect health care provision may have on study power and methods.

Protecting against broad *therapeutic misconception*:

1. Design and establish a context-relevant education strategy for communities.
2. Study information provided to participants needs to communicate the objective of the health research and the relationship of the research with the health care system, and distinguish the differences between the two activities.
3. Ascertain and implement appropriate standards of prevention against the target disease (e.g. malaria) and related matters of poor health. A sustainable disease prevention plan needs to be agreed (disease management, diagnostics, prevention, and treatment) to meet basic health needs and support local health education. This reaffirms that the trial intervention (e.g., candidate vaccine) per se cannot be relied upon to protect against disease and ill health.

Research Agenda

1. Designing and evaluating effective tools for communicating research risks with participants and their communities.
2. Integrate research programs into local health care settings, and optimize shared system learning.

Educational Implications

1. Undue inducement, community disparity, and therapeutic misconception must be explicitly addressed and evaluated in ethics review processes.

Appendix

Interview Guide: The Role of International Vaccine Studies and the Health Care Development of Resource-Limited Regions

Unique Participant Number:

Three Letter Participant Code:

Expected duration of the interview: 1 hr.

Introduction and Consent Process.

This interview will be asking questions about the conduct of the malaria vaccine trial. The questions will consider the interaction between the international vaccine trial and the local health and research systems, along with health care in the community.

It is important to hear your own views and opinions. There is no right or wrong answers to these questions—just ideas, experiences, and opinions which are all valuable. It is very helpful to hear all sides of an issue—the positives and negatives.

The responses collected from this interview will be anonymous. The information you provide will be evaluated without your name and with no links to personal identification.

The information we learn from this study will show how best to conduct malaria vaccine trials with the health and research systems in which they are carried out.

Please ask me any questions you may have about this interview before we start, and feel free to stop me at any time during the interview if you have any further questions.

Consent to Proceed.

The interview will now start with first a few questions about you and your involvement in the malaria vaccine trial, before moving on to specific topic areas.

A. Respondent Details
   (1) Present position/post:
   (2) Number of years in this post:
   (3) Academic/professional training:

B. Human Capacity
   - Can you please describe your role with the malaria vaccine trial?
   - Linked to that above question, I would like to ask if there have been any professional development or training opportunities arising from your involvement in the malaria vaccine trial.
   - Please give examples from your personal experience.

C. Health Research for Development
   - I would now like to explore your perception of Health Research for Development. Could you please explain how you understand this concept?
   - If possible please give practical examples from the malaria vaccine trial and/or general examples?

D. Capacity Building
   - In your opinion, has the vaccine trial led to capacity building in (a) research infrastructure and (b) local health care?
   - If yes, what is the impact of such changes on these systems?
   - If no capacity building has resulted, what is your opinion on that?

E. Standard of Care
   - In the following questions, I would like to know about the practical considerations and challenges when implementing a Standard of Care across a multicenter malaria vaccine trial.

F. Health Services
   - Has the vaccine trial led to changes in the provision of healthcare services for (a) participants and (b) community?
   - If so, could you describe to me a few of those changes?
   - In your opinion, what is the impact of such changes on the health system in this region?

G. End of Trial
   - What happens now that the trial is ending?
   - How has this been organized?
   - What is your opinion of how the end of the trial has been organized?

H. Future Improvements
   - Given the views you have already provided, in your opinion, if you hosted another vaccine or similar trial what would you do differently:

Nudges:
   a. capacity building
   b. provision of health services
   c. Standard of care

I. Is there anything else that you would like to add?

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