GOOD COLLABORATIVE PRACTICE - PERSPECTIVES FROM A PAEDIATRIC MALARIA VACCINE TRIAL IN GHANA AND TANZANIA

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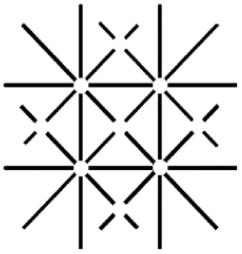

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Inauguraldissertation zur Erlangung der Würde eines Dr.sc.med. vorgelegt der Medizinischen Fakultät der Universität Basel

2013 - 2018

Dedicated to my Grandparents

Science knows no country, because knowledge belongs to humanity, and is the torch which illuminates the world.

Louis Pasteur, (1822 – 1895) French biologist, microbiologist and chemist renowned for his discoveries of the principles of vaccination, microbial fermentation and pasteurisation.

DECLARATION

This dissertation is the result of my own work and includes nothing, which is the outcome of work done in collaboration except where specifically indicated in the text. It has not been previously submitted, in part or whole, to any university of institution for any degree, diploma, or other qualification.

Signed:_____

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SUMMARY

The fostering of international partnerships and collaborative health research programmes has been identified as vital for reducing disease burdens, morbidity and mortality in low and middle income countries. This ethics project investigates what constitutes good collaborative practice in international health research partnerships.

Chapter 1 presents the project background and objectives. In brief the project sets out to understand the roles and responsibilities of collaborative research partners operating in low resource settings from the perspectives of stakeholders in Ghana and Tanzania. The methodology is based on the inclusion of 52 semi-structured, interviews with major stakeholders in an international multicentre partnership between GlaxoSmithKline (GSK, Vaccine Developer) and the global health non-profit product developer PATH and its Malaria Vaccine Initiative program (PATH/MVI, Funder-Development Partner), (RTS, S) (NCT00866619). This included teams from four clinical research centres (two centres in Ghana and two in Tanzania) and various collaborating partners. The interview transcripts were evaluated with thematic coding.

Chapter 2 presents a review of ethics guidance, industry guidelines and legislation for international health research partnerships. The main findings show that good collaborative practice guidance needs to be established in international and national health research governance. At a minimum this includes: i) shared research agenda setting with local leadership ii) capacity assessments with co-ordinated development action plans, and iii) construction of a memorandum of understanding (MoU).

Chapter 3 presents empirical data on how to construct collaborative health research for local development. The main finding shows the importance of local research leadership. A locally-led project ensures that the project agenda and activities align with local research and health priorities; capacity strengthening opportunities and; promote decentralized health system decision-making.

Chapter 4 presents empirical data on the ethics of healthcare delivery in the course of research. The main findings show integration of international research into local health care settings needs to take account of background inequalities and possible sources of community disparity. Importantly research must retain independence of the research

program from the health services and yet sustain a functioning partnership that continuously informs and communicates with the local population and healthcare providers.

Chapter 5 presents empirical data on end of trial obligations for international partnerships. The main findings showed that the concept of continuity of care should be the guiding principle of any service handover from research teams to local health authorities and; an actionable post-trial treatment access pathway needs to be established with a wide diversity of stakeholders.

Chapter 6 presents an overview of the project and finds that fulfilling the obligations of good collaborative practice requires that research is developed in a manner that strengthens national research capacities integrates with regional health care settings and fosters local leadership.

Chapter 7 presents the ethics discussion and goes on to propose a new research ethics framework based on the principles of public health ethics entitled, The Global Population Approach. The ethical foundation of the framework guides partnerships to form a social contract that equitably distributes risks and promotes common interests.

In conclusion the past 30 years have seen rapid changes in the format and organisation of international health research partnerships. This has led to significant improvements in global health. However the gains have been uneven and major health inequalities persist within and among countries; disproportionately affecting populations of low resource settings. Limited attention has been given to how partners of international collaborative research function and whether these constructs serve local population health. Crucially there is a need to recognise research as a tool of public health. International collaborative partnerships can support this goal by developing local research capacity (leadership, skills and infrastructure) that delivers on context-sensitive health solutions and; protects and promotes local population health, both locally and globally. Equally, research governance and regulatory frameworks need to endorse provisions of good collaborative practice that support and co-ordinate a network of robust research systems worldwide.

CONTRIBUTIONS

This project is part of the Global Public Health Ethics programme at the University of Basel, funded by the Swiss Tropical and Public Health Institute and the Institute for Biomedical Ethics; and constructed in partnership with the Ifakara Health Institute, Tanzania and INDEPTH Network, Ghana

The thesis body is a compendium of journal articles (Chapters 2 – 5) that have been drafted for publishing in academic peer review journals. As first Author on each of these papers I have initiated and led the group on project planning, literature reviews, resource and data collection, transcription, data analysis, defining core thematic concepts, manuscript drafting and final submissions. This work is my own. David Shaw, as first supervisor, consolidated the data analysis review, supported the critical thinking in the development of manuscripts and assisted with the editing of drafts. Given the interdisciplinary nature of the project the expertise of other authors has been vital for the set up of the study and to expand on certain topic areas in greater depth. The following Authors have given time, advised on project protocol, data collection and, provided critical thought and constructive comment in respect of draft manuscripts. In addition each author reviewed and agreed on the final drafts for submitted papers where they have contributed. A listing of the drafted manuscripts and the respective contributors can be found directly following the thesis table of contents.

Chapters 1 and 6 are my own work where I am sole author. David Shaw has continued to offer supervisory support on this portion of writing.

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Bernice Elger, Professor and Head of the IBMB. She has taught and written widely in bioethics and health law. She is also an Associate Professor at the Center for Legal Medicine, University of Geneva.

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The PhD years have been a journey across ideas, continents and cultures. In conclusion I find myself agreeing with the famous author and poet Maya Angelou, "We are more alike my friends than we are unlike". Moving from the UK to Kenya, Switzerland to Ghana and Tanzania, from start to finish, this project, would not have been possible without the support of many people.

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A warm thank you to the Merker Family, friends for many generations, the friendship continues whole heartedly today. The whole family has hosted me for many enjoyable get-away weekends in Baden. A home away from home. In Basel, Meret Merker has helped me with all the important things (house-hunting, Rheinschwimmen and Morgenstreich), kept me smiling and shared the occasional glass of wine.

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x

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Table of Contents

LIST OF PUBLICATIONS

1. Ward, C.L., Shaw, D., Sprumont, D., Sankoh, O., Tanner, M., Elger, B, Good Collaborative Practice: Capacity Building Governance of International Health Research Partnerships, Globalization and Health, 2018, 14:1; doi.10.1186/s12992-017-0319-4 © Author(s).

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2. Ward, C.L., Shaw, D., Anane-Sarpong, E., Sankoh, O., Tanner, M., Elger, B, Defining Health Research for Development: The Perspective of Stakeholders from an International Health Research Partnership in Ghana and Tanzania. Developing World Bioethics. 2018 Dec; 18(4):331-40

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3. Ward, C.L., Shaw, D., Anane-Sarpong, E., Sankoh, O., Tanner, M., Elger, B, The Ethics Of Health Care Delivery In a Paediatric Malaria Vaccine Trial: The Perspective Of Stakeholders From Ghana And Tanzania. Journal of Empirical Research on Human Research Ethics, 2018, 13.1: 26-41.

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4. Ward, C.L., Shaw, D., Anane-Sarpong, E., Sankoh, O., Tanner, M., Elger, B, The Ethics Of End Of Trial Obligations In A Paediatric Malaria Vaccine Trial: The Perspectives Of Stakeholders From Ghana And Tanzania. Journal of Empirical Research on Human Research Ethics, 2018, 13.3: 258-269.

   ……..……Chapter 5

LIST OF TABLES

Chapter 1

Chapter 3

Chapter 4

LIST OF FIGURES

Chapter 3

Chapter 4

Chapter 5

Chapter 6

Chapter 7

LIST OF ACRONYMS AND ABBREVIATIONS

BRTC	Bagamoyo Research and Training Centre
CCCGH	Canadian Coalition for Global Health
CDC	Centre for Disease Control and Prevention
CIOMS	Council for International Organizations of Medical Sciences
COHRED	Council on Health Research for Development
COSTECH	Commission for Science and Technology
CRO	Clinical Research Officer
CTPC	Clinical Trials Partnership Committee
CWC	Child Welfare Clinic
DoH	Declaration of Helsinki
DHO	District Health Officer
DNDi	Drugs for Neglected Diseases initiative
E6 (R1)	Good Clinical Practice Guidance Document of International Conference on Harmonization
E6 (R2)	Integrated Addendum to Good Clinical Practice (GCP) Document of International Conference on Harmonization
EDCTP	European & Developing Countries Clinical Trials Partnership
EKNZ	Ethikkommission Nordwest- und Zentralschweiz
EU	European Union
FDA	Food and Drug Authority
GAVI	Global Alliance Vaccine Initiative

GCP	Good Clinical Practice
GEP	Good Epidemiological Practice
GHS	Ghana Health Service
GLP	Good Laboratory Practice
GMP	Good Medical Practice
GSK	GlaxoSmithKline (vaccine developer)
HCV	hepatitis C virus
HDSS	Health and Demographic Surveillance Systems
HIC	High-Income Country
HIV	Human Immunodeficiency Virus
IAVI	International AIDS Vaccine Initiative
IBMB	Institute for Biomedical Ethics
ICESCR	International Covenant on Economic, Social and Cultural Rights
ICH	International Conference on Harmonization
IHI	Ifakara Health Institute
INDEPTH Network	Network of Health and Demographic Surveillance Systems
IRB	Institutional Review Board
JTEG	Joint Technical Expert Group
KCCR	Kumasi Centre for Collaborative Research
KEMRI	Kenya Medical Research Institute
KHRC	Kintampo Health Research Centre
KNUST	Kwame Nkrumah University of Science and Technology

KFPE	Commission for Research Partnerships with Developing Countries
LMIC	Low and Middle Income Countries
MCTA	Malaria Clinical Trial Alliance
MDG	United Nations Millennium Development Goals
MOH	Ministry of Health
MOU	Memorandum of Understanding
MVI	Malaria Vaccine Initiative
NIMR	National Institute for Medical Research
PATH	A non-profit organization funding and developing global health innovation
PDP	Product Development Partnerships
PI	Principal Investigator
PMVT	Paediatric Malaria Vaccine Trial
REC SOPs	Research Ethics Committees Standard Operating Procedures
RTS, S	The scientific name given to this malaria vaccine candidate
Swiss TPH	The Swiss Tropical and Public Health Institute
TB	Tuberculosis
TDR	Special Programme for Research and Training in Tropical Disease
TRREE	Training and Resources in Research Ethics Evaluation
UNDHR	Universal Declaration of Human Rights
UN SDGs	United Nations Sustainable Development Goals
WHO	World Health Organisation

1 INTRODUCTION

1.1 Background

1.1.1 Collaborative Research and Global Health

The 2016 WHO World Health Statistics Report - Monitoring Health for the Sustainable Development Goals – presents data showing that significant gains in life expectancy have been made globally since 2000, but major inequalities persist within and among countries.[1] Dr Margaret Chan, Director-General of WHO commented that "The world has made great strides in reducing needless suffering and premature deaths that arise from preventable and treatable diseases but the gains have been uneven."[1] In this context of global health disparities, the fostering of international partnerships and collaborative health research programmes have been identified as critical for tackling health inequalities and health system problems worldwide.[2] In particular, collaborative research in global health has been identified as essential to combatting debilitating and fatal disease in low and middle income countries (LMIC).[2-6] The[7, 8] conduct of health research is vital worldwide for reducing disease burdens by helping evaluate epidemiology and the safety, efficacy and effectiveness of new health interventions, therapies and vaccines.[9] To achieve this goal, global health research collaborations must co-ordinate a complex array of multinational and multidisciplinary teams to run intervention studies in low resource settings; regions of endemic disease, poverty, challenging socio-political- economic structures and limited healthcare access.[3, 9-12]

International co-operation in health research has mobilised the exchange of resources, research methodology, clinical skills and science to find health solutions for pressing needs worldwide; and importantly against diseases of the poor. For example, malaria is just one of many diseases that disproportionately affect those living in poverty. To put it in context, there were an estimated 214 million cases of malaria worldwide in 2015, and an estimated 438 000 deaths. Approximately 90% of all malaria deaths occur in Africa and the majority in infants. In 2015, an estimated 292 000 African children died before their fifth birthday due to malaria.[13] Moreover, because malaria causes so much illness and death, the disease places immense pressure on individual and national resources. Many countries affected with malaria are already among the poorer nations and as such, the disease maintains a vicious cycle of disease and poverty.[14] Although existing interventions have helped to combat malaria in the last 15 years (global mortality rates fell by 48% between 2000 – 2015), the rate of reduction has started to slow in the past three years.[15] As a result collaborative research efforts are still seeking to develop a well-tolerated and effective vaccine with an acceptable safety profile. [16]

The past 30 years has seen a dramatic rise in the scale and scope of collaborative global health research. In some respects this echoes the trends of globalisation generally across all industry, but it also reflects advances in scientific technique, international commitments to health (Universal Declaration of Human Rights,[7] UN Millennium Development Goals[8] and Sustainable Development Goals[17]) and novel funding initiatives such as the Bill and Melinda Gates Foundation and Wellcome Trust.[3, 18] More widely, it is perhaps recognition of the global vulnerabilities that accompany a more integrated world and highly mobile societies of travel, trade and migration (economic and, natural and human-made disasters). The past 30 years have seen growing support for collaborative health research and the potential it has to combat global health disparities.[3, 6, 9, 19-22]

The achievements of collaborative research have however been constrained by limitations in international partnerships. Although collaborative research has generated new knowledge and advanced science, concerns have been raised against the effectiveness of partnerships in improving conditions of health and local health service systems in low resource settings.[22, 23] Questions have been raised as to what extent collaborative health research programmes have contributed to developing local conditions of good health.[24, 25] Moreover, particular criticisms have been made of the power imbalance in high- and low-income countries partnerships.[26, 27] Notably, the research agenda and partnership structure tends to be determined by high-income country (HIC) institutions. [21, 28] Moreover, the flow of funds in collaborative research tends to be controlled by, and favourable to, primarily the high-income international institutions (rather than local development where research takes place), and dissemination of results is directed at high impact journals and international conferences rather than local knowledge translation and improving conditions of community health.[2, 24, 29-32] Such criticisms have led to a growing body of debate over what constitutes an equitable partnership model, and how to structure collaborative governance to deliver on research which is inclusive of all stakeholders from design through to the dissemination and which supports the translation of results in health innovation. Ethically, this raises a question; to what extent do international collaborative research partnerships have a responsibility to improve conditions of health in low resource settings?[3, 18, 31, 33-40]

The overall goal of this project is to explore what constitutes good collaborative practice. First with a review of research governance and then followed by an empirical method. The empirical part is based on interviews with respondents in Ghana and Tanzania and wider international partners involved with conducting a longstanding multicentre collaborative research trial:

paediatric malaria vaccine trial (PMVT) of vaccine-candidate, RTS,S/AS01 (RTS, S) (NCT00866619), developed by GlaxoSmithKline (GSK, Vaccine Developer) and the global health non-profit organisation PATH and its Malaria Vaccine Initiative program (PATH/MVI, Funder-Development Partner).[15] Further detail of the trial can be found in the thesis Methodology (1.2) and Chapters 2 – 5. The study sets out to evaluate the ethics and practical responsibilities of collaborative research from the perspectives of all stakeholders in the international partnership operating across research centres in Ghana and Tanzania.

The objective of the project is to present the different stakeholder perspectives, opinions and constraints (financial, regulatory, political, social) that shape the collaborative dynamic and ultimately determine, the successes (and challenges) of partnership in global health research. The findings from this study explore how ultimately these different interests are confronted and accounted for in the context of a research program; and what factors in the collaborative determines the decision-making outcomes, research activity, and conduct of international health research in local health care settings.

1.1.2 Historical Context

Linking the work of international health research partnerships to reducing disparities in global health is not a new concept. Between individuals and at the institutional level the need for collaboration has been appreciated amongst scientists as early as the 19th Century. Louis Pasteur, celebrated not least for his discovery of the modern vaccine and saving millions of lives, is also famous for the quote that "science knows no country…" The statement shows an appreciation for our common humanity and the reliance of our health on mutual solidarity. Various research groups have also recognised the importance of partnership, scientific diplomacy and sharing in expertise to address pressing health issues worldwide. The Swiss Tropical and Public Health Institute (Swiss TPH) is a good example. The founder of the institute, Rudolf Geigy first began working in Tanzania in 1944 and over a number of different stages this work led to the development of Ifakara Health Institute in Tanzania. A site that at initiation in 1950s relied on the Swiss TPH (formerly Swiss Tropical Institute) for scientific and administrative direction, and by 1990s became, and remains, an independent and important research centre for Africa.[9, 41] Other initiatives - the Special Programme for Research and Training in Tropical Disease (TDR), along with The European & Developing Countries Clinical Trials Partnership (EDCTP) - have also been established to actively campaign and to develop strategies to overcome health research capacity barriers in low resource settings, to support collaborative research and to develop novel health solutions.[42-44] A variety of different

international collaborative partnerships have been formed with the intention of establishing research to combat disease and improve health in low- and middle-income countries (LMICs). [2, 12, 22, 45]

1.1.3 Policy

In policy, it is broadly accepted that collaborative research is necessary for advancing global equity and health in low and middle income countries. It was first formally recognised as a policy in 1990, in the Commission on Health Research for Development report entitled Health Research: Essential Link to Equity in Development.[6] Following this report, international partnership was formally recognised as a central driver to overcoming global health challenges.[35, 46, 47] This led to an increase in collaborative research conducted in low resource settings, which accounted for less than 10% of global research before 2000. Despite improvement and some achievements, disequilibrium still persists and policy is required to co-ordinate efforts and investments. [48-50] In 2015, a reported $3,041m was invested in neglected disease R&D (three quarters externally funded).[51] However, controlling for funds directed to Ebola research in 2014/15, this marked the third consecutive year of declining funding for neglected diseases, since 2009.[51] Moreover, even with an increased number of international collaborations and investments in global health research, national research systems and health care infrastructure of low resource settings remains limited.[22] Yet it is in these poorest regions where research-led solutions could bring the greatest impact to reduce high rates of morbidity and early mortality.[52] This challenge has been formally recognised in the WHO World Health Report of 2013, Research for Universal Health Coverage, which presents evidence-based arguments demonstrating that gaps in health research capacity in low resource countries have created a barrier between gains in scientific research globally and gains in population health locally. There are good examples of capacity strengthening activities between some researchers and institutions. However, it remains that there is still a lack of sufficient research capacity in low and middle income countries for independent research that generates local health evidence, strengthens health systems and informs policy.[22, 53, 54] In addition, where health research systems have been established in local settings they have tended to continue to rely on external support, and struggle with sustainability challenges. [21, 54, 55] This is particularly a concern given significant political and global uncertainty in recent years. As such, the gaps in research capacity strengthening within collaborative partnerships have been widely recognized as a missed opportunity for development in low and middle-income countries.[21] The World Health Report of 2013 advocates that in combination with collaborative research there is a need

to promote locally-led health research and capacity strengthening. This is deemed critical for overcoming global health challenges:

"all nations should be producers of research as well as consumers… and to make use of limited resources, systems are needed to develop national research agendas, to raise funds, to strengthen research capacity, and to make effective use of research findings."[48]

Moreover, in 2015, the UN Sustainable Development Goals (with 193 country signatories) provided further policy commitment to combine capacity building with international co-operation to develop systems globally and reduce poverty.[17]

Goal 3 on Health and Well Being states:

"Strengthen the capacity of all countries, in particular developing countries, for early warning, risk reduction and management of national and global health risks."[17]

Goal 17 on Partnership states:

"Enhance the global partnership for sustainable development, complemented by multi-stakeholder partnerships that mobilize and share knowledge, expertise, technology and financial resources, to support the achievement of the sustainable development goals in all countries, in particular developing countries."[17]

These new policy commitments codify and reflect some consensus on the need for international co-operation to also facilitate skills and structural development in low resource settings, along with advancing new gains in science. However, the implementation strategies of capacity strengthening are not so clear. There is an unresolved tension within collaborative health research programs as to whether there are positive obligations towards system capacity strengthening and creating health care access, beyond the "core" activity of generating new scientific knowledge.

1.1.4 Ethics

Ethical debate over what are the responsibilities of international health research in low resource settings towards participants and communities has given rise to fierce debate over the past 30 years.[29, 33-37, 56] The basis of these debates have centred around concerns that local research participants, their communities and the healthcare resources are exploited in the course of health research. In the main, the exploitation-debate has centred on whether there can ever be a favourable risk-benefit ratio in low resource settings to include vulnerable populations in

programmes of health research. The concept of a favourable risk-benefit ratio is a common guiding principle set out by research guidance in the Nuremberg Code (Point 6) [57] and Declaration of Helsinki (Points 16 -18).[58] Ethical debate has gone on to explore, challenge and argue how a favourable risk-benefit ratio is achieved when research is conducted with populations faced with a background of inequalities and limited healthcare access in low resource settings. The concern of exploitation is relevant to both sides of the risk-benefit ratio. It is argued that health research has the possibility to exploit vulnerable populations because the distributions of risk may be unfair. The second argument states health research has the potential to exploit vulnerable populations because the distributions of benefits may be unfair.[59, 60] Notably the Declaration of Helsinki (DoH), provides special protections for vulnerable populations (this includes populations living in poverty with limited access to health care services).[61] As it states in first published in 1964 with the latest (9th update) revision in 2013:

"Medical research with a vulnerable group is only justified if the research is responsive to the health needs or priorities of this group and the research cannot be carried out in a non-vulnerable group. In addition, this group should stand to benefit from the knowledge, practices or interventions that result from the research." [58]

In general, there is an acceptance of the above provisions of the DoH. However, ethical debate has scrutinised what it means to be "responsive to health needs or priorities of a group" and "stand to benefit". Underlying these debates is a tension between facilitating scientific innovation and protecting populations against exploitation.

In relation to the first concern of excessive risk, the approach to minimise research risk in low resource settings has on the whole been addressed under the doctrine of "responsiveness."[58, 62] A concept articulated by the DoH and The Council for International Organizations of Medical Sciences (CIOMS).[58, 62] The principle is that the ethical acceptability of a research programme is determined by the extent to which the research is relevant and, addressing the health needs and research priorities of the local community. Defining responsiveness has led to much discussion.[63-66] On a narrow reading the concept is a technical epidemiological enquiry into whether the target of research is a local community health need. However other commentators have campaigned for a wider concept of responsiveness that addresses a much broad array of factors that are needed to improve the conditions of health in a specific community setting and, not the science alone.[65] Such an approach demands that adequate system capacity strengthening accompanies health research innovation to facilitate local

community access to scientific advancement. This broad reading has most recently been reflected in the latest update of the CIOMS guideline.[62]

The grounds for expanding the responsiveness requirement are premised on fact that addressing local health needs should be a wider programme of inquiry undertaking research with local involvement, understanding of the local context and requiring integrating with local systems.[67] Commentators argue that the activity of research should expand and strengthen the capacity of health-related research and social structures in order to respond to the urgent health needs of a host community. [67, 68] Accompanying the advancement of science with the strengthening of research capacity in national systems provides the infrastructural conditions needed to effectively integrate care with specific settings. The argument being that both the capacity to respond (infrastructure), as well as the response (health innovation), are needed to effectively attend to local health needs.

Undertaking research for a health priority in a local setting, without adequate infrastructure or attention to the local context can compromise the effectiveness of the intervention. Ethically, this raises the question as to whether the research is in fact responsive if the results have no relevance for the local populations. As an analogy, it is similar to giving a community a fire engine in a region where there is no access to water. You may have addressed a priority, but you have not delivered an appropriate response in the given circumstances. In a health context, the most recent example of this tension can be found in the example of Sofosbuvir treatment for chronic hepatitis C virus (HCV).[69] Introduction of this new and highly effective treatment into a low resource settings (where 80% of the disease burden rests) requires renewed efforts and attention to the specific social and healthcare settings for a health impact to be possible.[70] The original care regime for the drug cannot integrate with weak healthcare settings and yet that is where it is needed most. Therefore, it is argued that only with a broader assessment of responsiveness can health innovation lead to improved local conditions of health.[67, 71] A programme of research has to give due attention to the education, prevention, screening, treatment, system and policy implications in any particular setting for a health intervention to be genuinely responsive and accessible to community health needs. An aspect of the project explores what are the capacity strengthening responsibilities of collaborative research to truly support responsive health research.

In respect of benefits, health research also has the potential to exploit vulnerable populations because the benefits of research can be unfairly distributed. Even where there are short term healthcare benefits for participants in a programme of research, it remains that these benefits

do not necessarily equate with the same gains that accrue to the sponsor-investigators of high income countries or their future patients.[56, 72] The frame of this debate has tended to be narrowed to an evaluation of what levels of benefits are permissible to include participants in a programme of research. In contrast to a broader question of what benefits are necessary to improve local conditions of health (sustain long term health system developments or provide access to healthcare).[73] For many years ethical acceptability of research has focused on three mains aspects, the adequacy of informed consent procedures, standard of care debate and, defining the reasonable availability of novel interventions proven effective.[74] Limited discussion has focused on what benefit participants or communities have taken from being involved with research, or whether the benefits were fair. This led to the proposal of a Fair Benefit Framework, defining what is owed to participants and communities involved with international health research.[34] The framework offed an alternative to the "reasonable availability" requirement (proven effective interventions should be made reasonably available to participants and communities involved in research). This reflected the fact that "reasonable availability" provision did not adequately protect against exploitation and often failed to award any benefit to participants and local communities.[75] This debate re-opened an examination of what are the responsibilities of international partnerships operating in low resources settings. However still commentators contend that the level of debate, including the Fair Benefit Framework, has defined the conditions for when international health research is safe and non-exploitative but not justified why research can be conducted with vulnerable populations in the first place. [74, 76, 77] This in turn has led to two problems. First, there is no consensus surrounding these constructs, evidenced both by the number of different ethics guidance documents surrounding health research activity (along with further disagreement over when a criteria has been fulfilled.) Second, the areas of research ethics that have been traditionally debated are important and do limit aspects of exploitation however, they fail to commit health research to better population health, global health justice and the reduction of health inequalities.[37, 40, 74, 78, 79] Which arguably (and ethically) should be the justification of collaborative partnerships and conducting global health research.[80] Other commentators have set out alternative frameworks to foster a better relationship between health research, justice and health equity.[36, 81] However it remains that practical implementation and uptake of a broader definition of requiring "groups stand to benefit" has received limited endorsement across guidance documents, grant applications, researcher dialogue and ethic committee review; limiting the impact of advancing academic debate.

For collaborative research to have a positive impact on health in low resource settings commentators have reasoned that beyond conducting the research to generate generalizable knowledge collaborative research must create access to products and actively strengthen local research capacity in the health care setting where studies take place.[35, 45, 82] In particular, skills and expertise of a collaborative partnership create a platform for mentorship and mutual learning between partners. Where successful, this can lead to the generation of centres of research excellence and a worldwide network of viable research centres. [9] Increasing locally viable and globally relevant health research capability is important for protecting against emerging diseases and supporting the development of further new interventions. Furthermore, integrating health research into a local health care system supports self-sustaining and resilient systems of local healthcare, a necessary condition for improved population health.

1.1.5 Research Governance

The advancing globalisation of health research has also fuelled efforts to establish international standards (See Chapter 2 for more detail). For example the industry guideline - International Conference on Harmonization Technical Requirements for Registration of Pharmaceutical for Human Use (ICH) Good Clinical Practice (ICH-GCP) - sets procedural requirements for the safe collection of health research and data integrity.[83] There is also guidance established around core bioethical principles, such as the Nuremberg Code, the Declaration of Helsinki and the guidelines of the Council for International Organizations of Medical Sciences (CIOMS).[57, 58, 62] In addition there is a plethora of national and institutional research ethic guidelines, and laws, that govern the conduct of health research.

In respect of guidance on collaborative practice, the latest CIOMS guideline sets out provisions (guideline 8) requiring the construction of collaborative partnership with capacity building and locally led research in order to deliver on the social value requirement of health research in low resource settings.[62] Even though the implementation and legal enforcement of CIOMS is limited, this guideline is internationally recognised and has begun to set a precedent for programmes of collaborative research and their responsibilities when operating in low resource settings. A full commentary is set out in chapter 2. Similarly, at national level countries tend to have some legislation which regulates and governs research activity in that specific country. This will differ between country jurisdictions and legal system structures. For example, in Ghana the Ministry of Health in Ghana takes an active role in health research oversight but without regulating a country-wide ethics review system. The principal Ministry of Health body concerned with human subject research is the Health Research Unit of the Ghana Health

Service, and an institutional review board (IRB) within the Ghana Health Service is responsible for the ethical review of research protocols as well as for monitoring ongoing research within the Ministry of Health. In addition, there are five other ethical review boards in Ghana linked to individual health research institutions. Consistency amongst these ethics review boards is achieved through shared standard operating procedures given to IRB and commitment to international ethics standards, although there are no official national ethics guidelines for human subject research. Moreover, the Clinical Trials Department of Food and Drug Authority (FDA), Ghana is responsible for authorisation and monitoring of clinical trials as required by the Public Health Act of Ghana.[84]

In Tanzania there is a more centralised approach governing research activity. There is one comprehensive national framework for promoting ethical human subjects research, including widely distributed national ethical guidelines (although not legally enforceable).[85] Moreover, international research protocols are reviewed by two separate government offices: the National Institute for Medical Research (NIMR), and the Commission for Science and Technology (COSTECH). In addition, the Tanzania Food, Drugs and Cosmetics (Clinical Trials Control) Regulations, 2013, provides for the regulation and control of clinical trials in Tanzania.[86] An evaluation of national legislation needs to be understood from the outset of a research programme, with an appreciation of how in-country laws and oversight may govern collaborative research. This is discussed in greater depth in Chapter 2. In some settings, legislation has started to demand greater obligations of collaborative research in terms of what programmes bring to a country, how they integrate and how they develop country healthcare settings and local systems of research. Mapping the governance requirements between partners is an important step of collaboration.

Looking across ethics guidance, policy and legislation, there is growing recognition that globalisation and multinational collaborations in health research bring both new opportunities and new responsibilities. Individual countries are actively building up national systems of ethical governance which go beyond just ensuring guidelines and regulations are implemented and followed. Governance provides a framework to ensure “research practice meets the requirements of scientific rigour and equally importantly respect for the rule of law, transparency, scientific and ethical accountability and freedom from corruption.”[87] This is an important point because at the root of the limitations that have faced collaborative research are criticisms that the constructs continue to endorse unjust research disparities and power imbalances between partner institutions depending on whether they originate from high income

countries or low middle income countries.[88, 89] Essentially collaborative research has been criticised for restricting the role of partners in low resource settings to data collectors without involvement in research design and strengthening research skills in local systems of health.[2, 28, 32, 54, 88] The criticisms made against the structure and activity of collaborative research, is that fundamental research functions are not shared equally amongst partners, often excluding low-resource setting partners from various responsibilities and opportunities: management of research budgets, protocol design, methodological decision making, data ownership and analysis, named grant holders, publication, promotion, fair remuneration or access to proven intervention which often has tended to remain with the high income institutions.[24, 26, 53, 90] This is a problem because then these research skills and infrastructures never build up in local health care systems where they are needed, nor ensure that the local research teams are self-sufficient and have adequate capacity to undertake health studies in the future.[27, 29] Clear and robust governance of partnerships is required to defend against destabilising factors in collaborative research.

Giving consideration to how members of a research partnership relate and interact brings attention to the fact that there is a distinction to be made between "well managed and ethically sound collaborations."[3] Even the word "partnership" has been criticised as a smoke screen, that does not account for the fairness and equality of a collaborative research project.[91] In response, some independent organisations have set out to develop guidance tools to incentivise and monitor ethically responsible collaborative partnerships in low resource settings: Access to Medicine Index; International Ethical Guidelines for Health-related Research Involving Humans;[62] Principles for Global Health Research; [92] A Guide for Transboundary Research Partnerships 11 Principles; [93] Where there is no lawyer: Guidance for Fairer contract negotiation in collaborative research partnerships. [94]

Academic literature has started to identify the problems associated with unequitable health research models and the negative impact this has on the potential of collaborative research, global health justice and reducing inequalities.[3] In response a number of policy tools have been established to try and align research initiatives with population health needs in low resource settings better. However, what appears missing from the dialogue is the experience and perspectives of collaborations themselves. It is not clear what are the barriers and enablers of fairer research in collaborations, or what hiders or helps effective communication, co-operation and co-ordination within partnerships and amongst various stakeholders. The dynamic of the collaborative has not been captured in previous work, and as a result there is a

lack of clarity over why collaborative research projects are not meeting their full potential to improve global health. Policy and guidelines appear to have provided the perfect recipe for delivering fair, equitable research that can reduce global health disparities. Yet, debate continues on the ethical acceptability of research in low resource settings and large disparities continue to exist globally between national healthcare settings, systems of research, access to healthcare and conditions of good health.

1.1.6 Study Objectives

The objective of this project entitled, Good Collaborative Practice – Perspectives from a Malaria Vaccine Trial in Ghana and Tanzania, is to identify and describe the opportunities and challenges of international health research partnerships operating in low resource settings. In particular the qualitative interviews presented the perspective of stakeholders involved with a multicentre collaborative research project (GSK PATH/MVI paediatric malaria vaccine RTS, S trial) operating in Ghana and Tanzania. Evaluation of the research governance, academic literature and thematic interview analysis (using qualitative data analysis software) informed the project findings and conclusions on the role and responsibilities of international partnerships operating in low resource settings. The research questions were as follows:

Literature and governance review:-

i. To critically analyse the research ethics governance landscape defining the role and responsibilities of collaborative research partnerships.

ii. To identify the strengths, weakness and gaps of current ethics guidance and legislation to endorse equitable research partnerships and capacity strengthening in international health research.

An empirical study from the perspectives of stakeholders involved with a collaborative research malaria vaccine trial in Ghana and Tanzania:-

iii. To define and evaluate the ethical challenges of designing and implementing collaborative health research for development in low resource settings.

iv. To assess the practical challenges and ethical consideration of an international research partnership integrated with a local healthcare system in low resource settings.

v. To establish what are the roles and responsibilities of collaborative research partnerships towards local healthcare and research settings at the end of trial.

1.2 Methodology

This project is part of the Global Public Health Ethics programme at the University of Basel, funded by the Swiss Tropical and Public Health Institute and the Institute for Biomedical Ethics; and in partnership with the Ifakara Health Institute, Tanzania and INDEPTH Network, Ghana

Full methods of the qualitative research project can be found in Chapters 3 – 5. This section on methodology has been added to give some further context about the set-up of the project. This section has two parts. Section one explains how the design of the study was constructed. Section two provides contextual background to the paediatric malaria vaccine trial (PMVT), the collaborative research programme on which this ethics study is based.

1.2.1 Study Design

1.2.1.1 Designing the Research Question

The research questions, protocol design, and methods of this project were developed through an iterative and collaborative process between the partner institutions based in Switzerland, Ghana and Tanzania, along with local contacts at each of the research centres and the support of KEMRI/CDC Centre for Global Health Research, Kenya. As a result, the research questions of this project have been informed and guided with the support of various experts working in the field of global health research, and with particular expertise in Ghana and Tanzania.

My contribution to the research questions has developed from both my professional training in research ethics and law along with practical field experience. In part the project proposal developed from preliminary investigations undertaken in my Masters Thesis, entitled: Vaccine Ethics: Upholding Social Value. In addition in preparation of designing the project there was a further review and evaluation of current literature and research governance (legislation, ethics guidance and policy). Most importantly, ahead of writing the research proposal, from June – August 2013, I spent eight weeks at the KEMRI/CDC Centre for Global Health Research, Kisumu, Kenya. This opportunity was kindly organised with the assistance of Research Officer Dr. Steve Wandiga. Spending time with the research centre provided me with significant insight into the practical considerations of planning and implementing public health surveillance systems and intervention (drug and vaccine trials) research in rural western Kenya. I had the privilege of being able to accompany a great variety of different research teams and their project activities. Key areas of work were in, malaria, tuberculosis (TB), human immunodeficiency virus (HIV), schistosomiasis, Health and Demographic Surveillance System and polio immunization programs. The work introduced me to a variety of different laboratory activities

at the research centre in Kisumu and, field experience around Lake Victoria, in rural villages, hospitals, local schools and informal urban settlements. This experience showed me the importance, (and challenges) of, community engagement, international partnership and conducting research through a multi-sectorial approach that involved local participants, communities, healthcare systems and governments as stakeholders. The eight weeks learning with the research teams in Kisumu Kenya greatly helped in the final construction of the research protocol and questions. This experience and the observations that I made informed my views and also allowed me to forge close links with experts from Kenya. In particular at The Centre for Global Health Research, Kisumu, Kenya. Kisumu town is the capital of Nyanza Province, Kenya, lying on the north eastern shore of Lake Victoria.

Importantly, each country and research setting has context-specific features with, different requirements and methods. For example, all the research groups that I have met across Kenya, Ghana and Tanzania have established forms of community engagement programmes, but the outreach methods, organisation and format of communication with communities is specific to each context. Therefore in designing the research questions and the protocols, it was very important to work with the teams and settings in Ghana and Tanzania to understand the set-up of each research centre and obtain specific advice and guidance on the study design. Moreover, the ethics review committee processes also vary in each country, and at each research centre, understanding of the local governance in this respect was crucial to the design and planning of the project.

As the research questions started to take shape around the ethics of international health research partnerships, initial contact with research teams working on collaborative research projects was established with the assistance of Professor Tanner of Swiss Tropical and Public Health Institute and research colleague Evelyn Anane-Sarpong, both who have extensive experience working in Tanzania and Ghana respectively. This also led to the project partnership with the Ifakara Health Institute, Tanzania and INDPETH Network, Ghana. Both organisation have advised extensively on study design, methods, planning and study implementation.

In January 2014, my research colleague, Evelyn Anane-Sarpong and I made an introductory visit to Tanzania and Ghana, where we met with the project partners Prof Osman Sankoh of INDEPTH Network, Ghana and Dr Mayombana and Sally Mtenga of Ifakara Health Institute, Tanzania. With their help and further assistance, introductions were made to various research centres and other relevant institutions, such as the Ministries of Health and ethics committees. At these meetings, early research ideas for the project were discussed with the various

stakeholders. The feedback on the research questions and practical advice provided in each country with each research group further helped define the study questions and methodological approach of the project. With the support and agreement of four research centres (two in Ghana and two in Tanzania respectively), an empirical research study was designed in partnership with local research teams representatives. Through consultation, it was agreed that the research project would include interviews with stakeholders involved with the collaborative research of an international paediatric malaria vaccine trial (PMVT) candidate RTS, S trial that was being conducted at all four research centres in both Ghana and Tanzania. The vaccine trial is a large, long standing, multicentre product development partnership between - GlaxoSmithKline (GSK, Vaccine Developer) and the global health non-profit organisation PATH and its Malaria Vaccine Initiative program (PATH/MVI, Funder-Development Partner), (RTS, S) (NCT00866619).[15] The research collaborative conducting the PMVT was formed of the product development partners (GSK PATH/MVI) and eleven research centres based across seven sub-Saharan countries (an eighth country was included for an additional part of the vaccine trial). The project included two of the eight countries, Ghana and Tanzania and their four research centres which are part of the PMVT. Local representatives from these four research centres advised on the national and institutional ethics review requirements, final study protocol and, the themes and questions set out in the semi-structured interview guide.

1.2.1.2 Ethics Approval and Permission

Permission to proceed with this study was provided by the GSK/MVI Ancillary Studies Review Committee on 18th July 2014, along with signed agreements from all the requested health research centres. 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). It was also approved by each country, Ghana: Ghana Health Service Ethics Review Committee, Kintampo Health Research Centre, 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 National Institute for Medical Research (NIMR); Ifakara Health Institute IRB. Tanzania Commission for Science and Technology (COSTECH).

1.2.1.3 Study Sites

Through November 2014 to September 2015, the interview respondents (senior researchers, research managers, clinicians, vaccination nurses and fieldworkers) were recruited from the four separate research centers: Ghana: (1) Malaria Research Centre, Agogo Presbyterian Hospital, School of Medical Sciences, Kwame Nkrumah University of Science and Technology, Kumasi; (2) Kintampo Health Research Centre, Ghana Health Service, Kintampo; Tanzania: (3) Bagamoyo, Ifakara Health Institute; (4) Tanga Research Centre (NIMR), Korogwe, National Institute for Medical Research. Also, the national and international institutions involved with the vaccine candidate trial were also recruited, e.g., GSK, PATH/MVI, government bodies, ethics review committees, and healthcare systems representatives. See Table 1 for further detail of the research centres.

	Ghana		Tanzania	
Research Group	KHRC[a]	KCCR[b]	BRTC[c]	NIMR[d]
Location	Kintampo	Agogo	Bagamoyo	Korogwe
Region	Brong Ahafo Region, Ghana	Agogo, Ashanti Region, Ghana	Bagamoyo, Pwani Region, Tanzania	Tanga Region, Tanzania
Main Government Health Facilities Involved with Participant Recruitment, vaccinations, follow up and routine care	Kintampo North Municipal Hospital	Agogo Presbyterian District Hospital	Bagamoyo District hospital	Magunga District hospital
Tertiary referral hospitals	Kintampo North Municipal Hospital	Komfo Anokye Teaching Hospital, Kisumu	Muhimbili National Hospital, Dar es Salaam	Bombo Regional Hospital, Tanga City

a) Kintampo Health Research Center (KHRC), Kintampo, Ghana; b) Kumasi Centre for Collaborative Research in Tropical Medicine (KCCR) in collaboration with the School of Medical Sciences of the Kwame Nkrumah University of Science and Technology (KNUST) Kumasi (Agogo), Ghana; c) Ifakara Health Institute, The Bagamoyo Research and Training Centre (BRTC) Bagamoyo, Tanzania; d) National Institute for Medical Research (NIMR), Tanga Research Centre Korogwe, Tanzania. See geographical locations on the map presented on the next page.

Table 1 Summary table of the four research centres detailing the research group, location and associated health facilities. Adapted from, Angwenyi et al.2015 [95]

1.2.1.4 Stakeholder Selection

The stakeholders invited to take part in the interviews were identified in accordance with the structure of the partnership of the paediatric malaria vaccine trial (See Chapters 3-5). The interviews involved representatives from all the different organisations that were involved with the collaboration on the organisation and implementation of this international multicentre trial in Ghana and Tanzania. At the research centres this included the local research teams, medical teams, vaccination nurses and fieldworkers. In addition local representatives of each health care

system (hospital managers and district health officers) were also included. Other institutions from Ghana and Tanzania involved ethics review committees, government officials from the Ministries of Health and, Food and Drug Authorities. The study also involved representatives of the international partners of the product development partnership. This included GSK (vaccine developer), Clinical Research Officer (CRO), PATH/MVI (Funder-Development Partner) and MCTA (capacity developer).

Participants of the vaccine trial (mothers on behalf of the infant-participant) were not included with the interviews for this project. Notably the paediatric malaria vaccine trial had recruited approximately 16,000 mothers and their children to participate across the seven countries. On average each research centre had recruited around 1400 infants enrolled for the vaccine trial.

The decision not to include mothers of the infant-participants in the interviews was taken because clinical research ethics and community engagement issues that surround research participants were not the main focus of this study, and as a result Mothers of infants were not involved in the interviews. Safeguarding the rights and health of infants in vaccine trials, especially within vulnerable populations (high disease burdens, low education levels of families and high poverty), is very important and a demanding area of ethical enquiry that has been addressed by a number of researchers previously in respect of this malaria vaccine trial.[98-104] Recruitment of infants and involvement of vulnerable populations is a topic which requires continued attention with every new study, new community, disease and intervention. Complex ethical challenges exist around recruitment, informed consent and adequate protections against possible research risks and harms. However, the focus of this study was on the construct of the collaborative partnership, and what ethical challenges are faced across, international, multi-stakeholder, health research partnerships. There is of course overlap between the two broad topics of participant protection and equitable partnerships in health research.

An effective collaboration is a key determinant for the protection of participant safety and context-sensitive study designs that are advantageous to local communities and offer sustainable benefits for improved conditions of health. To this extent including the fieldworkers from the community in the project was very informative. Fieldworkers are members of the local community employed in community liaison roles to inform, support and communicate with the PMVT participants (infants and mother) and the research teams. In addition the medical teams and vaccination nurses also worked directly with the trial participants from the community, and shared experiences from this perspective.

1.2.1.5 Empirical Research Results

Full details set out in chapters Chapter 3 – 5. In summary, there were five pilot interviews conducted in Switzerland and Ghana. These were part of the preliminary investigation and study design and not included in the final interview total. The pilot interviews helped develop the interview guide questions, strengthen interview methods and, provided an opportunity to familiarise with the sound recording equipment.

In total, there were 52 semi-structured interviews included in the project. Across research centres of Ghana and Tanzania, there were 31 individual interviews and 2 group interviews (1 with a team of vaccine nurses and 1 with a fieldworker team). In respect of wider partners (government bodies, ethics review committees members and health system representatives), there were 13 individual interviews. There were six interviews with the sponsor-investigator groups (GSK, CRO, PATH, and MCTA). Three were in person, two by phone, and one via Skype. A detailed breakdown of respondents and their role in the paediatric malaria vaccine trial is set out in the results section of Chapters 3 -5.

1.2.1.6 Dissemination

Dissemination of the results is an import aspect of this project. Undertaking an empirical ethics project with stakeholders from a multicentre research collaborative across Ghana and Tanzania provides an opportunity for sharing of experiences and mutual learning within the research collaborative and for the benefit of other health research partnerships. The dissemination of results will be delivered in several ways: publications in peer reviewed journals and a participant information results sheet. The information sheet will set out a broad overview of the research visits and be emailed to respondents. This is to recognise and thank respondents' for their involvement in the project and also inform them of the project findings. Second, also, the journal publications from the project will be shared with all study partners and the research centres in Ghana and Tanzania. Third, conference presentations also offer an opportunity to share the findings of this project. The project has been selected for the Oxford Global Health and Bioethics International Conference in July 2017, which has been previously well attended from candidates across the globe. Other international conferences would be a welcome opportunity to further present on the findings and in particular at African-led health research conferences, such as those organised by the INDEPTH Network.

1.2.2 Background to the Paediatric Malaria Vaccine Trial

1.2.2.1 Collaborative Research

Research collaborations, research partnerships, collaborative partnerships and collaborative research are labels used interchangeably through the literature and in this study. These catch-all phrases loosely describe a wide array of co-operative activities and a variety of different levels of association between organisations in international health research (between governmental-, non-governmental-, public-, private-, academic-, civil society-institutions).[105] [2] As a result, when discussing collaborative research programmes, it is important to define the specific partnership under consideration – who are the stakeholders, what is the structure and what are the objectives. In this section, detail is provided on the paediatric malaria vaccine trial (PMVT) that was the case example of collaborative research in this empirical ethics study. This PMVT was undertaken in a collaborative research project of GSK PATH/MVI known as a product development partnership; a specialised sub-set of public, private partnerships.

1.2.2.2 Development of RTS, S Candidate Vaccine by GSK/PATH MVI

Clinical development of the RTS, S candidate vaccine against malaria was undertaken in a public, private partnership between GlaxoSmithKline and the PATH Malaria Vaccine Initiative (MVI), which receives funding from the Bill and Melinda Gates Foundation. The trial was also supported by the Malaria Clinical Trials Alliance (MCTA), an African-led organization that was mandated to build capacity and share best practice for the conduct of clinical trials. This multi-centre efficacy trial was designed by the Clinical Trials Partnership Committee (CTPC), which had membership representing each of the academic institutions participating in trial conduct, GSK Biologicals, and MVI. (Leach 2011)

1.2.2.3 Product Development Partnerships

The GSK PATH/MVI collaborative partnership took the form of a Product Development Partnership. Product development partnerships (PDPs) are not-for profit organizations that build partnerships between the public, philanthropic, academic, and private sectors to drive the product development for neglected diseases in conjunction with external partners.[12] The construction of a PDP is in general established to discover and develop solutions to neglected diseases where no commercial incentives exist and where the disease is disproportionately affecting people in low resource settings. This is distinct from the pharmaceutical industry that has profits as one of the main objectives of product development. The PDP model, therefore, is to advance public health rather than commercial gain, but tends to operate with private sector

management practices and endorse industrial project management in their R&D activities. [106] Notably, PATH, the not-for-profit included in this project is regarded as one of the original architects of product development partnership models as an approach to overcoming research and development gaps that limit access to essential health technologies in resource limited settings. [107] Even across PDPs although their structure and objectives are similar, there are also differences, for example, some see additional objectives such as capacity-building, technology transfer and health care access as a key component of their work while others are solely focused on product development.[106] At the heart of this debate, and research project is whether collaborative research in low-resource settings should have a role in health care access and development activity, and furthermore whether in fact these objectives are being achieved.[12, 107]

1.2.2.4 GlaxoSmithKline (GSK) Vaccines

As stated on the GSK website: GSK Vaccines is active in vaccine research and development. Headquartered in Belgium, GSK Vaccines has 13 manufacturing sites strategically positioned around the globe. Of the 883 million doses of GSK vaccines distributed in 2016, over 80% went to developing countries, which include the least developed, low- and middle income countries.[108]

1.2.2.5 The Malaria Vaccine Initiative (MVI) of Funder-Developer, PATH

As stated on the PATH and MVI websites: PATH, funder-developer, is a leader in global health innovation. An international nonprofit organization, that operates to save lives and improve health, especially among women and children. The objectives of the organisation are to accelerate innovation across five platforms—vaccines, drugs, diagnostics, devices, and system & service innovations— through entrepreneurial insight, scientific and public health expertise, and focused on improving health equity. The organisation functions through mobilising partners around the world to take innovation to scale, working alongside countries primarily in Africa and Asia. PATH aims to generate innovation that disrupts the cycle of poor health in LMIC countries. [109]

The PATH Malaria Vaccine Initiative (MVI) is a global program established at PATH through an initial grant from the Bill & Melinda Gates Foundation. MVI's mission is to accelerate the development of malaria vaccines and catalyze timely access in endemic countries.[110]

1.2.2.6 Malaria Clinical Trials Alliance (MCTA)

As stated on the MCTA website: MCTA was established in 2007 (concluded 2010) as a new initiative by the INDEPTH Network to help conduct clinical trials of new drugs and vaccines to fight malaria within Africa. MCTA enabled African institutions and scholars to participate fully in the development of new tools for addressing malaria and in conducting interventions against malaria and created a long-term partnership between African and Northern institutions. The long term objective of MCTA was to identify, support, strengthen, mentor and network trial-sites to facilitate their self-sustainability, ensuring that trial sites remained functional beyond the end of a trial and thus increasing the number of sites in Africa ready to conduct trials for vaccine and drug interventions. MCTA ensured that the trial-sites were equipped with proper management, staff, database and communications systems and transparent financial systems.[111]

1.2.2.7 INDEPTH Network

As stated on the INDPETH Network website: The INDEPTH Network is a global network of health and demographic surveillance systems (HDSSs) that use epidemiological methods to map the health status of communities (in low resource settings where there is no formal, or fully comprehensive, national health reporting and surveillance). The HDSSs collect data from whole communities over extended time periods to better understand the health and population challenges in low- and middle-income countries.[112]

The next page presents a table giving an overview of Phase III (RTS,S) Paediatric Malaria Vaccine Trial, adapted from The Joint Technical Expert Group on Malaria Vaccines (JTEG) And WHO Secretariat Background Paper.[96]

Ages Included in Trial	Two age categories: children at the age of 6-12 weeks (infants) and 5-17 months (children) at first vaccination.
Time Period	2009 – 2015
Trial-Sites	11 centres in Burkina Faso (Nanoro), Gabon (Lambarene), Ghana (Kintampo and Agogo), Kenya (Kilifi, Kombewa, and Siaya), Malawi (Lilongwe), Mozambique (Manhica) and Tanzania (Bagamoyo and Korogwe).
Treatment Groups	Three treatment groups per age (1:1:1 randomization): R3R received RTS,S/AS01E for four vaccinations R3C received RTS,S/AS01E for three vaccinations and the control (MCC) for fourth vaccination C3C received the control (Rabies for 5-17 month children and MCC for 6-12 week infants) for the first three vaccinations and the fourth (MCC for both age groups) vaccination
Dosing Schedule	Doses are given on a 0, 1 and 2 months schedule, the fourth dose at 18 months after the 3rd dose.
Other Vaccines Administered	Infants receive Tritanrix HepB/Hib + OPV concomitantly with the first three doses and OPV concomitantly with the fourth dose. Additional vaccination with BCG, OPV birth dose, measles and Yellow Fever were given according to local EPI practice.
Follow up Time	Vaccine efficacy and immunogenicity are measured over a median of 38 (6-12 week younger age category) or 48 (5-17 month older age category) months after the 3rd dose.

Primary Objectives	Efficacy co-primary objectives: To evaluate the protective efficacy of RTS,S/AS01E against clinical malaria disease caused by *Plasmodium falciparum* in African children whose age at first dose will be from 5-17 months. To evaluate the protective efficacy of RTS,S/AS01E against clinical malaria disease caused by *Plasmodium falciparum* in African children whose age at first dose will be from 6-12 weeks and will receive the vaccine in co-administration with DTPwHepB/Hib antigens (Tritanrix HepB/Hib) and OPV. For the co-primary objectives, duration of follow-up was 12 months after completion of the first three doses.

Table 2 Overview of Phase III (RTS,S) Paediatric Malaria Vaccine Trial. Adapted from The Joint Technical Expert Group on Malaria Vaccines (JTEG) And WHO Secretariat Background Paper.[96]

1.2.2.8 Point of Clarification

In order to save confusion through the project, the term "participant" refers to infants (with their mothers) recruited into the paediatric malaria vaccine trial. Whilst, the term "respondent" refers to stakeholders interviewed as part of this qualitative ethics project.

In addition, reference to "the trial" or "PMVT" (paediatric malaria vaccine trial), refers to the activity of the paediatric malaria vaccine trial. Whilst, the term "the study" refers to this qualitative ethics project.

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2 COLLABORATIVE RESEARCH GOVERNANCE

Ward, C.L., Shaw, D., Sprumont, D., Sankoh, O., Tanner, M., Elger, B, Good Collaborative Practice: Capacity Building Governance of International Health Research Partnerships, Globalization and Health, 2018, 14:1; doi.10.1186/s12992-017-0319-4

2.1 Abstract

Title: Good Collaborative Practice: Reforming Capacity Building Governance of International Health Research Partnerships

Objective: In line with the policy objectives of the United Nations Sustainable Development Goals, this commentary seeks to examine the extent to which provisions of international health research guidance promote capacity building and equitable partnerships in global health research

Findings: Our evaluation finds that governance of collaborative research partnerships, and in particular capacity building, in resource-constrained settings is limited but has improved with the implementation guidance of the International Ethical Guidelines for Health-related Research Involving Humans by The Council for International Organizations of Medical Sciences (CIOMS) (2016). However, more clarity is needed in national legislation, industry and ethics guidelines, and regulatory provisions to address the structural inequities and power imbalances inherent in international health research partnerships.

Recommendations: i) shared research agenda setting with local leadership, ii) capacity assessments, and iii) construction of partnership memorandum of understanding (MoU). Moreover, the requirement of capacity building needs to be coordinated amongst partners to support good collaborative practice and deliver on the public health goals of the research enterprise; improving local conditions of health and reducing global health inequality. In this respect, and in order to develop consistency between sources of research governance, ICH-GCP should reference CIOMS ethical guidelines as the established standard for collaborative partnership. Moreover, greater commitment and support should be given to co-ordinate, strengthen and enforce local laws requiring equitable research partnerships and health system strengthening.

Conclusions: Given the strategic value of ICH-GCP guidelines in defining the role and responsibility of global health research partners, we conclude that such governance should stipulate the minimal requirements for Good Collaborative Practice; creating an equitable environment of inclusion, mutual learning, transparency and accountability.

Keywords: Global Health Research; Governance; Ethics; Collaborative Partnership; Capacity Building; Social Justice

2.2 Introduction

Health research is vital for better population health, equity, and national development.[1] As stated by The World Health Report 2013, Research for Universal Health Coverage: 'all nations should be producers of research as well as consumers.'[2] However, significant constraints on skills, expertise and finance inhibit countries with limited resources from carrying out such necessary research. In response, international collaborative partnerships have formed to bridge the health research gap in low- and middle-income countries. This has resulted in the production of new vital health data and scientific advancement, and yet persisting capacity gaps and health capabilities continue to exist between countries. Although the reasons for this reality are complex and multifaceted, one key aspect (the focus of this commentary) is achieving clarity on the role and responsibility of international health research partnerships in addressing matters of global health. The stifled progress of global health research activity is not so much a limitation in the science (although this remains a factor in respect of some diseases) but also an outcome of social and structural inequality. [5] To date, partnership approaches have sustained old ghosts: north-south dependency, distorted health research priorities, weak and unprepared health care systems, underutilized local professionals and knowledge, unfair distribution of risks and benefits and, insufficient access to life-saving interventions for populations most in need. [6, 7] Such factors destabilize regional development, health equity and the health of populations suffering from both endemic disease and poverty. Given this question regarding the responsibilities of ethical partnerships, this commentary explores the extent to which international health research guidelines and legislation - a crucial source of governance - require equitable partnership structures, and in particular capacity building. Fulfilling the obligation to engage in capacity building in this context means the advancement of systems, expertise and infrastructures of health research capabilities through improvement to operational, institutional and individual functions [6]. Capacity building is an ethical obligation premised on the principles of social justice and health equity; the principles respectively require the equitable distribution of risks and benefits in health research (social justice) and equal access to the resources needed to improve and maintain positive health outcomes (health equity) [7]. The objective of capacity building is to "develop individuals, organizations and societies (individually and collectively) to perform functions, effectively, efficiently and in a

sustainable manner to define objectives and priorities, build sustainable institutions and bring solutions to critical national problems" [8]. As recognized by other authors, a strengthening effect through partnership may also be possible in high-income countries and across a broad variety of collaborative arrangements [9]

Where governments are unable to sufficiently establish the infrastructure, skills, and systems to conduct health research, there is an ethical duty amongst the partners of an international collaborative to build and support capacity. This is crucial in respect of addressing public health. For example, the process of building and strengthening public health capacities (in part through collaborative research) is necessary for the function and effective implementation of the International Health Regulations [10]; an international agreement of all WHO member countries designed to strengthen health security through sample collection and information sharing [11]. Failure to collaborate, or collaborate effectively, slows national and global responses to disease threats and places lives at risk, disproportionately affecting the most vulnerable [12]. The need for capacity building to establish equitable and sustainable collaborations is strongly advocated by the UN Sustainable Development Goals and the latest CIOMS ethical guidance update. Practically, the commitment of partners to capacity building is crucial for global health research to overcome inherent power differentials within collaborative research, to support local research-leadership and, to fully engage and integrate research into local healthcare settings. Fulfilling these capacity building objectives ensure that health research is able to respond to local health needs and can assure [13] the safety and health of local and global populations [12].

Increasingly, international collaborative research is being asked to consider the local interests of resource-constrained partners and the responsibility of collaborations to safeguard against the potential for structural exploitation when operating in resource-constrained settings [6, 14]. In some instances, research partnerships have actively (and explicitly) incorporated capacity building objectives in conjunction with disease and intervention research [4, 15, 16, 17, 18]. This approach has not only been regarded as ethical but also essential for responding to local health needs, through bolstering both the health-related social structures, and addressing the urgent health needs of the affected populations [6, 19]. Research collaborations are central to the exchange of capacity. The professional and institutional links that form within multinational networks create a

partnership-platform for expertise sharing, knowledge transfer and system strengthening [12]. However, attempts to establish effective capacity development approaches in global health research remain disjointed and inconsistent [20]

The commentary in this instance reflects on collaborative global health research partnerships operating in resource-constrained settings. These settings are characterised by poverty, weak healthcare systems, and high burdens of diseases; conditions that disproportionately affect disadvantaged populations and sustain vicious cycles of impoverishment [21, 22, 23]. The major concern of global health research is that despite increased investment in research programs with multiple international partners, there has been much less advancement in low- and middle-income countries accruing their own research capacity and strengthened systems of health to protect their populations [24]. This is ethically challenging and compromises the overall goals of collaborative research to improve public health and reduce global health disparities [2, 4]. For global health research partnerships to successfully respond to the health needs of vulnerable populations living in low-resource settings, an international collaborative partnership must succeed in addressing a range of complicated objectives: on the one hand generating health data and generalizable knowledge (the scientific goals), whilst on the other hand, attending to structural limitations of resources and infrastructure (the capacity goals). This requires navigating a diverse set of challenges including a range of access barriers to effective interventions and under developed health and research systems. Accounting for these different goals is important to deliver on the overall public health objective of improving conditions of health, both locally and globally.

The recognised need for global research capacity worldwide represents a new shift in thinking, with the objective being to provide all countries with health capabilities to monitor, prioritize and maintain local conditions of good health. This approach is founded on the idea that there is no global health security, without global health justice protecting health as a human right. Meeting this commitment requires locally relevant, system-integrated health research. The spread of the Ebola and Zika viruses outbreaks are just two recent cases that exemplify why local capacity is both urgent and necessary to protect the health of populations both within countries and worldwide [11, 25, 26].

2.3 A Changing Governance Landscape

Over time, as global health research has advanced, legislation and ethics guidelines have had to change, challenged with shifting paradigms: scientific advancement, the recognition of human rights, societal development and evolving international commitments. On the whole however international health research governance and guidance has been slow to, and inconsistent in, recognizing the principle of sustainable capacity building [27].

Endorsing the role of capacity building in partnerships has been reinforced by the United Nations Sustainable Development Goals (SDGs), 2015, (agreed upon by 193 countries) and the CIOMS guidelines (2016). These two recently published guidance documents incorporate capacity building into the standards they set, and this indicates commitment to a change in approach, at least within policy. In particular, Goal 17 of SDG states, "Enhance North-South, South-South and triangular regional and international cooperation on and access to science, technology, and innovation and enhance knowledge sharing on mutually agreed terms." Additionally, Goal 17 also has a standalone Capacity Building Task which states, "Enhance international support for implementing effective and targeted capacity-building in developing countries to support national plans to implement all the sustainable development goals, including through North-South, South-South, and triangular cooperation." These high-level international commitments now need to be translated into practical activities on the ground. The responsibility to do so rests with governments, legislatures, industry, NGOs and civil society.

In line with this new agenda of capacity strengthening, the latest version of the ethical research guidelines from CIOMS (2016), provides structured guidance for fulfilling capacity building objectives and equitable partnership within programmes of collaborative research [28]. Focusing in on the structure and responsibilities of partnership recognizes all stakeholders as equal, shifting the decision-making structure away from the donor-recipient dynamic often present in north-south collaborations. Addressing the ethics of the partnership in a way that goes beyond traditional research ethics (sound science, participant safety and autonomy), the CIOMS guidelines identify a crucial point: the act of entering into partnership has accompanying ethical responsibilities. This

marks the need for collaborative research partnerships to contribute to sustainable capacity building activities that brings structured changes to local skills, knowledge, and systems. This is important because aiming to combat one specific health disease through collaborative research or even providing a one-off research training amongst partners will not alone secure conditions of good health for a population; co-ordinated commitment towards institutional and national capacity building is also required. Threats to health will always evolve and emerge and therefore public health requires the presence of functioning, and responsive, health and research systems. As such, CIOMS guideline states that research projects should have "local principal investigators". This requirement ensures community consultation, context-relevant deliberative decision-making and engagement with local partners and research programs that integrate with local healthcare settings. As stipulated by the updated Guideline 8, "engaging with the community is necessary to deliver on the social value of research and respect for individual and community rights" [28]. To fulfil this objective, it is important to have partnerships that are not led solely by the funding partners, and this is achieved through ethical partnership governance – good collaborative practice - that recognises the contribution (financial or otherwise) or all partners [29, 30]. Structuring the partnership, decision-making and partner-roles through ethical governance creates an equitable collaborative environment of inclusion, transparency and accountability [29]. Capacity strengthening objectives, are not merely operational choices but ethical requirements to achieve the necessary structural changes that establish local leadership, mutual knowledge sharing, and a commitment to regional health improvements [31].

2.4 Dominance of ICH-GCP

While the United Nations and CIOMS guidance adopts a new and more promising approach, one significant impediment acts as a barrier to translation of these essential principles into practice; the International Conference on Harmonization Technical Requirements for Registration of Pharmaceutical for Human Use (ICH) Good Clinical Practice (ICH-GCP). ICH-GCP guidelines have come to define the obligations of the research enterprise, and govern the role and responsibilities of international health research programmes. However, the adoption of ICH-GCP has been driven by the interests of the pharmaceutical industry [32]. This has perpetuated an overemphasis on clinical research guidelines that is distinct from broader objectives of collaborative research and, we argue, at odds with the objectives of the UN Sustainable

Development Goals. ICH-GCP sets out to protect against human rights violations in health research by referring to the Declaration of Helsinki (DoH) and Nuremberg Code (and even in this respect its success in achieving this aim has been questioned) [33]. However, this narrow focus overlooks the partnership issues of international collaborative health research, with respect to ethical governance, social justice and promoting equity, despite these being the practical challenges of global health research today. As such, the acquired superiority, and overwhelming reliance on ICH-GCP as ethics guidance is problematic, and stands at odds with the commitment of all sectors to implement strategies that fulfil the UN Sustainable Development Goals. The aim of protecting participants from harm has become too narrowly construed to the limited framework of the researcher-participant relationship [5]. The harm or exploitation of a complex multi-stakeholder collaborative partnership can be much wider, and these concerns and risks need to be addressed with the community and the healthcare system where the research takes place [34]. At present under ICH-GCP, poorly- resourced research institutes are often instructed as service centers, rather than treated as equal collaborating partners. We argue that greater consideration needs to be given to Good Collaborative Practice, as well as Good Clinical Practice. Inequitable partnerships pose a direct threat to public health [30, 35]. Inherent injustice between partners can lead to disruption in programmes of research and public health [36, 37], compromise trust in local and global systems and [11, 12]; may even result in costly (time, money and reputation) legal consequences [38]. It is most unfortunate that the ICH did not take the opportunity of the revision of GCP in 2016 to incorporate a statement on partnership considerations and capacity building. During the review process there were repeated calls for the guidance to be updated with partnership governance and greater consideration for the needs of resource-constrained settings and yet, these safeguards have not been incorporated into the new updates [39, 40, 41].

The dominant agenda of the ICH-GCP provisions misdirects partner communication, limits collaboration, and blocks ethics review processes; leaving questions on capacity strengthening and equitable practice unaddressed.[41, 43] Proponents of ICH-GCP state that a broader agenda for development is not the role of GCP guidance. However, this is no defense since the uptake, and use of the guidance has significantly changed beyond its original purpose.[44] Furthermore, the point is that an agenda for development *should, and can,* be part of the role of the guidance; and especially so if we agree that health, and not merely data, is the end goal of a collaborative health

research partnerships. ICH-GCP has come to define the obligations of the research enterprise, but with no acknowledgment of the need for national health capabilities to develop; ethical requirements of social justice and health equity. Indeed, the adoption of ICH-GCP has been written and driven by the interests of the pharmaceutical industries.[45] This has perpetuated an overemphasis on clinical research guidelines as distinct from broader public health requirements. This highlights yet another consideration for the conduct of global health research: whose interests are actually being represented?[46] ICH-GCP sets out to protect against human rights violations in health research by reference to the Declaration of Helsinki (DoH) and Nuremberg Code. However this overlooks the ethical issues of international collaborative partnerships on justice and equity which require commitments of capacity building; and yet this is a practical reality of global health research today. As such, the acquired superiority, and overwhelming reliance on ICH-GCP as ethics guidance is problematic. The ethical concerns to protect participants from harm have become too narrowly construed to a limited framework of clinical conduct and negligence in the researcher-participant relationship.[7] The harm or exploitation of a complex multi-stakeholder collaborative partnership can be much wider, and these concerns and risks need to be addressed with the community and the healthcare system where the research takes place.[47] Silence in ICH-GCP on capacity building undermines a commitment to design data collection in a manner that engages community, strengthens national health research and improves health in resource constrained settings. Governance to support locally led health research is not only ethical but also critical for overcoming current challenges in global health.[1, 6] Action needs to be taken so that governance incentivizes sustainable capacity strengthening requirements in collaborative partnerships.

At present under ICH-GCP, poorly- resourced research institutes are often instructed as service centres, rather than treated as equal collaborating partners. We argue that greater consideration needs to be given to Good Collaborative Practice, as well as good clinical practice.

2.5 Recommendations: Good Collaborative Practice

Moving forward, what changes are needed to incorporate sustainable capacity strengthening into collaborative partnerships? One is to increase awareness amongst global actors, funders, institutions, researchers and ethical review boards. In particular, it should be noted that the ICH-

GCP requirements are ethically valid only to the extent that proper procedure must be followed when conducting health research; but this is only one criterion for what makes health research ethically acceptable. [48, 49, 50] The ethical lens of good clinical practice needs to be widened beyond the limited protection of the participant towards a collectivist approach of good collaborative practice.

The interests of partners need not be the same, but they should be reciprocal. Therefore we recommend the process of creating a joint MoU to foster the spirit of collaboration better. We further recommend that the MoU could be a document with set criteria to direct negotiations; for example, requiring details on the constitution of the partnership and capacity strengthening in relation to the individual, institutional and operational obligations. The MOU process should be structured to facilitate communication across partners of complex collaborative research. This approach is important for defining the interests and needs of the various stakeholders; the research priorities and; the joint capacity agendas. Through co-operation partners can then form a balanced operational relationship of understanding that (fairly and transparently) allocates resources, responsibilities and project ownership amongst all partners. The partnership co-ordination set out in an MOU is crucial for realising the shared responsibilities and rewards of global health research. For example, establishing equitable partner inclusion on collaborative research protocol design, project implementation, standards of care, data handling, scientific analysis, authorship, intellectual property rights and; access to novel health research and innovation.

In the same way that an ethics committee examines an informed consent form to ensure protection of individual participants, review of the memorandum of understanding would allow oversight of capacity strengthening commitments, equitable resource allocation and evaluate the social value of the study. Procedurally, the MoU process could be stated in ICH-GCP and enforced through national legislation in much the same way as is seen with the participant informed consent process.

A second approach, beyond awareness and education, would be to co-ordinate, strengthen and enforce local laws requiring equitable research partnerships and system strengthening. Clearer agreement within guidance provisions in legislation would also have the benefit of streamlining

protocol reviews across different ethical review boards and regulators, while also reducing procedural time delays, especially in multi-center studies.

The third option would be to change the ICH-GCP guidelines themselves to secure good collaborative practice through ethical partnership governance and capacity strengthening requirements. This could have been done in 2016, but the opportunity was missed. This approach honors nation state sovereignty and promotes local health research capabilities.

2.6 Conclusion

The long-term objective for the global health community is to establish self-sufficient healthcare systems worldwide that can undertake research and respond to changing health environments. The need for autonomous and locally-led systems of health research has been better recognized with international policy campaigns, and in novel ethical research guidance. These sources have adopted various conditions requiring that local capacity building is supported in collaborative health research. Arguably, no further progress in establishing global health research systems will be achieved if the limited scope of ICH-GCP continues to take priority, as the only or overriding criteria of ethical health research. At present, this international standard of health research does not require capacity building, locally-led research or even community engagement. We argue that this needs to change. Ethical research requires that Good Clinical Practice is complemented with Good Collaborative Practice. Together, such guidance will govern international health research partnerships that nurture sustainable health research-, and health- systems in accordance with their mission; to address global health inequalities and improve local conditions of health worldwide.

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3 HEALTH RESEARCH FOR DEVELOPMENT

Ward, C.L., Shaw, D., Anane-Sarpong, E., Sankoh, O., Tanner, M., Elger, B, Defining Health Research for Development: The Perspective of Stakeholders from an International Health Research Partnership in Ghana and Tanzania. Developing World Bioethics. 2018 Dec; 18(4):331-40.

3.1 Abstract

Title: Defining Health Research for Development: The Perspective of Stakeholders from an International Health Research Partnership in Ghana and Tanzania

Objectives: The study uses a qualitative empirical method to define 'health research for development.' This project explores the perspectives of stakeholders in an international health research partnership operating in Ghana and Tanzania.

Methods: We conducted 52 key informant interviews with major stakeholders in an international multicentre partnership between GlaxoSmithKline (GSK, Vaccine Developer) and the global health non-profit organisation PATH and its Malaria Vaccine Initiative program (PATH/MVI, Funder-Development Partner), (RTS, S) (NCT00866619). The respondents included teams from four clinical research centres (two centres in Ghana and two in Tanzania) and various collaborating partners. This paper analyses responses to the question: What is Health Research for Development?

Results: Based on the stakeholders' experience the respondents offered many ways of defining Health Research for Development. The responses fell into four broad themes: i) Equitable Partnerships; ii) System Sustainability; iii) Addressing Local Health Targets, and iv) Regional Commitment to Benefit Sharing.

Conclusion: Through defining Health Research for Development six key learning points were generated from the four result themes:1) Ensure there is local research leadership working with the collaborative partnership, and local healthcare system, to the align project agenda and activities with local research and health priorities; 2) Know the country-specific context - map the social, health, legislative and political setting; 3) Define an explicit development component and plan of action in a research project; 4) Address the barriers and opportunities to sustain system capacity. 5) Support decentralised health system decision-making to facilitate the translation pathway; 6) Govern, monitor and evaluate the development components of health research partnerships. Overall, equity and unity between partners are required to deliver health research for development.

Keywords: Health Research; Development; Collaboration; Equity; Empirical

3.2 Introduction

The role of research in advancing robust, functional and equitable health systems has been recognised for some time, [1-3] and most recently in the UN Sustainable Development Goals.[4] This is a welcome reminder of the importance and urgency of finding methods and resources to overcome the barriers present in low-resource settings where research capacity is limited, and a country's ability to address global health challenges is significantly reduced.[2] Establishing health research systems and activities in a country is important for development because it enables "countries to capitalise more effectively on the supply of ideas, translate research into effective interventions and design resilient health strategies."[5] Moreover, the conduct of local research is critical for adapting approaches to specific settings and maximizing the success of health policies.[6] Overtime more and more funding initiatives have aimed to strengthen health research capacity in Low and Middle-Income Countries [7-9]. In this paper, we concentrate on one particular initiative construct, Product Development Partnerships (PDP). These partnerships form international collaboration between scientists in wider multi-stakeholder programmes of research. This approach has the potential to reduce global health disparities through developing cost effective solutions to disease along with offering complementary activities that contribute to country development.[10] In this instance, our paper is based on stakeholder views from one specific long-standing partnership, between GlaxoSmithKline (GSK, Vaccine Developer) and the global health non-profit product developer, PATH, and its Malaria Vaccine Initiative program (PATH/MVI, Funder-Development Partner). Through partnership this collaboration has developed a malaria vaccine candidate (RTS, S), and has conducted Phase II/III in-human paediatric trials across seven (with an eighth country included for a further lot-to-lot consistency and non-inferiority study) sub-Saharan African Countries (NCT00866619, NCT01323972).[11, 12] This paper is based on interviews with stakeholders of the vaccine candidate trial from two of the countries, Ghana and Tanzania.

A collaborative partnership such as GSK/PATH MVI is tasked with successfully developing a new health intervention for, and with, low resource countries. Over the course of the malaria vaccine candidate trial, the partnership has incorporated different ways to build up scientific research capacity in the countries (Ghana and Tanzania) where the intervention (RTS, S malaria vaccine candidate) has been tested. Through PATH MVI Initiative (MVI) and with funding from the Bill and Melinda Gates Foundation, the GSK/MVI malaria vaccine trial worked with the INDEPTH

Network, Malaria Clinical Trial Alliance (MCTA) “to facilitate site preparation for the effective conduct of (malaria vaccine) clinical trials and simultaneously promote the long-term development and sustainability of clinical trial sites in resource-constrained countries in the developing world".[13] The partnering of GSK/MVI with MCTA actively promoted the objective of constructing health research for development by both collecting data on the safety and efficacy of a potential new malaria vaccine candidate and; strengthening the research capacities of the countries in the locations where the research was being conducted.

The 2016 WHO World Health Statistics Report - Monitoring Health for the Sustainable Development Goals – presents data showing that significant gains in life expectancy have been made globally since 2000, but major inequalities persist within and among countries.[14] Dr Margaret Chan, Director-General of WHO commented that “The world has made great strides in reducing needless suffering and premature deaths that arise from preventable and treatable diseases but the gains have been uneven.”[14] In this context of global health disparities, the fostering of international partnerships and collaborative health research programmes have been identified as critical for tackling health inequities and health system problems worldwide.[15] In particular, collaborative research in global health has been identified as essential to combatting debilitating and fatal disease in low and middle income countries (LMIC).[15-17] Therefore, the conduct of health research is vital worldwide for reducing disease burdens by helping evaluate epidemiology and the safety, efficacy and effectiveness of new health interventions, therapies and vaccines.[2] To achieve this goal, global health research collaborations must co-ordinate a complex array of multinational and multidisciplinary teams to run intervention studies in low resource settings; regions of endemic disease, poverty, challenging socio- political- economic structures and limited healthcare access.

Before the 1970s, the idea that scientists and researchers from institutions of advanced industrialised nations had a role in research capacity strengthening and health system development was very limited, and it was even more rare to find a programme of capacity strengthening accompany clinical research.[3] It was the pioneering work of groups such as TDR (the Special Programme for Research and Training in Tropical Diseases of the World Health Organisation), and the Commission on Health Research for Development (COHRED) that first assigned funding and implemented programmes to provide support to strengthen local tropical disease research capacity; recognition of the fact that health research has a critical role in the development of low-income and

middle-income countries.[2] Over time, this work led to the evolution of the concept, Health Research for Development, a campaign for equitable research in low resource settings. The concept was formally established in a landmark paper in 1990s by the Commission on Health Research for Development.[18] Health research for development is an approach to health research that was articulated with the intention to engage international partnerships in "strengthening the governance, management, and systems of resource-limited countries to enable research, science, technology and innovation to improve health, equity, and development."[18] The Commission paper was the catalyst for more NGOs, charities, foundations and governments to fund and support health research capacity strengthening programmes. The concept of health research for development has evolved slowly as a new mode of operation facilitating international cooperation between partners, mobilisation of resources, and support for strengthening national research capacity. Today, health research for development remains a focus to "improve equitable health outcomes and sustained well-being in populations around the world through a multidisciplinary, problem-focused approach to research and practice."[18] At the heart of this concept is the idea of mutual learning for change.

Some ethics frameworks have been established in an attempt to define the responsibilities of international health research partnerships in low resource settings, such as the Council for International Organizations of Medical Sciences (CIOMS) Ethical Guidelines; the Fair Benefits Framework [19]; Human Flourishing Framework [20] and Health for Justice.[21] However, these frameworks are academic in nature, and further contextually-relevant practical guidance is needed to implement ethical conduct in global health research.[22, 23] For example, to improve uptake of ideas on ethical partnership and health research for development, some independent organisations have established new mechanisms to educate, govern and monitor equitable global health research partnerships and to foster national capacity strengthening: KFPE Guidelines for Research in Partnership with Developing Countries, 11 Principles.[24]; the TDR/World Health Organisation ESSENCE report, Six Practices to Strengthen Evaluation of Research for Development [25]; the COHRED Research Fairness Initiative;[26] Canadian Coalition for Global Health Research (CCGHR) Principles on Global Health Research;[27] INDEPTH-Network partnership and;[28] The Access to Medicine Index.[29]

This paper seeks to inform better guidance on Health Research for Development by discovering how the term is understood by implementers of international health research. In undertaking this study, we explore the views of those carrying out health research in the context of an international

partnership operating in Ghana and Tanzania. The aim of this work is to ascertain how programmes of international health research can deliver on research for development in low resource settings.

3.3 Methods

An qualitative research method was employed to capture and analyse how Health Research for Development is understood from the perspective of various stakeholders working in an international research collaborative, GSK/MVI malaria vaccine candidate trial RTS,S, in Ghana and Tanzania.

3.3.1 Study Population

All respondents were involved in the conduct of an international malaria vaccine candidate trial carried out in Ghana and Tanzania between 2009 and 2014 (GSK/PATH MVI, RTS, S) (NCT 0086661).[11] This study population was selected because it was one of the largest (multi-centre studies across 11 research centres, 7 African nations, enrolling 16 000 infants), most long-standing (ongoing for more than six years), and most advanced (paediatric phase III) research trials being conducted in Sub-Saharan Africa. The vaccine candidate trial and the two specific countries of Ghana and Tanzania were selected with the assistance of the Swiss Tropical and Public Health Institute. The interview respondents (clinical and research team members) were recruited from four separate research centres: Ghana: (1) Malaria Research Centre, Agogo Presbyterian Hospital, School of Medical Sciences, Kwame Nkrumah University of Science and Technology, Kumasi; (2) Kintampo Health Research Centre, Ghana Health Service, Kintampo; Tanzania: (3) Bagamoyo, Ifakara Health Institute; (4) Tanga Research Centre (NIMR), Korogwe, National Institute for Medical Research. In addition, the national and international institutions involved with the vaccine candidate trial were also recruited, e.g., GSK, PATH MVI, government bodies, ethics review committees, and healthcare systems representatives.

The qualitative interviews were conducted to improve understanding of Health Research for Development from the perspective of an international collaborative partnership implementing health research in resource-limited regions. We used a purposive sample and applied the approach of intensity sampling,[30]. We selected a sample which is known to be information-rich, due to the scale, level of international collaboration and the considerable length of time that the phase III vaccine trial had been on-going at the research centres based in Ghana and Tanzania.

3.3.2 Sample

Individual semi-structured interviews were employed except on two occasions where group interviews were adopted for two groups of front-line staff (vaccination nurses and fieldworkers). The responses of these latter two groups were obtained in the format of group interviews (involving four individuals per group) because, following preliminary consultation, it was determined they felt more comfortable speaking in a group format. Methodologically this was also agreed acceptable as the respondents in these groups were peers with equivalent training and experience in their respective roles. The structure of the project was designed following an initial scoping visit by the corresponding- and third- author to Ghana and Tanzania in January 2014. In each country, we developed the project in partnership with country contacts, and also institutional contacts to guide and facilitate the recruitment of eligible interview respondents. All identified interviewees were sent invitation requests informing them of the study and inviting their participation. The interview data is collected solely by the corresponding author (November 2014 and September 2015) during country visits to Ghana and Tanzania, in addition to phone and Skype interviews with international partners.

The specific roles of respondents and their research centre affiliation have been withheld to protect the anonymity of the interviewees. A unique ID has been designated to each respondent.

3.3.3 Study Instrument

A semi-structured interview guide was constructed following a review of current literature and consultation with project partners in Switzerland, Ghana and Tanzania. Overall, the questions consider the interaction between the international vaccine trial and the local health- and research-systems. This paper presents responses from the interview question: "how do you understand health research for development?" The interview guide was developed with a qualitative methods advisory group that consisted of the paper’s authors, qualitative research methodologists and country experts from Ghana and Tanzania. The interview 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 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 with the final interview data set of 52 interviews (N=52). The semi-structured interview introduced the main research topic areas while

enabling respondents to determine the depth and direction of their responses. Follow-up questions were also used to obtain further explanation and clarification where necessary. Permission to proceed with this study was provided by the GSK/MVI Ancillary Studies Review Committee on 18th July 2014, along with signed agreements from all the requested health research centres. 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). It was also approved by each country, Ghana: Ghana Health Service Ethics Review Committee, Kintampo Health Research Centre, 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 National Institute for Medical Research (NIMR); Ifakara Health Institute IRB; Tanzania Commission for Science and Technology (COSTECH).

3.3.4 Informed Consent

The corresponding author conducted all 52 interviews in English between November 2014 and September 2015. All respondents were notified that the interview audio would be recorded. Written and oral informed consent was obtained ahead of the start of a respondent interview. The informed consent process informed respondents that interviews would be saved under a non-identifiable code anonymously, and confidentiality would be protected. Also, respondents could end the interview at any time, or refuse to answer any specific question(s).

3.3.5 Interviews and Transcriptions

Interviews lasted between 35 minutes and 2 hours, and this length of time was determined by the respondent, given their engagement with the topic and availability. The average interview duration was 50 minutes. The first author transcribed 40 interviews in full, and 12 interviews were transcribed by two departmental assistants, and then reviewed for accuracy by the corresponding author. Departmental assistants were subject to the same terms of project confidentiality.

3.3.6 Data Analysis

The interview transcripts formed the basis of raw data for this research. The transcripts were read multiple times by the corresponding and second author ahead of coding. The corresponding author manually coded all the transcripts to map responses to the question of how is Health Research for

Development understood. Repeated ideas were identified across the transcripts and constituted into sub-themes. The sub-themes were then grouped, and this led to the establishment of themes, and the development of theme narratives.[31] To limit researcher bias, the second author consolidated the coding using the same approach. The repeated ideas, themes, and narratives were compared and discussed between authors to reach agreement on the structure of the paper and the narrative of the results and discussion sections for this article. Quotes presented in the results were selected because they are most representative of the specific themes.

In the results below we first describe the characteristics of our respondents. Then we present the responses under four broad themes. Finally in the discussion we consider how these responses define and inform Health Research for Development.

3.4 Results

3.4.1 Respondent Disposition

In total, there were 52 semi-structured interviews. Across the research centres of Ghana and Tanzania, there were 31 individual interviews and 2 group interviews (1 with a team of vaccine nurses and 1 with a fieldworker team). In respect of the wider partners in Ghana and Tanzania (government bodies, ethics review committees members and health system representatives), there were 13 individual interviews. There were 6 interviews with the sponsor-investigator group (GSK, CRO, PATH and MCTA); of these interviews there were 3 conducted in person, 2 by phone, and 1 via skype. See figure 1 on the next page presenting total respondent numbers for each stakeholder group.

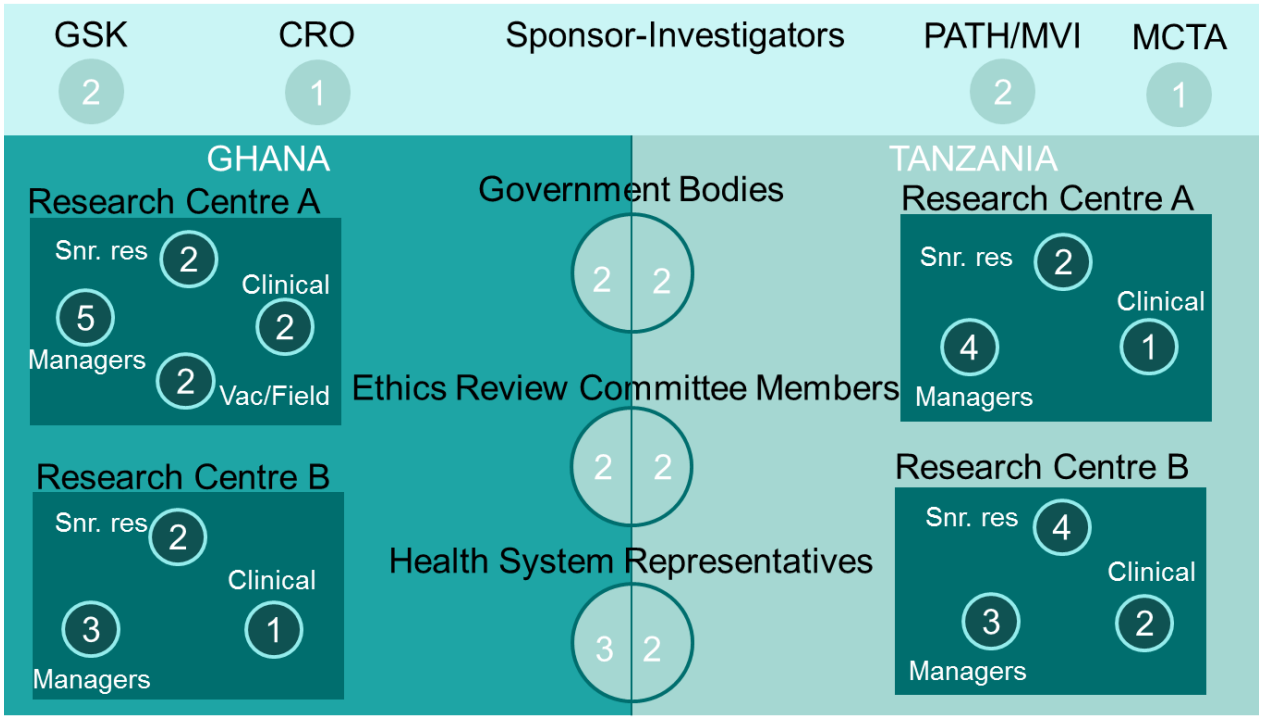

Figure 1: Numerical Values Representing the Number of Respondents in Each Stakeholder Post. GSK, GlaxoSmithKline (vaccine developer); CRO, Clinical Research Officer; PATH/MVI, Malaria Vaccine Initiative (funder-development partner); MCTA, Malaria Clinical Trials Alliance (capacity developer); Government Bodies, Food and Drug Administrations and Ministries of Health; Ethics Review Committee Members, National and Institutional Ethics Review Committee Members; Health System Representatives, Hospital Managers and District Medical Officers; Snr.res, Senior Researchers; Vac/Field, Vaccination nurses or Fieldwork teams (group interviews); Clinical, clinical (medical) personnel; Managers, operational research managers (e.g. data manager, lab manager, fieldwork manager, quality assessment manager)

3.4.2 Qualitative Results

The exact term Health Research for Development was new to respondents, but all were able to interpret the phrase and provide an answer reflecting on their experiences working in international health research. The responses fell into four themes: i) Equitable Partnerships; ii) System Sustainability; iii) Addressing Local Health Targets, and iv) Regional Commitment to Benefit Sharing. Under these themes of Health Research for Development, several recommendations were identified; these are summarised in Table 1.

Table 1: Summary of Respondents' Main Themes and Recommendations on Health Research for Development.

Health Research for Development Themes	Respondent Recommendations
Equitable Partnership	• Conducive research environment • Local research independence • Increased role of local governments • Defined allocation of partner roles • Professional recognition • Engage local communities as partners
System Sustainability	• Invest in local human resources • Advance local skill base • Expansion of institutional research capacities • Health research integrated with health services and local settings. • New employment opportunity • Develop training institutions • Planning for future research
Addressing Local Health Targets	• Research to solve local health problems • Context-relevant health solutions • Inform local health policy decision-making • Health for economic development
Regional Commitment To Benefit Sharing	• Community education • Advance health seeking behaviours • Ancillary care • Post-trial access

3.4.2.1 Equitable Partnership

The results showed that the theme of equitable partnerships in international programmes of health research is an essential aspect of constructing health research for development. The relationship, expectation, and interaction between international and local partners, requires clear definition and an active process of engagement. Professional recognition between colleagues and across partnerships was stated by several respondents as an important mechanism to sustain excellent communication and robust functioning collaborations with supportive communities. Moreover, the distinction between donor-led projects and independent research was raised several times by respondents. In connection to this, the vital role of governments in taking responsibility for health research was also addressed. Respondents identified Health Research for Development as a mechanism to establish conducive health research environments in low resource settings.

Snr. Researcher, Epidemiologist, (GH/A/4): *I would wish that the ministry of health would set out the priorities, but they don't! So it is more donor-driven. Donors come with "ok I want to do this." You put your act together and help yourself by helping them help you. So we can get our money, but it is still donor-driven. They help you to solve a problem, but they dictate what the problem is. That is the downside. So today, if they tell you they want to do something in malaria, and then even though you have Ebola, you have to go with malaria. So we go with it until we build enough capacity and find enough money.*

Establishing capacities to carryout independent research were seen by respondents as central to development, and the key to improving population health.

Snr. Researcher, Epidemiologist (TZ/B/44): *Since the mid-90s we have done work on bed nets. This work on bed nets was conducted over almost a decade, and bed nets now are being used everywhere, they are also being produced in this country, and the Institute is not participating in the production of these bed nets in any way; to the extent that, if the people, who are producing the bed nets, want to do any improvement on the bed nets, they have to ask somebody else.*

Over-reliance on donor-led health research was found to undermine development, innovation and the responsiveness of local health and research systems.

Research Manager (GH/B/25): *It [Health Research for Development] would, for me, be the way to go to eradicate diseases; that is to empower research in Africa. And that would really*

bring development that we are looking for… We are relying solely on foreign aid or funders who come out…, but we don't really see the drive for research to bring along the research that is needed. For me, no one understands the problems of African like the Africans.

Strong partner-relations were seen as an important means to overcome "donor-dominance" and foster effective international collaboration. Communication, professional recognition, and community engagement were identified as key aspects of equitable partnerships.

Clinical, Physician, (GH/A/10): *Obviously relevance comes also from the recognition. It is not enough that you in the district feel that what you do is relevant. It is also that those who are in the metropolis, in the centres, in the ministries, in the universities acknowledge what you are doing, and sort of testify that it's relevant…So I think at the study level recognition is done very well. This study has given individuals that have worked on the study a lot of pride. We have teams of fieldworkers, interact with families, who look at patients, health and longitudinal ways, environmental factors, and I am absolutely delighted that all this is happening in the district.*

A Health Research for Development approach accounts for the community contribution to programmes of health research, and also the costs to the community. In addition, community interests and needs are recognised and accommodated in to the research objectives, and translation of results.

Research Manager, (GH/A/11): *I think what it [Health Research for Development] basically means is to go beyond designing studies, designing research only to get data to publish. It should have an impact on those collecting the data, those whose data you have been collecting. Protocol may be designed to achieve a certain aim or end point, but beyond that there should also be the social intervention in the communities where the study is being done.*

3.4.2.2 System Sustainability

Health Research for Development was often defined as when a study leads to the sustained expansion of institutional research capacities, especially local human resources. Moreover, a few respondents focused on the importance of integrating health research with health services and local settings. Health research programmes designed with a development objective were seen to establish systems which support future research and healthcare services.

Snr. Researcher, Epidemiologist, (TZ/A/52): *Research can bring improvement in infrastructure, improvement in human resources, improvement in accessing maybe healthcare for the community. With my experience with RTSS, actually RTSS vaccine trial brought a lot of development in many ways: Jobs, lots of development, infrastructure - that lab [laboratory] was built under the same trial which now the whole community is benefitting from, because they have state of the art equipment and brought in personnel.*

Health System Representative, (GH/A/06): *I think it is part of the research, to try and identify what you are doing, where you are falling short, and then try to improve. I believe it is a general and total review of all the facilities. I mean all the services, all the components that we have in the system. We should not be at a standstill. It should develop, I mean with time. I believe the coming of this research and others actually is seen as a form of development.*

Investing in training, education and leadership for local research and healthcare teams were identified as major objectives of Health Research for Development and considered very important for sustainable change.

Snr. Researcher, Epidemiologist, (TZ/B/44): *We strongly believe when we do this type of international research we train the people who will be leaders tomorrow and who will make a difference to this country. First, they will get the exposure, they will get the skill, they will get the understanding of what it takes to make changes, and bring innovation.*

Vaccine Developer, GSK, (BE/A/52): *one of the big aspects of this project is that it brought quality jobs and jobs that were key to providing a huge amount of opportunity to African staff. Would it be travel, doing masters, attending conferences, but also you know they are obviously having publications and sometimes access to jobs.*

Snr. Researcher, Epidemiologist (TZ/A/42): *One increases the knowledge in terms of the on-job training or having formal training, changing from having a certificate to diploma, to a degree or a Masters, PhD and so forth that is one in terms of educational development. The second point is in terms of the skills development without having any formal certificate, or formal diploma or formal degree, the skills development that is the on-job training.*

Collaborating with local teams and advancing research capacity can also have a spill-over effect and support the development of the healthcare systems. Moreover, sustained research centres became training institutions for future generations of early-years researchers and healthcare staff.

Snr. Researcher, Epidemiologist (TZ/B/49): *You're giving some new knowledge, improving and providing training to the health care personnel and once that research has come to an end, they will still maintain that knowledge to provide care to the hospital, or the healthcare facility where the research was conducted. That is the way I see it, research for development.*

Ethics Review Committee Member, (TZ/A/35): *You see like we used to have one doctoral researcher, and he was maybe, maybe working with another senior researcher but now he can stand on his own, and he is teaching other researchers.*

Health research operating in local systems also brings new experiences and development opportunities to the wider community.

Snr. Researcher, Epidemiologist, (TZ/B/37): *Some of them [community members] involved themselves as health workers in a clinical trial to help with follow up. Now most of the health workers are involved in other trials. Because from the RTSS we train them, so they have more knowledge and skills. Some of them even went back to school and got other certificates, so you can see how this health research made a development in people.*

3.4.2.3 Addressing Local Health Targets

Most frequently respondents talked about Health Research for Development, in terms of the generation of a successful health intervention targeted at resolving a local health issue.

Funder-developer, MVI PATH, (GH/A/27): *In any given society you have health problems which are slowing down or even hindering the development of a particular society. So if you do research to solve that problem, then it is research for development. That means getting solutions to health issues, which definitely encourages development.*

Clinical, Physician, (GH/A/07): *If 100 children are dying in 100 minutes, and you are able to save 10%, 10 of them, you have gone a long way to save these people who one day may be presidents, head of states, and are able to develop a nation.*

For some respondents, Health Research for Development related to the ability of health research data to inform policy. Development was seen as creating access to new health interventions by advancing national policy and practice with innovative, evidence-based approaches to improving health.

Snr. Researcher, Epidemiologist, (TZ/B/24): *The research evidence is supposed to guide policy decision and programme uptake. So if you look at the context in which we are working now, I am far, far, far in a better position to advise the policy people on the health issues that are occurring and the decisions that they should be taking in order to improve the lives of people in Ghana.*

Structuring research with mechanisms to translate findings into effective policy was identified as an important feature of Health Research for Development. This includes accepting negative results, where a tested intervention is shown to have no health impact.

Research Manager (TZ/B/26): *So even if for example the vaccine that we are trying, if at the close of the day, the results, somebody would describe it as negative, these are still the results, and that is the role the research aspect plays. Research is providing information for policy decision makers to base their understanding and reasoning to decide.*

Many of the respondents made a link between health research and developmental economics, recognizing that improved health would allow governments, communities and individuals more time and money to spend on other activities rather than on addressing ill-health.

Vaccination Team (group interview), Nurse (GH/B/29): *Yeah so it [health research] would help in the development, because if the population is not falling sick, it will help the development of the country, even the children: if they are not sick, then their parents have time to do their own work, then contribute to the development of the country.*

3.4.2.4 Regional Commitment to Benefit Sharing

Regional commitment, to bring better health to local communities, and not just generate more health data is identified as necessary for Health Research for Development. In particular, health research programmes were identified by numerous respondents as vehicles for advancing the health education levels of local communities, and an opportunity to positively change health seeking behaviours.

Government Official (TZ/A/31): *I think in communities where the trials were done, there is actually less malaria now, and I think they [community members] are more educated, because they have been fed information, health information how to prevent and take care. Medical care also, it is usually improved in those trials and those areas where the communities, the trials are ongoing and usually even when the trial ends, usually you will find facilities that are being used and more access to medicines and things like that.*

The presence of an international collaboration brings changes to the provision of care, both for participants and their communities

Snr. Researcher, Epidemiologist, (TZ/B/40): *Health Research for Development, for me, is to ensure that the people around the communities in the area benefit from our presence there. So for example, the insistence, on making sure that the services we provided are not only for the study subjects. The services that are provided are for everybody, meaning that if we are required by international standards, whatever to provide a certain standard of care, this standard of care should be accessible to everyone and for the people in the whole community.*

Post-trial access agreements were identified as a potential benefit of health research to communities if the agreements are honoured.

Snr. Researcher, Epidemiologist, (TZ/A/39): *Like if you tested the bed nets and then confirm that they can reduce the malaria, and then it will be prudent to ensure that we have universal coverage of bed nets in the community that participated in the research; although previous experience has shown that, that has not been the case.*

3.5 Discussion

The results of our qualitative study provide substantial insights into how stakeholders define Health Research for Development. Interpretations of the concept differed between stakeholder groups, but not between the two countries involved in our study (Ghana and Tanzania). All stakeholders agreed that local research and health is an important development goal for international health research programmes. A number of research mangers noted that development enables countries to independently generate contextually relevant solutions to their own health problems. Notably, the funders and governmental bodies interpreted Health Research for Development as research that targets local health priorities. The senior researchers and ethics committee members tended to link health research to health policy and practice and identified the need to translate new research into community health gains. The research teams generally, and especially amongst the vaccination nurses and fieldworkers, those working closest with the community understood health research for development to be the economic benefit that would be gained if an effective intervention, such as a vaccine could be introduced to the community following successful research. These results open up the discussion on how to define Health Research for Development, and show the diversity of impact that health research has when operating in weak healthcare systems. Below we turn to each theme in turn.

3.5.1 Equitable Partnership

Constructing an equitable partnership aligned with local health research priorities is an important baseline for guiding collaboration between local systems and health research partners. The results identified structural features of partnership that promote Health Research for Development and, can counteract distorting influences such as funding (which may distance research projects away from national health research priorities). The three structural aspects are: i) equitable representation of all relevant stakeholders in the research enterprise, ii) integration with the national healthcare system and iii) local research leadership. A locally-led research agenda was described in one interview as a means of "empowerment." Moreover, through research prioritization a culture of deliberation is created, with advocates and beneficiaries of community health leading the process. The outcome of such an inclusive process shapes the design of health interventions, research agendas, and study methodologies to account better for the local healthcare setting and relevant social-economic factors; optimising the social value of international health research partnerships. The creation of an inclusive partnership structure is also an important step to secure the

commitment of local and national governments to better support research and the translation of results.[2] Therefore the relationship between international partners and governments needs to nurture collaborative working, cost-sharing, and coordination of equitable partnerships. Ultimately, sustained systems of health research will only be supported by countries if local actors are involved and appreciate the value of undertaking such work. This country-inclusive approach is a recognised principle of effective international development co-operation.[32]

Markedly, respondents stated that the inflexibility of traditional funding structures within health research programmes continues to distort organisational structures, exclude local stakeholders and skew appropriate alignment between population health needs and health research activity. A Health Research for Development approach requires governance, monitoring and evaluation to ensure that partnerships are equitable from the inception of the research project. For example, this may require that the research enterprise supports leadership training through providing appropriate courses and mentorship. This approach is important to ensure the research is locally led and that those research leaders can take informed decisions on priority setting, strategic planning, and resource allocation.[3] This minimizes the possibility of exploitation and also strengthens local research capabilities and develops the structures of the healthcare systems. Ethically, Health Research for Development defines a partnership structure that fosters local decision-making and global collaboration in health research.

3.5.2 System Sustainability

Health Research for Development was defined by many participants as establishing sustainable health research capacity. For example, the conduct of research and especially the PDP platform provides an opportunity for researchers to exchange research skills, participate in knowledge-sharing, develop centres of excellence and, build-up professional networks. The research process is equipped to build sustainable capacities across partnerships in low-resource settings. The concept makes these opportunities an objective of a research partnership, and this was exemplified in the case of the GSK/PATH MVI malaria vaccine candidate trial through its collaboration with the Malaria Clinical Trial Alliance (MCTA), supporting clinical trials site development in Africa.[33] A similar approach has also been taken by other partnerships such as International AIDS Vaccine Initiative (IAVI), over the course of developing a vaccine against Aids and, Drugs for Neglected Diseases initiative (DNDi) while working to combat neglected diseases.[34-36] Health research

generally in a low resource setting may as a consequence bring some new opportunities to a region, but the objective of Health Research for Development is to actively plan research to integrate with local healthcare settings, mobilise necessary infrastructure and, exchange skills to construct a sustainable system. Respondents reported that additional training, education and mentorship best supported local system building. To establish this, it is important to define an explicit development component with an agreed plan of action in a research project.[37]

Moreover, collaborations that take steps to move away from unbalanced partnerships to ones of shared ownership demonstrate a commitment to the Health Research for Development objective. As a respondent noted, "one study does not make a research centre." Affording ownership and building capacities promote a research project from an individual study, towards the development of a research platform.[2, 38] The ability to sustain capacity was raised throughout the interviews. How it is achieved varies between programmes, but typically requires establishing structures that are financially independent with local autonomous decision-making powers. [37] To build sustainable research capacity into research partnerships, stakeholders need to address the barriers and opportunities to sustain system developments; for example, maintenance of equipment and incentives to retain highly skilled researchers locally.[39]

Endorsing a development objective in health research is not merely an operational decision of capacity strengthening.[37, 40] Research partnerships do not only bring finances, but they also create a forum for communication, sharing expertise, building trusted professional relationships, and coordinating multi-sectoral partners. Constructing such a conducive research environment provides the conditions in which locally-led systems can be built to deliver on evidence based practice, treatment and disease prevention.[41] Building a community of local researchers that are engaged in a global network shows respect and solidarity for communities with urgent health needs, and overtime will strengthen health security globally.

3.5.3 Addressing Local Health Targets

Delivering on improvements to local health was described in the interviews as an important aspect of Health Research for Development; both through improving health capacity for the communities and by improving the translation of findings into public health action. It was recognised by all the stakeholders of the research partnership that health research had the potential to target local health through different means: establishing health education, providing additional ancillary care in health

services, improving health research skills and infrastructure and, through delivering new health interventions. This broad understanding of how health research supports local health is outlined in recent literature which discusses the true effects of health research for local study populations. Arguably, there is both a trial effect and an infrastructure effect.[22, 42, 43] Industry and ethics guidelines tend to focus on direct trial effects and have given less consideration to infrastructure effects, and the responsibility to contribute to research capacity - a pillar of health system development.[42] This discussion brings into question the public health value of health research for resource-limited regions. Health Research for Development promotes the goal of public health through addressing the broader ethical considerations of equity and improving local health capabilities. Critical for addressing local health targets is the adequate framing of development objectives through knowing the country specific context. This requires comprehensive mapping of mapping the social, health, legislative and political setting.

3.5.4 Regional Commitment to Benefit Sharing

An effective Health Research for Development approach demonstrates regional commitment by enhancing translation of health research into good health policy and practice, and this was strongly emphasised by senior researchers and ethics committee members as the key function of Health Research for Development. However, this component of many research programmes has been identified as the major weakness, and greater support is needed for research to deliver on policy recommendations, improved standards of care and creating access to new interventions.[3] The strength of conducting health research in local contexts allows a health intervention to be evaluated with awareness of socio-economic determinants, local care seeking behaviours, and barriers to access along with an appreciation for regional resource constraints.[44] This broad understanding of an intervention’s effectiveness in a particular setting enhances the value of the research for beneficiaries through facilitating the dissemination and translation of results.[45] Moreover, Health Research for Development advocates decentralised health system decision-making to facilitate translation, engaging communities, healthcare facilities, and policymakers along the pathway.[46] The aim being to establish regional commitment and overcome the communication gap often reported to exist between researchers, health systems, and policy makers.[46] Research dissemination through a decentralised system of health facilitates communication and enhances local commitment, political uptake and the responsiveness of new health interventions to local

settings.[47, 48] As respondents noted, the design of research programmes must account for the translational factors very early on in research planning to best achieve the goal of improved health.

3.6 Limitations

This study was subject to some limitations. One limitation is that the results may not be relevant to other programmes of health research. The research programme was a phase II/III clinical trial for a paediatric malaria vaccine candidate and the budget included skills and site capacity building. As noted in the literature, clinical trials are often better funded than other programmes of health research and tend to undertake important development initiatives in the regions where they are conducted.[42] However, the presence of PDPs and the testing of vaccines in resource-limited regions is becoming a more regular occurrence, and this response group is representative of such studies. The fact that we involved two different countries, Ghana and Tanzania, one in West and one in East Africa also adds resilience to the findings. Secondly, respondents were speaking in English, which for the majority of respondents was their second language, and this may have altered how responses were articulated, or analysed.

3.7 Conclusion

The concept of Health Research for Development has been the focus of recent campaigns and guidance documents. This study is unique in providing empirical evidence on how to define the concept from the perspectives of stakeholders working in international research partnerships in Ghana and Tanzania. The results identified four major themes, namely, Equitable Partnership, System Sustainability, Addressing Local Health targets and Regional Commitment to Benefit Sharing. Six learning points for achieving Health Research for Development were distilled: 1) Ensure there is local research leadership working in collaboration with the PDP, and healthcare system, to align project agenda and activities with local research and health priorities; 2) Know the country specific context - map the social, health, legislative and political setting; 3) Define an explicit development component and plan of action in a research project; 4) Address the barriers and opportunities to sustain system developments; 5) Support decentralized health system decision-making to facilitate the translation pathway; 6) Govern, monitor and evaluate the development components of health research partnership.

Finally, the opinions and experiences of stakeholders of international health research show that an unequivocal commitment to equity and unity between partners is required to construct health research for development.

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4 GLOBAL RESEARCH AND LOCAL HEALTH CARE

Ward, C.L., Shaw, D., Anane-Sarpong, E., Sankoh, O., Tanner, M., Elger, B, The Ethics Of Health Care Delivery In a Paediatric Malaria Vaccine Trial: The Perspective Of Stakeholders From Ghana And Tanzania. Journal of Empirical Research on Human Research Ethics, 2018, 13.1: 26-41.

4.1 Abstract

Objectives: This study explores ethical issues raised in providing medical care to participants and communities of low resource settings involved in a phase II/III Paediatric Malaria Vaccine Trial (PMVT).

Methods: We conducted 52 key informant interviews with major stakeholders of an international multi-centre PMVT (GSK/PATH-MVI RTS, S) (NCT00866619) in Ghana and Tanzania.

Results: Based on their stakeholder experiences the responses fell into three main themes: i) Undue Inducement; ii) Community Disparities; iii) Broad Therapeutic Misconceptions

Conclusion: 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 favourable 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.

4.2 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.[1] As a result, scientists seek to find a malaria vaccine suitable for African children could be a valuable complement to existing control measures.[2] To evaluate the safety, efficacy and protectiveness of a possible paediatric 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 children in any setting because of their vulnerability, inability to give informed consent and increased propensity to adverse reactions. [3, 4] Moreover the regions where the PMVT takes place are in general low resource settings characterized by weak healthcare systems, under-funded public health facilities, drug shortages, unmet population healthcare needs.[5-7] 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).

4.3 Ethical Guidance on Providing Health Care in Research

Ethics guidelines for conducting research in international settings - in particular The Declaration of Helsinki (DOH) by the World Medical Association (WMA),[8] and The International Ethical Guidelines for Health-related Research involving Humans by The Council for International Organizations of Medical Sciences (CIOMS) [9] - clearly state that there is a duty for research teams to provide over the course of a trial. The requirement of researchers to provide adequate health care is advocated for on four broadly accepted premises: “the welfare principle, rule of rescue, justice, and entrustment.[10-12] 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. 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. [12 - 20]

The positive impact that can be made by integrating research into a given health and social system are widely documented.[6, 15-17] 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 (approx. 4 -6 years). Long term benefits have also been reported regarding improved physical infrastructure, better-trained staff, and community health seeking behaviours. While few would argue with the goal of providing healthcare over the course of conducting a PMVT in a community, the complexity and sensitive nature of the responsibility requires scrutiny. Providing extensive healthcare in the course of a research programme 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 healthcare provided in low resource setting research. First, there is a question of disparity. Improving access for one part of the population but not another can increase regional and community inequalities, especially in impoverished settings. Even to improve one section of a hospital but not the rest can create social tensions.[5, 18] Second, when access to healthcare becomes the main incentive for a parent to enrol their child in a trial, then the appropriateness of this inducement needs to be carefully assessed.[19] For example, is a participant that has no access to healthcare able to weigh up the risks of entering into a trial? Third, the provision of the PMVT health care may erode trust in routine public health services. [17] Fourth, another major concern relates to the study power. When the healthcare experience in a program of research is significantly improved (but different) compared with the "real-world" setting, it may not be possible to see all effects of a new intervention within the frame of a phase III trial. For example, In the RTS, S malaria vaccine study, 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."[2] These challenges present the difficult balance between protecting research participants and obtaining intervention data for the social good.[20] Underlying all of these issues is the inherent conflict between the different objectives of healthcare service provision and health research. The defining goal of health research is the generation of generalizable knowledge and not the promotion of individual patients' health ("best interest").[21, 22] As Pinxten states, "there is an ethical

rationale to separate research from routine care where possible. Routine care and clinical research each have their own agenda."[23] However what is ethical becomes more nuanced and convoluted when hosting 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. Moreover, where the international research collaboration has the expertise, proximity and finances to respond to participants unmet healthcare needs, this arguably gives rise to a general duty of rescue.[21] That said, for the two activities to become inextricably interlinked can lead to participants misconception on the role, objectives and limits of health research.[21, 23]

The objective of this paper is to address the ethical issues raised by provision of healthcare during the conduct of a longstanding PMVT in resource constrained settings. The results and discussion present the challenges and responsibilities associated with the special contract of trust that forms in the relationship amongst the research team, health care system, the participants and local communities.

4.4 Methods

A key informant, semi structured, interview method was selected to understand stakeholder perspectives on the practical considerations and ethical challenges of delivery healthcare in the course of a paediatric malaria vaccine trial.

4.4.1 Study Population

All respondents were involved in the conduct of an international malaria vaccine candidate trial carried out in Ghana and Tanzania between 2009 and 2014 (GSK/MVI, RTS, S). The vaccine candidate trial and the two specific countries of Ghana and Tanzania were selected with the assistance of the Swiss Tropical and Public Health Institute. The interview respondents (clinical and research team members) were recruited from four separate research centres:

Ghana: (1) Malaria Research Centre, Agogo Presbyterian Hospital, School of Medical Sciences, Kwame Nkrumah University of Science and Technology, Kumasi; (2) Kintampo Health Research Centre, Ghana Health Service, Kintampo.

Tanzania: (3) Bagamoyo, Ifakara Health Institute; (4) Tanga Research Centre (NIMR), Korogwe, National Institute for Medical Research.

In addition, the wider partners of the PMVT were also included: government bodies, ethics review committees, and healthcare system representatives. The international partners were also included as respondents: GSK, Clinical Research Officer (CRO), PATH/MVI and, MCTA.

The map on the next page (Figure 1) presents the geographical locations of the research centres and shows the 2009 malaria endemicity across the Africa region.

4.4.2 Sample

Individual semi-structured 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 (involved four individuals per group). Fieldworkers are members of the local community employed in community liaison roles to inform, support and communicate with the PMVT participants (mothers and infants) and the research teams.[24] Full list of stakeholders set out in

Table 1 and Figure 1 in section 4.4.1.

The interview strategy was designed following consultation with local partners at all the research centres during a preliminary scoping visit. A scoping visit by the authors CLW and EAS to Ghana and Tanzania was carried out in January 2014. The method was designed through a participatory process with the advice of local partners. The interview data was collected independently by the corresponding author. Local country partners and institutional contacts facilitated the recruitment of eligible interview respondents. Invitations with additional study information were sent out to potential respondents.

The specific PMVT roles of respondents and research centre association have been withheld to protect the anonymity of the interviewees.

4.4.3 Study Instrument

A semi-structured interview guide was developed following a review of the current literature. The guide was developed with a qualitative methods advisory group consisting of the paper's authors, qualitative research methodologists and country experts from Ghana and Tanzania. The interview was then piloted with medical researchers based at Swiss Tropical and Public Health Institute (Swiss TPH) who have extensive experience of conducting clinical trials in resource limited regions (in particular 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).

4.4.4 Ethical Approval

Permission to proceed with this study was provided by the GSK/MVI Ancillary Studies Review Committee on 18th July 2014, along with signed agreements from all the requested health research centres. 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). It was also approved by each country, Ghana: Ghana Health Service Ethics Review Committee, Kintampo Health Research Centre, 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 National Institute for Medical Research (NIMR); Ifakara Health Institute IRB. Tanzania Commission for Science and Technology (COSTECH);

4.4.5 Informed Consent

The corresponding author, CLW, conducted all 52 interviews in English between November 2014 and September 2015. All respondents were notified that the interview audio would be recorded. Written and oral informed consent was obtained ahead of the start of a respondent interview. The informed consent process informed respondents that interviews would be saved under a non-identifiable 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).

4.4.6 Interviews and Transcriptions

Interviews lasted between 35 minutes and 2 hours (50 minutes on average). Respondents answered various questions around the role and responsibilities of multicentre international vaccine studies in resource limited regions. This paper presents results on one aspect of this interview, the relationship between the PMVT and the healthcare services where the study is conducted. Author CLW transcribed 40 interviews in full, and 12 interviews were transcribed by two departmental assistants, and then reviewed for accuracy by author CLW. Departmental assistants were subject to the same terms of project confidentiality.

4.4.7 Data Analysis

The interview transcripts formed the basis of raw data for this research. The transcripts were read multiple times by CLW and DS ahead of coding. Author CLW coded all the transcripts with

qualitative research software MAXQDA. Repeated ideas were identified across the transcripts and constituted into sub-themes. The sub-themes were then grouped, and this led to the establishment of themes, and the development of theme narratives.[25] To minimize researcher bias, author DS consolidated the coding by reviewing all codes, and sub-themes to ensure agreement and consistency in theme-definitions and groupings.

In the results (section 4.4) we first describe the disposition of the respondents (4.4.1) and then the qualitative data by themes (4.4.2).

4.5 Results

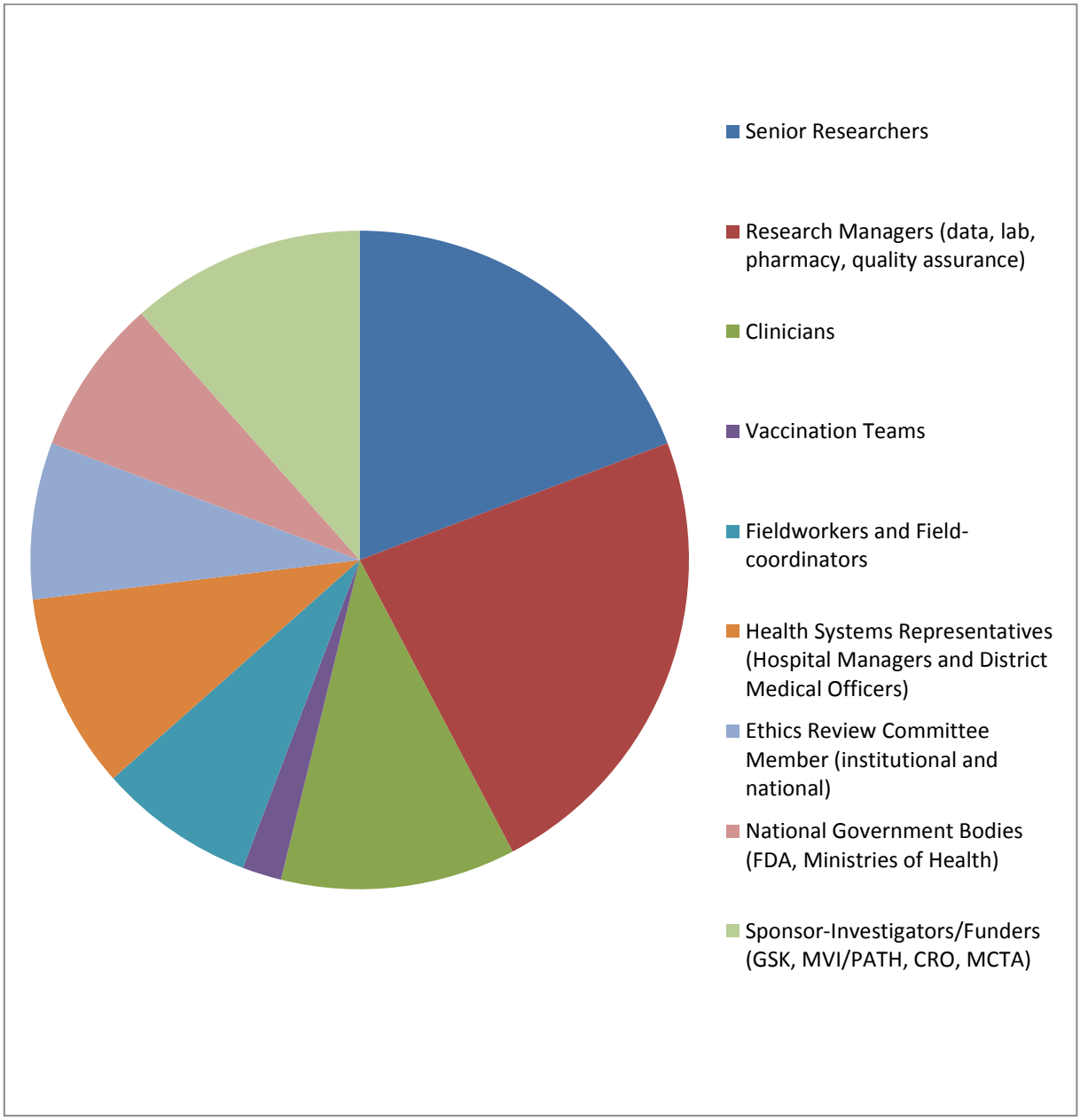
4.5.1 Respondent Disposition

In total 52 interviews were conducted. See Table 1 for a summary of the respondents' categories as a total, by country and institutions and see Figure 1 presenting stakeholder roles.

Table 1 Number of Respondents shown as a Total, per Country and Institution

Group	Number of Respondents
Total	52
Ghana	
Research Centers A, GH	11
Research Centre B, GH	6
Ethics Review Committees	2
Health System	3
Government	2
Tanzania	
Research Centre, A, TZ	7
Research Centre, 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 Trial Alliance (MCTA)	1

Figure 1 Pie Chart Presentation of Respondents Roles in the Paediatric Malaria Vaccine Trial



4.5.2 Qualitative Results

The interviews (N=52) were coded and three major themes emerged: i) Undue Inducement, ii) Community Disparity iii) Therapeutic Misconception. The results are presented under these headings:

4.5.2.1 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, if he is not even interested, all he knows is that he is going to get some benefits from it. 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 paediatric 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.

Snr. Researcher, Epidemiologist (TZ/A/44): *We already knew that they will get better care with the level of personnel that we have and, the standard procedures that we say 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 enrol 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-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 comes out. 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 provided safeguards against research harms, and poor health.

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

4.5.2.2 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 local standard of care.

The topic of disparity, and the difference it made to 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 costs removed.

Clinical, Physician, and (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.*

Snr 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 program has been very sick as compared to the one who was part of the program.*

Snr Researcher, Epidemiologist (TZ/B/30): *Even when we wanted to share the workload, the community would prefer to come see the physician who is employed by the project. 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.

4.5.2.3 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.

4.6 Discussion

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

4.6.1 Undue Inducement

Undue inducement is addressed in ethics guidelines and literature as an incentive that persuades a participant to volunteer against their better judgment or deeply held beliefs.[9, 26] 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 Mothers had full appreciation of the possible risks of research for their Infant.

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 favourable risk– benefit ratio.[26] 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 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. A further safeguard against undue inducement that may be considered would be to have the informed consent processes, and guidance on risks delivered by an impartial team who have no interest in the study recruitment numbers.[9] Technology can also support this process. A mobile phone platform could assist in educating and objectively assessing mothers' comprehension of the risks of research with, for example, a mobile phone survey. The appropriate strategy has to be determined by the community context and setting. Defending against undue inducement is essential for the conduct of safe and ethical studies. Inducement of healthcare can place a child's health at risk and potentially lead to harm.

The interview responses showed that access to healthcare remains the main reason for mothers to enrol their infants in the PMVT, in line with recent literature. [5, 15, 28-34] 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 healthcare may not amount to undue inducement, the participants' voluntariness is compromised. This makes participants vulnerable because participating in health research should not be a prerequisite for obtaining access to healthcare [23, 35, 36] However, in the absence of social-political and structural change on the ground, researchers and fieldworkers must navigate this ethical responsibility of upholding robust consent procedures in a context of limited community healthcare options. Where the provision of care in a context of suffering is at odds with the freedom of choice, this needs to be recognized as a vulnerability, but not a barrier.[37] Protecting against this vulnerability requires the research to be responsive to local health needs.[8] The research must be introduced to the community with caution. [38, 39] This requires careful application to the appropriate ethical, regulatory and political (including local leaders and opinion-makers) committees. In addition, where possible it is important for research programs to identify the influencing factors and attempt to eliminate these aspects as far as possible. For example, as the medical staff commented on in this study, the PMVT provided sufficient medical staff to meet the needs of the research and the routine paediatric care ward. Lastly, reporting on situations of ethical concern 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 will also contribute to strengthening the local health system.

4.6.2 Disparity

A concern raised by supplementing a weak healthcare system with the resources from a PMVT is that doing so may increase community disparities. The standard of care selected for a trial is critical to addressing this concern.[40, 41] 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 the official national guidelines. In practice, this still requires that under-resourced public district hospitals had to be improved even to meet national standards. The clinicians involved in the PMVT emphasized that they treated all patients equally, and the same treatments and procedures were provided at the paediatric 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 non-participants. In addition, all direct and indirect costs of healthcare 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.[5, 42, 43] In addition unequal treatment may incentivize those not profiting to seek healthcare elsewhere, for example using unregulated drug stores or traditional healers, and this can further exacerbate poor health outcomes.

Poorly planned medical components of research projects can leave participants feeling used and with the view that the healthcare system is uncommitted.[44] [5] The challenge is to retain the independence of the research program from the health services and yet support a functioning partnership with the community.[32] One example presented by Pratt et al., defines a situation where a research unit in a region with no healthcare joined with a medical NGO into a single organization, to fulfil the moral obligations of providing care for a wider population, while gathering research data.[45] Devising the appropriate medical care plan for the setting regarding the nature, coverage and time frame of the care to be given is crucial to alleviate the risks caused by community disparity.[4]

Practical and ethical issues also arise unplanned, 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.[10] This can be hugely beneficial to the communities and healthcare settings, both for providing additional health resources, and also as a mechanism to evaluate, inform and strengthen local healthcare procedure. Our participants and the literature seem to be in agreement that a research team should not undermine or absolve the public health service of their responsibilities and funding commitments.[26, 33] [46] To maximize the learning opportunity between the research and the healthcare system, all unplanned healthcare 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 healthcare during a PMVT is that a disparity exists between the research healthcare 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 (under resourced) public health facilities in the wider population. This improved healthcare 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.[40] These known affects must be accounted for in the study design, and post licensure surveillance strategy in order to deliver quality data, assure compliance with ethics, limit harm and retain trust in research.

4.6.3 Therapeutic Misconception

The precise definition of therapeutic misconception is debated in the literature, but in the round, it is understood as a participant failing to understand the intent of research, and equating the activity of research to health care.[47] There was agreement across the interview responses that the integration of the PMVT and supplementation of healthcare services had the potential to give rise to a therapeutic misconception because the two services were very closely interlinked. The shared components of the clinical trial with the healthcare 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 fieldworker who stated that the community members referred to them as "family." Equally a recent paper by Angwenyi, V., et al, defined the function of the PMVT in a local health system as a “short term complex health service delivery intervention.”[5] This very close relationship may pose a risk because communities become dependent on the health research team for access to healthcare if the care is not absorbed into routine district health care services. Creating dependency both fosters a therapeutic misconception and 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.[48].

Another factor fuelling a possible therapeutic misconception is that communities’ previous knowledge of health research will have been limited or non-existent, whereas experience with hospitals is more common place. Therefore, as the fieldworkers stated, the natural association from the community perspective is that the healthcare providers, or those who are providing healthcare, are acting to directly benefit their health.[49] The roles, responsibilities, and objectives of the two enterprises become conflated. Clearly defining and introducing the goals and interests of research into an existing healthcare 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 other aspects of child health and 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 healthcare undermines informed consent processes and the participant's autonomy. It will also place healthy infants health at risk.[50] It is therefore very important to design and establish a context-relevant education strategy for communities. Information provided to participants must communicate the objective of the health research, the relationship of the research with the healthcare system and also, distinguish the differences between the two activities. For example presenting the key aspects of research compared with healthcare in the informed consent process and, display illustrative posters at clinic visits to ensure participants comprehension.[47, 51]

Furthermore, if a participant contracts the disease (e.g. malaria) that they believe they should be protected against, then this may also damage their 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 programs of public health. Notably, it was clear that the PMVT study took extensive steps to prevent risky behaviour through education on alternative malaria prevention and the administration of bed nets to mother and children; this also help reinforce the message that there was no guarantee of protective effect from the candidate vaccine.

The results have shown that managing the realities and expectations of the study participants is challenging, especially since the concepts of a trial are highly technical (randomization, placebo, protectiveness) 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.[49] Issues of therapeutic misconception must be explicitly identified and addressed in the research protocol and furthermore held to account by ethic review processes. The Table on the next page (Table 2) presents on overview of recommendations to defend against ethical challenges in the delivery of healthcare with programmes of research.

Ethical Considerations	Reccommendations
Undue Inducement	• Employ culturally-relevant and context-appropriate tools to actively explain risks and evaluate participants' comprehension. • Require a favourable risk/benefit ratio. This is ensured by locally responsive research that has undergone appropriate scientific, ethical, legal, cultural and political review. • Establish a shared reporting system with the healthcare setting to record and evaluate ethical issues and solutions.
Disparity	• Engage with the local healthcare system and come to a joint agreement on the standard of care, nature, coverage and time frame of supplementary support. • Uphold the independence of the research program from the health services and support a functioning partnership with the community. • All unplanned healthcare 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. • Acknowledge and address the effect health care provision may have on study power and methods.
Broad Therapeutic Misconception	• Design and establish a context-relevant education strategy for communities. • Communicate the objective of the health research, the relationship of the research with the healthcare system and also, distinguish the differences between the two activities.

Table 2 An Overview of Ethical Responsibilities and Best Practice Recommendations for Health Care Delivery in the Course of Research.

4.7 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.

4.8 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 favourable 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 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 healthcare per se is not problematic where the study risk-benefit ratio is favourable. 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 the 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.

4.9 References

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5 END OF TRIAL OBLIGATIONS

Ward, C.L., Shaw, D., Anane-Sarpong, E., Sankoh, O., Tanner, M., Elger, B, The Ethics Of End Of Trial Obligations In A Paediatric Malaria Vaccine Trial: The Perspectives Of Stakeholders From Ghana And Tanzania. Journal of Empirical Research on Human Research Ethics, 2018, 13.3: 258-269.

5.1 Abstract

Objective: This study explores stakeholder experiences and perspectives on end of trial obligations at the close of a phase II/III Paediatric Malaria Vaccine Trial (PMVT) [GSK/PATH-MVI RTS, S) (NCT00866619].

Methods: We conducted 52 key informant interviews with major stakeholders of an international multicentre PMVT in Ghana and Tanzania.

Results: Based on their stakeholder experiences the responses fell into four main themes: i) Communicating End of Trial; ii) Maintaining Healthcare Services; iii) Dissemination of Results; and iv) Post Trial Access.

Conclusion: Interviewee responses shared important practical experiences and insights that complement current thinking in the literature on research ethics guidance. Based on the interview findings the following recommendations emerged: 1) End of trial communication must be accompanied with information on personal and family healthcare responsibilities; 2) Establish public health indicators to measure the impact of research on a healthcare system; 3) Design a gradual exit strategy from a healthcare setting with opportunity to address unplanned events; 4) Endorse a principled approach of continuity of care when designing a health care service handover, and; 5) Devise an actionable post-trial treatment access pathway with diverse stakeholder representatives.

5.2 Introduction

The global health community ranks immunizations against infectious diseases amongst the most cost-effective public health interventions for reducing global child morbidity and mortality.[1, 2] A natural consequence of this drive for new childhood vaccines is the need to test 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 under 5 years of age against disease. This empirical ethics project adds to current literature on what makes research in vulnerable populations ethical. In particular the focus of this article is on the end of trial obligations. At the close of a pediatric malaria vaccine trial (PMVT), from the perspective of stakeholders involved with a PMVT operating in Ghana and Tanzania. The study is based on the perspectives of stakeholders involved with a pediatric malaria vaccine trial (PMVT) conducted in Ghana and Tanzania.

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" [6] 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" [7] It rather reframes the scope of possible benefits to "interventions identified as beneficial in the trial".[8] On a narrow reading, this change appears to restrict the end-of-trial responsibility of research programs and no longer addresses the fact that, by the very nature of health research, many trials do not result in any effective intervention for participants and the local .[9] A further consideration, Weigmann adds is that "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."[10] This has led commentators to argue for various alternative forms of benefit sharing models with the Fair Benefit Framework being the dominant alternative. [11-15]

Although differing approaches to benefit sharing are debated, the concept itself is generally accepted and required as a vital component of the social value of research. [16, 17, 18]

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 [19-24]. 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.

5.3 Methods

A semi structured 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 centres of 7 African countries between March 2009 and January 2014 (GSK/MVI, RTS, S).[25-27] 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-investors). The results reported in this article are part of a larger research project on Good Collaborative Practice in Low Resource Settings. The results in this paper 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; see Ward et al. (Developing World Bioethics 2017), and The Ethics of Health Care Delivery in Research, see Ward et al. (The Journal of Empirical Research on Human Research Ethics (JERHRE) 2018). These earlier papers provide extensive detail on the methodology used in the interviews. In this current article, we have analysed 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.

5.4 Results

5.4.1 Respondent Disposition

The figures (Figure 1 and 2) below describe the disposition of respondents. In total there were 52 key stakeholder interviews. Figure 1 presents the roles respondents had in relation to the PMVT. Figure 2 describes the stakeholders by country location.

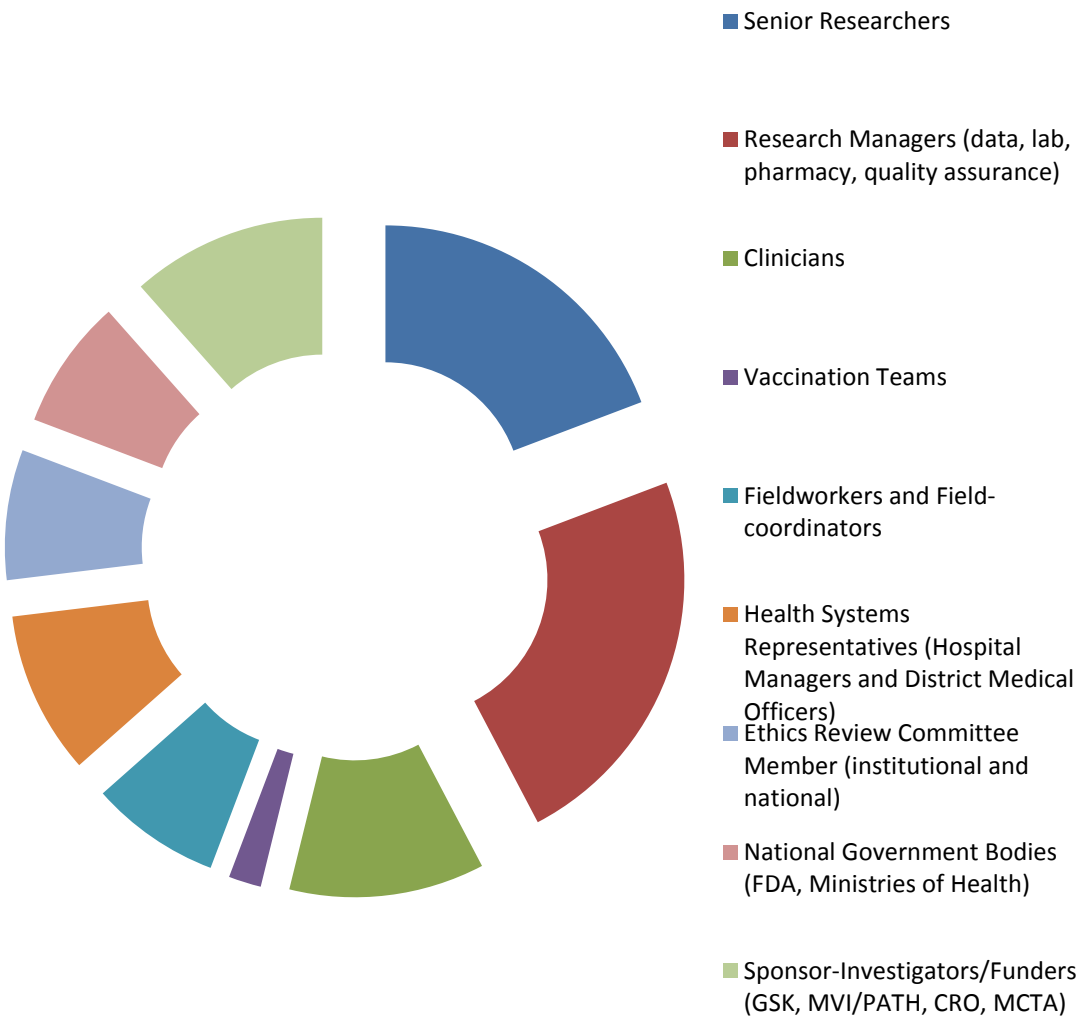

Figure 1 Loop Chart Presenting Respondent Roles in the Paediatric Malaria Vaccine Trial

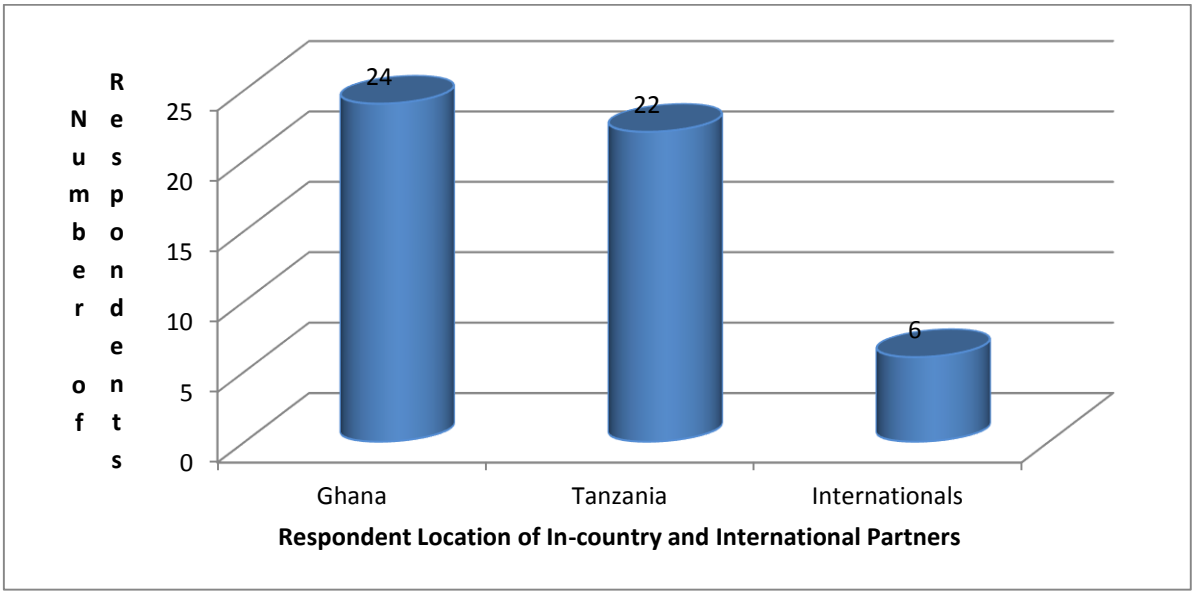

Figure 2 Bar Graph Presenting Country Locations of Respondents

All interviews in Ghana and Tanzania were face-to-face. Interview with the wider international partners were a mixture of face-to-face, phone and skype depending on the respondent location. The results present stakeholder considerations at the end of the PMVT.

There were four main result themes: i) Communicating End of Trial; ii) Maintaining Healthcare Services; iii) Dissemination of Results and iv) Post Trial Access.

5.4.2 Qualitative Results

5.4.2.1 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 both in terms of their connection with the research program and their access to healthcare services.

Snr Researcher, Epidemiologist (GH/B/27): *For the field it was very critical for us to get in touch with our field worker, 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 end of study communication with the community.*

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 healthcare advantages end.

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

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.

Fieldworker (GH/A/33): *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 side effect that maybe will take four or five years before you will experience it.*

Expressing appreciation and thanking participants and communities for their participation was an important aspect of disengagement and maintaining trust.

Snr Researcher, Epidemiologist (TZ/A/52): *We gave them certificates that the study has ended, so that every group that was graduating from the study were given this certificate, thank you for participation. The village leadership was also notified when the study ended, and of course the district was also notified*

Many of the medical doctors spoke of the importance of encouraging participants to continue to use the healthcare services even after the end of the PMVT. There was differing opinion amongst respondents on whether health gains and positive health seeking behaviour could be sustained in the community without the support of the PMVT.

Clinical, Physician, (GH/A/10): *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.*

Research Manager (TZ/B/49): *Because we gave them education, 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 transport fee, 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.

5.4.2.2 Maintaining Healthcare Services

The topic of maintaining improved healthcare services and infrastructure after the end of the PMVT was raised by most stakeholder representatives. There is a tension 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.

Ethics Review Committee Member (GH/B/19): *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.*

Snr Researcher, Epidemiologist (TZ/B/17): *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 on having the structure. 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.*

The research centres reported that the infrastructure and equipment remained with the hospitals and available to communities. However there was concern over the cost of maintenance.

Snr Researcher, Epidemiologist (TZ/A/41): *We handed back the Ward [to the local health authorities]. The paediatric Ward with all the facilities which were there, which were bought by the project, so it was handed back to them, 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 by, routinely by other people…The problem I see is the maintenance…because the government cannot afford it.*

Snr Researcher, Epidemiologist (TZ/A/44): *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.*

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

Clinical, Physician, (TZ/B/51): *The nurses there have been here most of the time, have the training 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.*

Conducting the PMVT in a healthcare setting offered various learning opportunities. One medical doctor described how the PMVT had discovered the extent of anaemia in their community and employed a nutritionist in the paediatric ward to support families; this service was 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.

Snr Researcher, Epidemiologist (TZ/A/43): *Yeah, there are no longer any specialist clinicians but my impression is that during this interaction which lasted for about five years. I want to believe that it changed these juniors who are now in the hospital, and they are now practicing much better than before.*

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

Snr Researcher, Epidemiologist (TZ/B/36): *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.*

Vaccine Developer, PATH, (TZ/A/13): *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.*

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

Government Official (GH/A/11): *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 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 programs are part of our annual programmes.*

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

Clinical, Physician, (GH/A/07): *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.*

5.4.2.3 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.

Vaccine Developer, PATH, (GH/A/05): *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.*

There was agreement amongst stakeholder responses that dissemination of results was not reserved only for the end of the study. It required a strategy that continually informed regional stakeholders over the course of the PMVT.

Snr Researcher, Epidemiologist (GH/B/24): *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 from the word go in the progress of the work.*

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

Vaccination Nurse (GH/A/23): *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.*

Snr Researcher, Epidemiologist (GH/B/21): *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 down to that level of people's understanding.*

Vaccine Developer, PATH, (GH/A/05): *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.*

5.4.2.4 Post-trial Availability

The issue of post-trial availability was mainly discussed amongst ethics committee members. This is the concept that any successfully developed intervention (e.g. malaria vaccine) will be made available to the communities where the research took place (DoH, CIOMS).

Ethics Review Committee Member (GH/B/19): *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 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 (TZ/B/37): *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 concentration.*

It was mentioned by a few respondents that the logistics, organisation and planning of post-trial availability requires many stakeholders beyond the researcher team. However all the respondents explained that the negotiating was between the ethics committee and the research teams.

Ethics Review Committee Member (GH/B/15): *Many times they [The research team] will already have the World Health Organisation involved in the vaccine that they are going try, and updating them on the progress, so 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 they will be looking at the bills, and figuring out what does it mean financially to them to do that.*

Establishing a mechanism for post- trial access requires establishing a system of country preparedness to be able to roll out the product.

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

The concept of post-trial commitments was also challenged in the context of a PMVT because to bring a vaccine to market requires further testing and extensive regulatory review before receiving permission to be licensed and rolled out.

Snr Researcher, Epidemiologist (TZ/A/39): *Like a vaccine trial you can not 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.*

Although post-trial access is arguably a long term consideration, a need for early planning is required with appropriate stakeholders.

Ethics Review Committee Member (TZ/B/43): *I mean for example hepatitis B vaccine has been you know the standard of care in Europe and US for many years, before we could get it into our people here, if you want to get a hepatitis B vaccine, I remember when I was going to study, I was required to have a hepatitis B vaccine I had to go and get in it under a private hospital here, and it was not cheap, it was very expensive. So there are all these dynamics on who needs the product and how can you get it there. 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 seen from previous products, the lessons, and they saw the need to engage the national governance 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 ministry of health, from ministry of finance, ministry of women, children, from research institutions, from academia. You need like a mixture of experts of policy, who need to sit and look at the decision making framework.*

5.5 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.

5.5.1 Communicating the End of the 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 instil 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. [29].

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 behaviours 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 behaviour 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 centres. For example, one research centre 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 centres 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 behaviour 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.

5.5.2 Maintaining Healthcare 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 [3, 30] To maintain 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.[31]. 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 healthcare setting. Involving a capacity developer partner could help with this aspect. For example the Malaria Clinical Trial Alliance, capacity-developing organisation, accompanied the PMVT, or an alternative option would be to involve an organisation such as COHRED who offer helpful monitoring tools, such as the Research Fairness Initiative (RFI).[32] Impact data will help inform shared system learning and increase the overall social value of the collaborative partnership. In addition, this data can 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 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, [4] [7] [33] [35] there is very limited guidance on community debriefing at the end of a research study.

Across the responses, there was the general sense that maintaining continuity of care for the participants would be advantageous but there was less clarity over how to achieve this. The research teams explained that the infrastructure and additional equipment from the PMVT are left to the hospitals for the general benefit of the community. However the issue of whether future maintenance costs could be covered was raised several times. Especially in respect of equipment which used disposables such as x-ray film and biochemistry reagents. The fluctuation in services is a concern because it has the potential to create distrust in the local public services, and to demoralize hospital staff.[36] An international collaboration creates an opportunity of mutual learning between systems, and to be most advantageous it is important to also establish mechanisms that can sustain these improvements. Notably, skills and

education training with local research teams and health professionals were considered sustainable because these skills had the potential to be passed on to colleagues throughout the hospital setting. On the other hand, it was also mentioned that additional healthcare professionals brought in by the research were disbanded at the end of the trial. In particular, it was mentioned that it was the more specialised health practitioners that were no longer employed by the hospitals, for example that paediatricians or nurses specialized in handling severe malaria cases.

An exit strategy needs to account for the disruption to local healthcare services and possible harm that can be caused in dismantling health services.[37] Moreover, as an ethics committee member mentioned: "it does not sound right." 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. Harnessing best practice in healthcare system is a significant benefit that provides an opportunity to expand and strengthen local capacity. Angwenyi et al. suggest “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”.[31] For the research team to state they have no responsibilities in the health services at the end of trial may deny the community from benefiting from their trial participation. Significantly, there is extensive literature and ethics guidance on community engagement at the start of a study but very limited guidance on community disengagement.

Guidance from the local partners and consideration of novel mechanisms are needed to sustain continuity of a care as a benefit during the transition of healthcare duties. [38, 39] This is an area of further research which would be well served by more research teams sharing their experiences as we have presented from this PMVT.

5.5.3 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. [15, 40] Identification of the appropriate opinion leaders needs to be supported by community liaison teams, participant advisory groups, health authorities and sociologists. [37, 41] Time and

careful assessment are needed to understand who represents a community and in what capacity. It is important to avoid endorsing inequitable structures in a region, for example, partisan politics, local rivalries or discrimination.[42] A further aspect to consider is the order in which you approach different members of a community. Guidance on local hierarchies and social graces are important to maximize the social value of results, and acceptance of findings amongst local and national health authorities. The acceptance and uptake of publicly available results are vital for policy change and improved healthcare practices.[15] 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.

5.5.4 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. [43-46] Poor implementation guidance has become a major barrier to fulfilling the ethical requirement of post-trial access to novel health innovation. [8, 47, 48]

Notably, post-trial availability was almost exclusively only mentioned by the ethics committee members. One senior researcher made the point that the concept had no application in the context of vaccine research because of a 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.[49] 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 in a research proposal and offer other forms of compensation in lieu.[50] 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.[51] 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 "focused on delivering outcomes for the communities where trials are conducted. 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."[47]

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.[44] 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.[55] We argue 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. Notably the latest updates of both the Declaration of Helsinki (2013) and CIOMS Ethics Guidelines (2016) state post-trial access is an ethical requirement, but it is a responsibility not only for the researcher.[17, 43] The responsibility is to be shared amongst stakeholders including governments, sponsor-investigators and other relevant parties to deliver on this commitment. As one respondent stated in the results, "the logistics, organization, and planning of post-trial access require multiple stakeholders" (such as WHO and Global Alliance Vaccine Initiative (GAVI). Important to this point is to also forge national, in-country links amongst research programmes, the national FDA, ethic review committees and relevant ministries (Health, Child Welfare, Education etc.) The question then becomes in this broad structure, of international and national partners, is it possible to create priorities for intervention roll out, where the communities of these countries have been

involved with the testing of the intervention? The practical mechanics of building post-trial availability into a larger global health agenda requires further research.[56] On the whole the main negotiations on research benefits, including post-trial availability remains between the ethics committee and the principal investigator of the research team.[48] A major difference of the PMVT was the early involvement of national FDA and National Ministries, so that the trial findings could be efficiently scaled to national level. Respondents in the interviews remained hopeful this would help expedite access to a vaccine if it received licensing approval. Further monitoring of the effectiveness of this partnership structure as the vaccine moves through later development and regulatory stages would be helpful to report.

A possible alternative is to establish in conjunction with 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. Early in-country planning will facilitate delivery of post-trial access, and furthermore support a broader goal of overcoming the 'research to policy to practice' pathway. [57]

5.6 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.

5.7 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.[58]

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.

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6 RESULTS DISCUSSION

6.1 Summary of Main Conclusions

i. Governance provisions should define the minimal requirements for creating a good collaborative practice environment of inclusion, mutual learning, transparency and accountability. The following minimum steps need to be upheld in international and national health research governance: i) shared research agenda setting with local leadership ii) capacity assessments with a co-ordinated development plan, and iii) construction of a memorandum of understanding (MoU).

ii. Establish local research leadership to work in collaboration with international partnership and local healthcare systems. This will best ensure that the research agenda and activities align with local health priorities, system capacity strengthening and promote decentralized health system decision-making.

iii. Successful integration of health research into local health systems is important for strengthening partner dialogue and promoting sustained regional health improvements. Careful planning of the standard of care and implementation need to take account of background inequalities and possible sources of community disparity. The goal is to retain the independence of the research program from the health services and yet sustain a functioning partnership that continuously informs and communicates with the local population.

iv. International partnerships should aim to improve local conditions of health by conceiving programmes of research as tools of public health in the regions where they operate. At the end of a trial, the concept of continuity of care should be the guiding principle of any service handover from research teams to local health authorities and; an actionable post-trial treatment access pathway needs to be established with a wide diversity of stakeholders.

v. Overall, ethically a good collaborative partnership is a participatory process, responsive to regional health priorities and, improves local conditions of health. Fulfilling this obligation requires that research is developed as a social intervention, strengthening health systems through building national research capacities, and fostering local leadership.

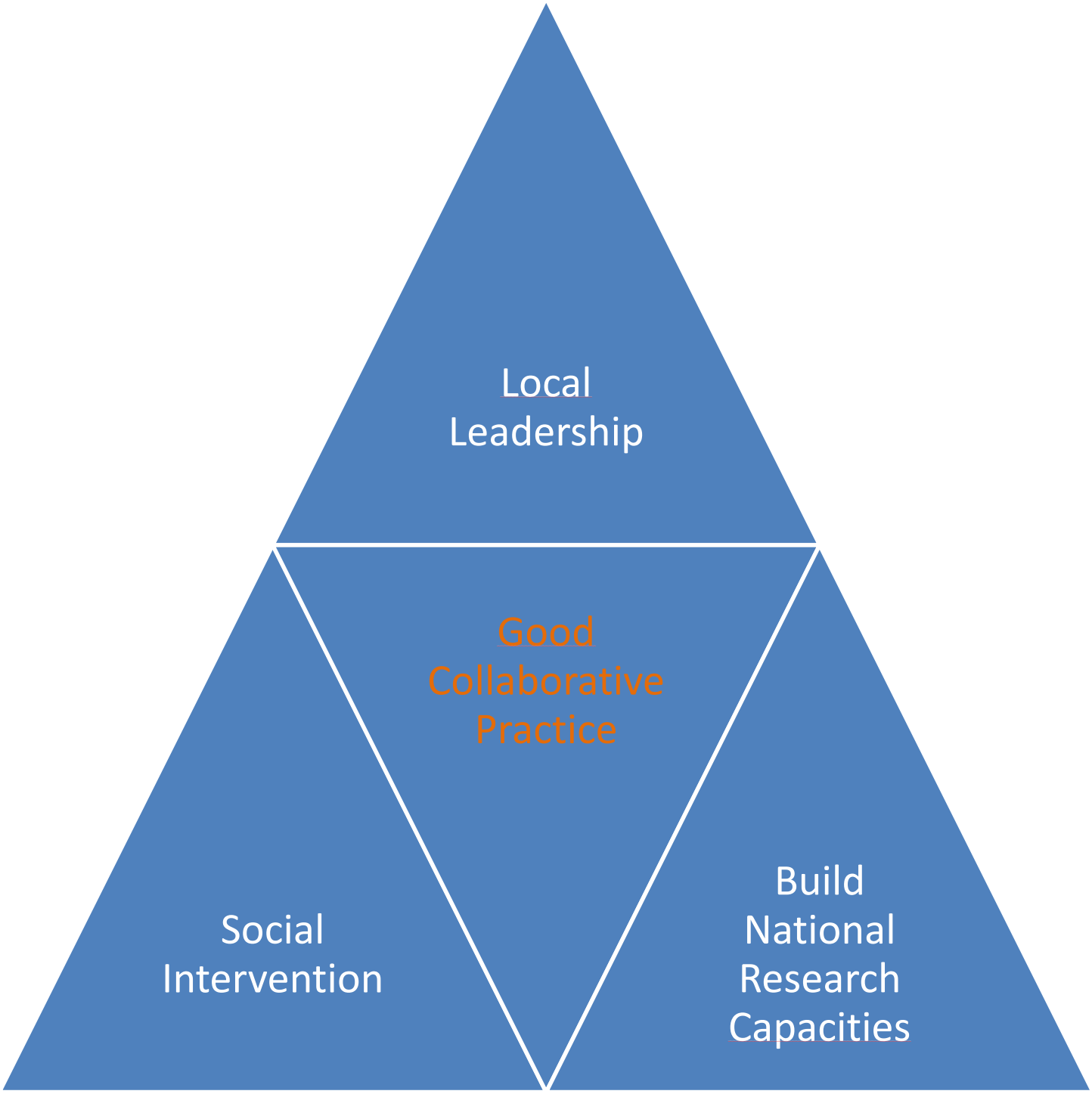

Figure 1 Schematic Representation of Good Collaborative Practice. This figure presents an overview of the three main partnership requirements for international health research to support local health and development.

6.2 Discussion

The concept of collaborative health research has been widely endorsed in policy and a number of research governance documents as an essential component of improving global health equity

and undertaking global health research in low-resource countries.[1, 2] Review of the literature and ethical guidance on international health research has identified different provisions that guide the role and responsibilities of collaborative partnerships (partnership principles). This includes international treaties, codes of practice, legislation (international and national), guidelines of professions, industry and ethics, practical implementation guides, academic literature and a variety of proposed ethical frameworks. Each guiding document purports to inform and bring greater clarity to the complex relationship of international health research conducted with vulnerable populations in low resource settings. Overall, undertaking this review has demonstrated that the ethical issues surrounding collaborative partnership (specifically those operating in resource-limited regions) are a relatively new topic in bioethics, having only started to formally develop in the past 20 years. Debates on partnership responsibilities in health research have attempted to standardise and guide the ethical conduct of collaborative research. Arguably, the variety of different guidance sources now available has to some extent added to the uncertainty over what is owed to research participants, the local healthcare settings and their populations.

The globalisation of health research (as with other industries) brings new issues in ethics, beyond the limited frame of the researcher-participant relationship. Greater attention needs to be given to what role global health research plays in low resource settings and global health development. New models of collaboration and funding in global health research have facilitated new opportunities to test advanced health technologies and developed capacity to involve wider populations and, varied disease targets across diverse health settings. Ethical guidance of partnerships operating in low resource settings is required to ensure collaborations are equitable, focused on improving local conditions of health and committed to reducing global health disparities. [3, 4] This project has addressed the ethical considerations of a collaborative partnership based on empirical data in the context of a paediatric malaria vaccine trial (PMVT) conducted in Ghana and Tanzania. In particular a consideration of this research project has been whether collaborative research projects are advantageous for public health and local development.

Limited investigation has studied what makes a collaborative partnership good, and very little research has explored this question from the perspective of stakeholders in low resource settings.[5] The project described here, has precisely this aim. This empirical ethics study provides vital insight into the complex decision making associated with an international PMVT conducted in Ghana and Tanzania. The findings present the perspectives of stakeholders

involved with an international research partnership. This project provides an account of the different considerations and challenges faced by a programme of international health research operating in low resource settings and, thereby contributing to the current knowledge of best practice in collaborative health research.

This study obtained exclusive permission from GSK and the PATH Malaria Vaccine Initiative (PATH/MVI) to interview all the relevant stakeholders involved in the conduct of a paediatric malaria vaccine trial (PMVT) (vaccine candidate, RTS, S) in Ghana and Tanzania. This qualitative project has collected extensive interview data (N=52) from across stakeholders of the partnership in Ghana and Tanzania, and with the wider international partners. As one of the largest and long-standing collaborative research programmes operating in countries of sub-Sahara Africa, the study has provided data-rich empirical evidence and deep ethical reflections on practical experiences. The analysis of the results has compared and contrasted the experiences from the field with current literature and governance to understand better the adequacy of current ethical instruction; be it comprehensive, ambiguous or possibly even absent in respect of collaborative health research partnerships.

The questions asked in this ethics project are important because the past 20 years has seen a considerable increase in international collaborative partnerships and investment into health research within low resource settings. This development on the ground has led to relatively new ethical debate around what are the aims of international partnerships, how are resources being distributed, what is being achieved and for whose benefit? Crucially, one major concern has been that, despite increased investment in research programmes there has been much less advancement in low- and middle-income countries accruing their own research capacity and strengthened systems to protect the health of their populations. [6] This is ethically challenging and remains problematic for protecting public health and reducing global health disparities.[2, 4] To successfully respond to the health needs of vulnerable populations living in low-resource settings, an international collaborative partnership must succeed in addressing a range of complicated objectives: on the one hand generating health data and generalizable knowledge (the scientific goals). Whilst on the other hand, attending to local conditions of health. This requires navigating a diversity of barriers, stifled access to effective interventions and strengthening under developed health and research systems (the development goals). Accounting for these different goals is important so that the conduct of health research is mutually advantageous for all the stakeholders involved in the collaborative research and can actually deliver on improved conditions of health. This project adds to growing debate over the

obligations of partnerships towards the development goals and raises ethical questions around social justice and health equity in programmes of international health research.

The first paper (Chapter 2) in this project entitled, Good Collaborative Practice: Capacity Building Governance of International Health Research Partnerships, evaluated research governance of collaborative partnerships. In particular, the first paper focuses on whether there is an ethical requirement to deliver on development goals, such as capacity strengthening when conducting health research in low resource settings. The analysis in this paper shows that the concept of capacity strengthening is supported as an ethical requirement of working in low-resource settings because it is necessary to deliver on the social value requirement of health research activity; social value being the primary condition of ethical acceptability for any programme of research. However, implementation guidance of development goals is limited and poorly supported across varied governance documents. A number of ethical frameworks have been proposed to establish what is owed to disadvantaged research participants in low resource settings, but there is very limited empirical evidence of collaborative partnerships. As a result, the project proceeded to develop as an empirical ethics study presenting the perspectives from a research collaboration operating in Ghana and Tanzania (Chapters 3 -5).

The second paper (Chapter 3) entitled, Defining Health Research for Development: The Perspective of Stakeholders from an International Health Research Partnership in Ghana and Tanzania, explored the development opportunities associated with health research and what it means in the context of an international collaboration.[7] The discussion in that paper went on to articulate the barriers and enablers to establishing effective development mechanisms in collaborative research partnerships. The stakeholder views, in general, reflected the same ambiguity that is found in the governance of collaborative research. There is awareness of a capacity strengthening requirement, but to what extent, and exactly which stakeholders should take responsibility requires greater clarity. For example what capacity is required to ensure partnerships are equitable, regarding skills, training and equipment and; what commitments are required to sustain health system strengthening in local settings? These topics generated diverse views amongst interview respondents. Most stakeholders accepted that collaborative research could bring positive changes to local health infrastructure, but there were opposing views over whether this infrastructure effect was an ethical obligation of a programme or just a possible consequence. Practically, the respondents explained that the possibilities of capacity strengthening in collaborative research come down to extensive partner dialogue. As a result, the outcome depends on the structure of the partnership and the negotiating power (generally

determined by finances and expertise) of respective partners. Many of the senior researchers in Ghana and Tanzania had found that over the course of the PMVT, they had become more aware (and informed) of the practicable capacity strengthening opportunities that collaborative research offered.

Clear guidance on defining capacity strengthening goals would help to empower local partners in stakeholder negotiations at the formation of a partnership. It is recognised that overly onerous stipulations for capacity strengthening may have a negative effect on health research if the requirements dissuade collaborative research activity. An appropriate balance needs to be defined between constructing an enabling environment for collaborative partnerships, whilst also avoiding over burdensome requirements. Ensuring local leadership was agreed important in this respect. Capacity building efforts should ensure local research teams have sufficient professional capacity to represent, lead and contribute to partnership decisions. This approach ensures partners with community interests are involved with all aspects of the process, adding to local development and strengthening research expertise in local healthcare settings. Moreover, local leadership better informs study design, protects the safety of participants, and promotes regional up-take of the research findings in the translation of results.

The findings made in Paper 1 (Chapter 2) and Paper 2 (Chapter 3) have helped inform the latest update of CIOMS (The Council for International Organizations of Medical Sciences) Guideline 2016, as part of the public consultation. The conclusions drawn from the first (Chapter 2) and second (Chapter 3) paper were submitted and included with the TRREE (Training and Resources in Research Ethics Evaluation) position statement responding to the CIOMS consultation. [8] The proposed wording on capacity strengthening that was set out in the position statement, and taken up directly by the CIOMS guideline was devised as a result of the study findings. See latest CIOMS Guideline 8, detailing the minimum requirements for capacity strengthening in collaborative partnership:

“To safeguard against power differences, innovative forms of collaboration should be considered. For example, the following three steps may promote inclusion, mutual learning, and social justice. At the start of collaboration and before even beginning a specific research project: i) determine the local research agenda; ii) determine capacity needs or priorities assessment amongst partners of international health research and iii) create a Memorandum of Understanding (MoU).”[9]

Turning now to the third paper (Chapter 4) entitled, The Ethics of Health Care Delivery in a Paediatric Malaria Vaccine Trial: The Perspective of Stakeholders from Ghana and Tanzania. The results presented in this paper demonstrate that a programme of health research in a low resource setting also presents an opportunity to access formal healthcare. This places a greater onus on research teams to defend against all possible risks of research. Importantly, the local health care professionals will be familiar with communities and are the most knowledgeable on creating effective outreach programs which are socially and contextually acceptable. Moreover integrating research with the healthcare setting is crucial for fulfilling the social value requirement of health research; it improves the integrity of the data collected, safeguards the health of participants and facilitates the translation of results. For successful integration of research into a healthcare setting this needs to be an inclusive consultative and deliberative participatory process to foster a trusting relationship. The experience of stakeholders showed that equitable participation in a collaborative partnership needed active management to overcome group dynamics distorted by the pressures of time, resources, language, cultural, educational and financial factors. These are all aspects which can lead to power differentials, creating barriers to collaboration and capacity strengthening. Stakeholders of a partnership will have different interests and objectives. To incorporate these various approaches adequate consultation is needed so partners can articulate, acknowledge and address different partner roles and responsibilities to protect and promote the health of local populations.

When collaborative research is effective, as was the general experience of the PMVT in this study, then the trial provides a conducive interdisciplinary environment to build local capacity. The experience of conducting a programme of research - study design, set up, data collection, monitoring, protocol and manuscript writing - has the potential to advance the capacity of local healthcare settings. For example, some respondents mentioned how the conduct of the health research changed the culture within the hospital setting on aspects such as recording full medical notes and giving sufficient time and respect to participants (mothers and infants). The positive effects of the PMVT on the healthcare setting were recognised widely by respondents. The success of the programme was associated with the fact that the research centres were developed in the local public health facilities (district hospital and local dispensaries). Other authors have also noted the conduct of the study led to infrastructure and skills development which supported both accurate data collection, and routine healthcare services.[10] Notably, improvements to local facilities and procedure are becoming a recognised benefit of integrating research into healthcare systems.[3]

Most importantly, effective team structures, regulation, and local leadership are needed to evaluate whether a favourable risk/benefit ratio has been achieved for communities that are enrolling into such trial programs. This is vitally important in a situation of background inequalities where the primary reason of participants for enrolling in a study is to access free healthcare. Our findings showed that although it is not unethical to enrol participants who seek healthcare it does exacerbate vulnerabilities which could place participants at a greater risk of research harm. The planning for a health research study and the implementation of appropriate ethical criteria require careful safeguarding against exploitation and harm. Significantly, the trust between communities, research teams, and a healthcare setting is the most valuable asset for the protection of participants, professional reputation and promoting good health in a community. Breaking this special contract of trust (particularly when participants have limited previous interaction with a hospital setting) can be exceptionally detrimental to health; in respect of physical harm and because participants may reject all aspects of formal health care and public health measures (such as routine childhood vaccine programmes) as a result.

The fourth paper (Chapter 5) entitled, The Ethics of End of Trial Obligations in a Paediatric Malaria Vaccine Trial (PMVT): The Perspective of Stakeholders from Ghana and Tanzania considers the ethical issues that present at the completion of a research programme. At the time of the interviews, the PMVT had just completed the final follow-up of participants and data collection. This offered a unique opportunity to explore with respondents what were the important considerations at the end of a trial, and what were the implications for the healthcare setting. Significantly the exploration of this topic with stakeholders also informed the question of what advantages are there for vulnerable populations and weak healthcare settings to become involved collaborative research. In general, all stakeholders agreed that participants enrolled in a trial should have a chance to benefit from the conduct and findings of the research along with their communities. Concerns were raised over the sustainability of system improvements, community health seeking behaviours and positive healthcare impacts. An interesting debate evolved over how access to post-trial interventions can be best achieved. It became evident that the implementation mechanisms needed much greater consideration, coordination, and clarity amongst stakeholders.

6.3 Summary of the Empirical Project Findings

Overall, the respondents in the interviews reflected a great enthusiasm and sense of optimism about what the PMVT had achieved at the respective research centres and for the health facilities in the local paediatric care wards. The organisation of the collaborative had

successfully supported research capacity strengthening in terms of research infrastructure and skills training. In addition the presence of the study made an impact as a social intervention improving local paediatric care, providing considerable employment and, developing clinical expertise in both local research and health services. Important to the success of the whole trial and cohesiveness of the research programme was the involvement of a capacity-development partner, Malaria Clinical Trials Alliance (MCTA). The MCTA development component recognised the importance of local research leadership and assisted in building the necessary skills, training, equipment and critical thinking required of each centre to contribute to the success of PMVT.

Notably, the capacity building was designed explicitly for the conduct of the PMVT, rather than a wider capacity assessment of how research could support the healthcare setting. This is perhaps a limitation of developing capacity in association with a specific trial. For example, the laboratory facilities were available to the hospitals for some shared use, but there were not defined structures for joint sharing in local health data. For example one doctor mentioned that the study had helped detect a (previously unknown) high anaemia rate in infants of that region, but there was not a formal process, or explicit agreement with the hospital for capturing such public health findings. This is a possible consideration for future trials given the volume of local health data being collected. Every effort should be made to not only have a research programme that is associated with a healthcare setting (for the purpose of a trial), but also a research programme that can complement a healthcare setting, to improve local conditions of health. Joint planning and, involvement of local health systems in public health surveillance and research would develop and sustain structures to strengthen the local health setting. This differed between centres to some extent depending on whether they were members (or not) of the INDEPTH Network of Health and Demographic Surveillance Systems. Member sites were already embedded in a wider public health surveillance system which facilitates joint system learning.[11] An alternative approach, advocated by independent organisation such as The Global Health Network [12] and, TDR,[13] is to support country based trial capacity that is not disease specific. This establishes research infrastructure and skills that are there to serve the local health planning. Trials and studies can then be conducted on a wide range of diseases, with varied management options and, not only drug and vaccine intervention trials.[14] Moreover, closer evaluation of what aspects of partnership - either linked or independent of a trial - facilitate or inhibit locally-led research is most important to building sustainable research capacity.

The mandate of MCTA had a long term capacity goal that research centres would be ready to take on new research projects in the future. Yet, uncertainty around centres abilities to maintain core staff, functions and scientific equipment was a concern raised by respondents, in particular from managers and field staff. Arguably if long term research capacity development is a defined objective of collaborative partnership then adequate assessment should accompany this aim. A number of the research groups and MCTA have shared their experiences on the capacity building aspect of the PMVT.[15-17] However as an objective of collaboration this should be further evaluated in much the same way that the clinical results are, with "rigorous attention to methodological design, analysis and reporting standards."[4] Tools such as the COHRED Research Fairness Initiative can help partnerships build in standardised reporting methods and assessment of capacity building efforts.[18, 19]

The collaborative partnership did develop strong local leadership and had a governance structure that allowed for inclusive partner decision-making. During the conduct of the PMVT research centres were represented in the (in the decision making cohort) Clinical Trials Partnership Committee (CTPC). In addition, each group developed their own context-specific standard operating procedures from the joint protocol. Respondents in the interviews identified this as an important step for establishing local ownership in the project and developing culturally appropriate research methodology for patient recruitment in the respective settings. Moreover, the CTPC created an opportunity for shared learning between different principle investigators, and research settings across the African region, forming not only north-south, but also south-south development opportunities. There was however still a sense that this was donor-led research project because of the funding structure, the (vertical) disease specific nature of the partnership and, the fact the protocol had been developed externally to the countries by the sponsor-investigator group, GSK/PATH MVI. In addition country partners were of the view that the inclusion of a clinical research organisation representing the sponsor-investigators, limited dialogue around the development opportunities of research and reduced equity in the partnership. On an associated point, there were still aspects beyond the data collection where local research teams felt excluded. Notably the scientific analysis, product development strategy and product-linked rewards (e.g. patent royalties).

The health care provision at each health facility markedly improved with resources provided from the trial. This was of great benefit to the local population, in particular the enhanced laboratory facilities, paediatric wards and additional transport. A major challenge for the PMVT, and especially for the medical teams and field workers, is the balancing act between

attending to the local disparities in healthcare access and retaining the independence of research from the health care services. Maintaining the conceptual distinction between the research and the provision of health services is vitally important for the safety of participants and local communities. In addition, the provision of any additional health services must not mislead or create unsustainable dependencies. This can be harmful to the health of individuals and public health. Tragically one respondent spoke of a small child dying because the mother could not reach the allocated fieldworker for transport. This illustrates the danger of creating excessive dependencies and adequate safety-netting needs to be in place to limit this risk. This is a challenging task in resource limited settings and this makes it all the more important. The research process should facilitate and endorse agency in health seeking behaviour and provide clarity on the role of research. Equally in respect of public health, some mothers had mistaken the vaccine trial for routine childhood welfare clinics. Such misunderstandings could place infants at risk of not receiving necessary childhood immunisations or early years care. These risks need to be actively defended against. As a practical suggestion this may be overcome with the use of a coloured armband for physicians when working in a research capacity, or by having appropriate information posters on clinic walls during research-sessions.

The end of the study led to changes in health care access for local populations. Research teams and health services need to work closely together, during any such transition period, to evaluate possible risks, and address them with clear hand-over plan and extensive dialogue with relevant parties (Hospital managers, district health officers, Ministries of Health). On the whole, it appeared the end of the study 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 what were the responsibilities of the research team towards 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 scrutinised to ensure uniformity across the research centres. At the end of the study, to support local community health one research centre took a decision to fund health insurance for participants to reduce disruption to service provision and health access. This was not provided by all research centres or co-ordinated 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 if the health needs of all participant were adequately and consistently addressed by the research programme and; what are the sponsor-investigator responsibilities towards health care provision in the period of transition when a trial ends. The presence of research in a health care setting should be

structured in a manner that optimises shared system learning and improves the local health care setting. To a greater extent the PMVT achieved this through improving local research, clinical and laboratory skills and in addition, supported local health education and good health seeking behaviour 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.

Post-trial availability continues to be a complicated and uncertain topic. It was not widely addressed in the interviews by research teams but all the ethic committee members mentioned the topic. More generally respondents mentioned that the PMVT had supported decentralised healthcare systems and involved a broad range of national stakeholders in a comprehensive communication strategy throughout the life cycle of the research programme. These features were considered important for enhancing national awareness of the vaccine-candidate's developments and for advancing system requirements to prepare for a possible priority roll out of the vaccine at a later date. The broad communication strategy of the PMVT, with involvement of Ministries of Health, Ethic Committees, FDAs and international funders (e.g. Save the Children, Global Alliance Vaccine Initiative) appeared to be a new (or different) approach which was warmly welcomed by respondents, and provided assurance to local research committees that if the product was effective then it would be available to the countries and populations. As a point of caution, broad stakeholder involvement is important, but also requires a strong commitment to professional codes of conduct in order to retain independent institutions and decision makers. The freedom to challenge research results or implementation policies is crucial for patient safety, public health and appropriate use of resources. A pervasive narrative of conflicts of interests has plagued both the health and development sector in the past, and it remains important to defend against such failings and/or even the possible perception of any such conflicts.[20] Detailed reporting and commitment to open sharing on scientific progress and requirements for treatment access pathways is crucial for supporting a transparent process. A further study may wish to conduct a full analysis of the strengths and weaknesses of the communication strategy and its effectiveness for the development of the vaccine and conditions of local health.

This project has provided an exclusive opportunity to obtain insight into the objectives, structure, and functions of a PhaseII/III PMVT operating in Ghana and Tanzania. This explorative study has provided information on the practical challenges and ethical decision-making processes that take place when a collaborative research project is conducting health

research in low resource settings. The interview responses present the perspective of major stakeholders in a programme of international health research. In doing so, this project has shared valuable experience and discussions on the constitution and conduct of collaborative partnerships. The results of the project are intended to inform best practice in future studies and encourage stakeholders of new research programs to ask questions going into partnership. Upholding an equitable partnership dynamic is necessary to move collaborations beyond data collection towards forging centres of excellence, improved conditions of local health and a worldwide network of robust health systems.

Set out below is an overview of best practice learning points for Good Collaborative Practice shared across chapters 2 – 5:

6.4 Best Practice Learning Points

6.4.1 Governance

Governance is needed to co-ordinate, engage and motivate stakeholders to deliver on equitable health research partnerships that promote communication, co-operation and co-ordination:

- Define the minimal requirements for creating an environment of inclusion and mutual learning through a programme of: i) shared research agenda setting with local leadership, ii) system capacity assessments with a co-ordinated development paln, and iii) construction of a memorandum of understanding (MoU)
- Co-ordinate, strengthen and support enforcement of local laws requiring equitable research partnerships and sustainable capacity strengthening in resource-limited regions.
- Incorporate collaborative partnerships requirements into ethical practice and industry regulation: locally-led research, capacity building, and equitable partnership.

6.4.2 Structure

Establish local research leadership working in collaboration with partnerships, and healthcare systems, to align research agendas and activities with local health priorities:

- Know the country specific context - map the social, health, legislative and political setting.
- Define an explicit development component and plan of action in a research project.

- Address the barriers and opportunities to sustain system developments;
- Support decentralized health system decision-making to facilitate the translation pathway.
- Govern, monitor and evaluate the development components of health research partnership.

6.4.3 Integration

Integrate health research into local health system to strengthen partner dialogue, cultivate and promote sustainable regional health improvements.

- In partnership with the local healthcare system come to a joint agreement on the standard of care, nature, coverage and time frame of health care support from the programme of collaborative research.
- Retain the independence of the research program from the health services and sustain a functioning partnership with the community.
- Design and establish a context-relevant education strategy for communities that explains the objective of the health research; the relationship of the research with the healthcare system and also; distinguish the research activity from health care services.
- All unplanned healthcare provision events should result in a joint case review between the research and hospital setting to identify where gaps or oversights that may exist in routine care to promote mutual system learning.

6.4.4 Sustainability

Endorse multi- disciplinary stakeholder commitment to reduce global health disparities and improve the living standards of communities living in low resource settings. Regardless of the setting, participants and their communities in a trial should benefit from the conduct and findings of research.

- Design a gradual exit strategy from a healthcare setting with opportunity to address unplanned events and end of trial responsibilities.
- Uphold continuity of care when planning service handover from research teams back to local health authorities at the end of the trial.

- End of trial communication should promote improved conditions of good health: provide additional information to successfully transition healthcare responsibilities of personal and family health back to community members and local health authorities,
- Devise an actionable treatment access pathway for post-trial availability with diverse stakeholders.
- Establish public health indicators to monitor the positive and negative impact of collaborative research on a local healthcare systems and healthcare access.

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7 ETHICS, MORAL THEORIES AND ETHICAL FRAMEWORKS

7.1 General

Collaborative research has the potential to promote and sustain health in the worlds' poorest countries and to reduce overall global health disparities.[1] International co-operation can facilitate the sharing of scientific knowledge, methodological expertise and vital resources worldwide; enabling health research to reach populations living in poverty, along with strengthening local health system capacity and providing access to novel health interventions.[1-4]

The objective of this project has been to explore what is good collaborative practice and; what are the roles and responsibilities of international research partnerships operating in low resource settings. The results of the study articulate how to implement good collaborative practice and, conduct ethical international health research that is committed to equitable partnership, improved local conditions of health and, reduced global disparities. This project has been informed by stakeholder interviews from an international partnership (GSK/ PATH MVI) paediatric malaria vaccine trial (PMVT) in Ghana and Tanzania. The interview responses from the project present the perspectives of relevant partners working together in collaborative research. In addition, these responses have been compared and contrasted with attention to current literature, research governance, and ethical discourse. The findings show the ethical challenges of good collaborative practice, the practical considerations and suggested best practices. Overall, the results show that effective international partnership depends on the ability of projects to build mutual respect amongst stakeholders, strengthen local systems and willingness for all partners to share and learn in different methods across various contexts. Taking such an approach to collaborative research maximises the social value of international partnership and embeds health research into a wider framework of global health justice and health equity. The project demonstrated that collaborative research is capable of improving the conditions of health for participants and communities of low resource settings. Moreover, the project showed that the activity of collaborative research is a highly complex dynamic that require active stakeholder engagement. Effective governance is needed to ensure that stakeholders operate in an ethical manner, both in respect of patient safety and partnership responsibilities. This is vital for research activity to be advantageous to local populations and health care settings.[5] Improving local conditions of health goes beyond sound science and,

protecting the safety and autonomy of participants (both of which remain important goals). Further, improved conditions of health depend upon local system developments. Therefore for collaborative partnerships to be advantageous to the local setting where the research is conducted the activity ought to increase local research capacity, support health system strengthening, and facilitate access to effective treatments and interventions. Few would argue that these are laudable goals, and moreover offer the best approach to securing local and global population health. However there is opposition to these broader development obligations that place greater responsibilities on collaborative research beyond data collection and product licensing.[6] The objections rarely challenge the ethical premise that collaborative research in low resource settings should link to better conditions of health, social justice and development. Rather, it normally comes down to two economic arguments - money and time. A natural tension exists between the pressure to produce scientific outputs (win grant proposals, generate data, publish in high impact journals) and achieve long-term capacity building objectives.[7] Ethically, this raises the question, is there a moral duty that collaborative research has obligations of development (capacity building, system strengthening and facilitating access to health care), beyond knowledge generation or, is this merely supererogatory?

7.2 Empirical Ethics

The changing dynamics of global health research through increasing multinational collaborations has been accompanied with recent attempts to define and articulate the ethical obligations of international partnership in low-resource settings.[8-11] Admittedly, there are a variety of reasons that international collaborations may conduct research in low-resource settings (lower costs, specific disease targets, larger population samples etc.). This project has focused on one partnership (GSK/PATH MVI) formed with the fundamental goal of improving health outcomes for disadvantaged populations and global health equity. For example the research target (in this instance malaria) is a disease that disproportionately affects the populations of low resource settings in sub-Saharan Africa and negatively impacts on community health and regional development. The conduct of such research in low-resource settings is critical and, when responsibly carried out, is not inherently unethical. As demonstrated in this project by the GSK/PATH MVI trial conducted in Ghana and Tanzania. For example the product profile of the vaccine candidate (RTS, S) has been designed to protect the health of children under five years old in endemic malaria regions, and the vaccine is tested with the populations it aims to benefit. Moreover, the approach taken by GSK PATH/MVI was not only to develop a product that was relevant to the population where the research was

conducted. The project committed to improving local conditions of health, through further partnering with Malaria Clinical Trials Alliance (MCTA), a capacity development partner. In conjunction with MCTA, the programme of research had a specific mandate (and budget line) to develop the research centres in the different settings and to integrate with local hospitals, provide care and support the translation of trial results in the countries. In Chapters 3 – 5 the stakeholders of the PMVT gave their perspectives on the strength and challenges in conducting collaborative research.

Notably, the explicit development approach taken by the PMVT influences the findings of this project and, answers to the question of whether there is a moral duty that collaborative research fulfils broader development responsibilities. The PMVT considered in this project was highly resourced and represented a gold standard for conducting clinical trials in low resource settings. As the WHO report stated, "The RTS,S program [PMVT] has been conducted as a public-private partnership between GSK and the Malaria Vaccine Initiative at PATH since 2001, and is a leading example of this type of public-private partnership approach."[12] Arguably, it may be concluded that other projects would not have the same means to recreate the development goals defined and largely achieved by the PMVT. This challenge amounts to a pleading of: "just because you can, does not mean we should." Conscious of this argument, it remains, that there are broad learning points which translate and are relevant across all programmes of collaborative research operating in low resource settings.

The first point is that health research in low resource settings should be structured to support local research leadership and social inclusion. This in itself will strengthen local healthcare settings. The international partnership has an opportunity to not just deliver finance and new science, but provides a platform to support capacity development, skills exchange and mutual learning for change. Second, initiatives will differ in terms of objectives, the involvement of different skills, human resources, finances and systems; however the important point is that there is ethical governance coordinating all of these factors - transparent, equitable and, accountable decision making processes amongst partners.[13] Important to this end is how are partnerships structured. An inclusive research structure needs to be actively maintained throughout the lifecycle of a partnership. This involves acknowledging and addressing decision-making powers and, as far as possible alleviating power distortions. An effective partnership structure can then address substantive questions - what are the research objectives? How are roles, responsibilities and rewards assigned and distributed across partnerships? How is health promoted and protected across a research programme? An inclusive and clear decision

making framework in a collaborative is a key component of good governance and relevant to all partnerships regardless of funding or size. In the case of the PMVT, the "multi-centre efficacy trial was designed by the Clinical Trials Partnership Committee (CTPC), which had membership representing each of the academic institutions participating in the trial with GSK and MVI."[14] This does not rely on greater funds but rather mutual respect and shared commitment (Chapter 2). Bottom-line arguments that there is not enough money and time are disparaging and dangerous. Failings to establish inclusive partnership with local representation and leadership have compromised good science, slowed response times to public health emergencies and undermined the appropriateness of interventions, even in situations as pressing as the recent Ebola and Zika viruses outbreaks.[3, 15, 16] The presence of a collaborative partnership should foster local leadership and participatory advancement of local health care settings (Chapter 3). Ethically this is a requirement of social justice and health equity, and practically it is a requirement of public health. In the spirit of collaboration there needs to be active partner engagement with a clear decision-making framework, and a collective commitment to sharing in knowledge and resources.

7.3 Moral Theories

7.3.1 Stand to Benefit

Ethical research frameworks have attempted to address challenging questions as to: what are the global health research priorities, who is setting the agenda and, what is owed to participants, communities, and the health care settings where research is conducted? Extensive work has been done comparing leading ethical frameworks and this will not be duplicated again here. [9, 17] Nevertheless, a brief summary of the moral theory of each research ethics framework will be presented, and in doing so will explain their limitations. The starting point to understanding what are the responsibilities of collaborative research, is a general principle endorsed by the founding sources of research ethics, namely The Nuremberg Code and the Declaration of Helsinki: groups involved with research should stand to benefit from the results.[18, 19] Hard to disagree with, but in practice fulfilling this ethical obligation has been riddled with contention and disagreement across various spheres of ethics and health research communities.[20-24] Therefore, the principle - to stand to benefit - as a commitment of research is noteworthy, but as a guiding tool for implementation, raises as many question (if not more) than it answers.

7.3.2 Reasonable Availability

In an early attempt – CIOMS ethical guidelines 1993 - to construct an instrumental definition of what it means to stand to benefit, a suggestion was made that there is an obligation to ensure "reasonable availability" of a proven intervention to participants and local communities.[25] It is a technical provision that states that any intervention proven effective in the course of research should be made reasonably available to the study participants. This construct of benefits has occupied debate on how groups stand to benefit.[26-28] In practice, the concept of reasonable availability has been criticised on pragmatic grounds because in-human research rarely leads directly to novel interventions that can benefit communities. Solely relying on this principle, as an ethical justification of research, has led to situations where participants and their communities are receiving no, or limited, benefits for having accepted the risks of a trial. Significantly, the limitations, weaknesses and insufficiencies of the concept were widely discussed around the early 2000s. This was primarily because of the increase of preventative HIV/AIDS vaccine trials being conducted with communities of low resource settings in sub-Saharan Africa.[29, 30] The studies were commended for recognising the importance of the deadly epidemic and seeking to find a solution (following considerable hesitation and delay in the research community). However the increased volume of studies with vulnerable populations led to ethical debate over whether the research was advantageous or exploitative of the local populations.

7.3.3 Fair Benefit Framework

Ethical concerns that the concept of "reasonable availability" did not protect vulnerable populations against exploitation led to the proposition of a new ethical framework, based on the distribution of fair benefits. Aptly named, the Fair Benefit Framework.[31] It is still today widely recognised as the main alternative to the reasonable availability concept, and has been further embellish with The Benchmarks of Ethical Research.[32] The further construction of "Benchmarks", implementation guidance built on the ethical framework of Fair Benefits, importantly recognises collaborative partnership as a crucial aspect of fairness.

The moral theory of the Fair Benefit Framework is structured on a concept of non-exploitation that endorses the principle of reciprocity. As Emanuel et al. has set out, one aspect of ethical research is compensating participants and communities involved with research. However, criticism of the framework has challenged whether it fulfils goals of beneficence.[33] Ballantyne described the Fair Benefit Framework as procedural fairness rather than a measure of normative fairness. [34] As such, the Fair Benefit Framework does not commit the generation

of health knowledge to the action of improving local conditions of health. As a comparator, the framework is based on the same theory as planting a tree for each one you chop down, but with no requirement to improve the quality of the forest. In the context of health and health research in low resource settings, the objective of collaborative partnership, whether implicit or explicit, is to develop interventions that improve the conditions of health for low resource settings, and not to just remunerate (be it in money or kind) a population for their participation in data collection. Given that is the aim of collaborative research, it would be contradictory if the process of research itself did not support and commit to improving local conditions of health. In much the same way that it would be morally reprehensible to sell handmade cloth bags - in order to raise funds for a new village school - where the bags had been made with child labour. Equally with health research, the set-up, conduct and outcome must promote health. In poor resource settings, if the aim of collaborative partnership is to address global health disparities this calls for a social justice approach that develops health care settings and includes local populations in the benefits as well as the risks of research. As such the formation of partnerships in low-resource settings needs to support health system strengthening and access to new products, so that communities can profit from the process and the products of scientific advancement. If the approach is not to improve the conditions of health in the local settings, then what is the purpose of conducting research in partnership format at all, and can it ever be ethically justifiable?

7.3.4 Linking Health Research to Better Conditions of Health

For health research to be designed in a manner that is responsive to the needs of the poorest it must also seek to address the wider barriers to health equality. Against a background of inequalities, health determinants are a complex interplay of socio-economic and political factors; access to research and health interventions being just one component of multiple determinants of health. Equitable practices in collaborative research will not overcome all health system weakness and health care access barriers, but that is not to say international partnerships has no responsibilities in development and social justice. The duty of collaborative research partnerships working in low-resource settings should be to contribute within their remit (science, research methodology, and capacity building) through addressing barriers to research capabilities and weaknesses in systems of health, in so far as the research interacts with those services. Such concepts have been articulated in two prominent alternative ethical frameworks to the Fair Benefit account: The Human Development Approach and, Research for Health Justice Framework.[10, 35] These two ethical theories attempt to address health inequities

between high and low-income partners of collaborative research based on moral theories of global justice and health equity respectively. The Human Development Approach is based on a philosophy of remedying systemic exploitation and background inequalities in social structures.[35] The Health for Justice Framework is structured on a health capability paradigm and that there is a universal responsibility to reduce global disparities.[10] These two approaches propose valuable and noble objectives for improving the health of vulnerable populations through the activity of research. Yet these two frameworks lack a clear explanation for why actors are obligated to commit to wider development goals in collaborative research. This weakness stems from the approach that both frameworks have taken, which is that they are set up in a dynamic of the 'haves' and the 'have-nots' (us and them): those who have good conditions of health and those who do not. The ethical arguments they present are therefore that those with good health should share and provide the same conditions to those who have not. Framing the moral duty on this premise fails to delineate why those with good health should support the less advantaged. In addition, distinguishing between the two groups in this manner is unfounded in the context of health (which I explain in the section below, 7.3.5); it does not commit political will and perpetuates unsustainable dependencies and vulnerabilities between health settings. These frameworks sustain traditional (and criticised) relationships of "health aid," defined by a context of donors and recipients. Set out below is an alternative moral theory that explains and commits stakeholders to good collaborative practice. A theory based on the fact that there is a common interest in health. Following on from this explanation a new research ethics framework is proposed, The Global Population Approach. It is underpinned by a collective moral theory of common interest and public health ethics.

7.3.5 Common Interest

In health, the separation of those with good health and those without cannot be substantiated, because health is a transient state. Given this context, when all populations have equal access to conditions of good health this provides for health equity and improves overall levels of health for everyone. Put another way, we are all vulnerable, when one country cannot provide conditions of good health for a population e.g. Inadequate capacities to monitor health, address health needs, or provide appropriate access to treatment. Threats to health quickly travel, mutate and compromise both weak and established systems, be it Malaria, Ebola, Zika or anti-microbial drug resistance; to mention just a few examples. The frameworks presented by London and Pratt do not address the social dimension of health. In other words, the frameworks do not adequately distinguish health from say, ice cream. It would be nice to share my ice cream with

my big brother, but do I have to? Health is different. Health is not merely an economic good; it is also a social good with intrinsic value to human life; therefore it is a fundamental right and access to the conditions of good health ethically should be equal.[36] Moreover because of the social dimension, health overall is enhanced for a society when each member has access to good conditions of health (ice-cream is not enhanced when you have to share it with your big brother). As Gostin remarks "Collaboration among countries, both as neighbours and across continents, should be about reducing shared risks and advancing common interests, affirming mutual responsibilities for human well-being, and building capacity collectively."[37] As a social good, there is a common interest to promote local and global population health. It is for this reason that collaborative partners are obligated to not only address science and participant safety, but must also commit to responsibilities to improve local conditions of health and development.

For the structure of an ethical health research framework to operate successfully, it has to be based on the fact that there is just one global population in a shared health environment. Notably, the latest framework of Wenner promotes that the justification of human subjects research must be fundamentally grounded in the value of the knowledge sought. Wenner criticises earlier ethical frameworks for failing to distinguish between benefits of research to communities that justify the conduct of research and those and that do not.[9] Moreover, Wenner explains that some benefits of health research may act as compensation for risks taken by a research population (non-exploitation) but do not justify the act of conducting research with that population in the first place.[9] This is an exceptionally helpful distinction and moves ethical thinking closer towards an idea of a common goal. This commonality is a value in research which is shared, regardless of the country from where you originate or the health conditions in which you live. Building on this concept - the value of the knowledge sought justifies the conduct of research – then it can be argued further that the perceived value of any health research is because of the potential power that knowledge has to improve health. The fundamental reason for collaborative partnerships forming and addressing disease, morbidity and mortality in low resource settings is the opportunity that research has to improve local conditions of health. Endorsing this approach is to understand research as a tool of public health. The presence of research being one determinant of health and, a recognised pillar of a functioning health systems and, not merely an initiative to generate data.[2] Following this logic, modern research ethical frameworks need a paradigm shift to commit research to improved local conditions of population health. Rather than base the responsibilities of collaborative partnerships on research ethics in a public health context, the guiding principles

should be of public health ethics in a research context. A new framework based on this premise is set out below.

7.4 Proposed Ethical Framework: The Global Population Approach

7.4.1 Guiding Principles

This project proposes a public health ethics framework for collaborative research conducted in low resource settings, entitled The Global Population Approach. The proposed framework shares in (and builds on) some earlier theoretical work articulated by Buchanan and Miller, entitled The Public Health Perspective of Research.[38] The key components of the suggested framework and practical application are informed by the conceptual and empirical work developed over the course of this project. This ethics framework informs good collaborative practice responsibilities through defining the constructs of equitable partnerships and the obligations of stakeholders in international health research partnerships. There are five guiding principles: 1) Promote and Protect Public Health 2) The Social Dimension 3) The Social Contract of Collaborative Research 4) Structural Foundations 5) Collective Endorsement. See Figure 1.

Figure 1 Schematic Diagram representing the five Guiding Principles of the Global Population Approach to Collaborative Research

7.4.2 Promote and Protect Population Health

Promoting and protecting the health of populations is a central tenet of public health activity.[39] Incorporating the ethos of public health with the activity of collaborative partnership, requires health research to be conducted in a manner that improves the health of disadvantaged populations.[40] A collective approach to achieving better health is well established in public health ethics. For example, take the widely accepted definition of public health from the Institute of Medicine which states public health as "what we, as a society, do collectively to assure the conditions in which people can be healthy" [41, 42] To date collective responsibilities in health research have received limited attention. Traditional research ethics has rather prioritised the individualist protectionist values of clinical research ethics – informed consent, data confidentiality and compensation for participation risks and harm. This is not to

discount the fact that safeguarding the rights of individual participants is a highly important condition of research that must be part of any ethical research framework. However, clinical research ethics alone does not sufficiently guide the role and responsibilities of good collaborative practice nor justify the conduct of research with vulnerable populations in low resource settings. Arguably, by excluding broader collective responsibilities that link health research to improved conditions of local health for local settings, ethical research frameworks have failed to fully protect the interests of vulnerable individuals and impoverished populations. Other, earlier commentators have also articulated this need to broaden research ethics and better address the concerns of persistent global health disparities and injustices.[43-46] This has led to discussion over the need for new values in global health research ethics, for example "solidarity, mutual respect, and a call to action."[47] These debates demonstrate growing support for a stronger collectivist theory in research ethics guidance and across obligations of good collaborative practice.

The objective of health research activity is often stated as the ability to generate generalisable knowledge that advances scientific understanding. Yet, the primary objective under a global population approach defines collaborative research as the opportunity to promote and protect the health of local populations. This aligns with the findings of the empirical research project. The stakeholders in the interviews clearly articulated that the purpose of entering into an international partnership is not merely generalizable knowledge to advance science, but rather the opportunity to develop systems and health interventions that promote and protect local populations. Shifting away from the "generalisable knowledge" objective is not a wholly new concept. It has been previously argued that industry requirements for drug development have already shifted health research away from this original objective, to a research objective of generating safety and efficacy data in order to comply with regulatory authorities.[48] This demonstrates that the focus of knowledge production in health research can and has shifted overtime. Moving forward, a global population approach, requires that the objective of collaborative research is targeted at improving local conditions of health and connected with the health systems of local populations.[49] This requires that the overriding objective of international health research partnerships is to protect and promote local population health.

7.4.3 Social Dimension

The foundations of public health ethics in The Global Population Approach, acknowledge that the social dimension of health binds individuals into one global population.[50] Hence, the name of the proposed framework. In the context of collaborative research, it is this shared global health environment - the reliance and interrelatedness of each individual's health on one another - that obligates international health research to act collectively and respond to wider determinants of health inequalities. With this approach each individual benefits from being members of a society that addresses the needs of everyone and, in doing so the society as a whole is healthier. Recognition of this social dimension in health obligates international health research partnerships to commit to good collaborative practice. To do so, requires not only good clinical practice and novel science, but also requires fulfilling responsibilities of capacity strengthening and regional commitments to improving local conditions of health (Chapters 2 – 5).

In some respects applying concepts of public health ethics to research aligns with current health campaigns for Global Health Security, (a popular advocacy tool of recent international health policy),[51] The security-rhetoric recognises the social dimension of (and threat to) health in populations. However the ethical premise of global health security is not based on a moral theory of collectivism in the same manner as a global population approach. Rather, it is individual countries choosing to act in co-ordination, and the objective (the prioritisation of resources and finances) is to protect regions of good health, not necessarily to improve the health of the "worst-off" and the most vulnerable members of society. Although at times this may be a consequence. By contrast, a global population approach seeks to improve overall population health, and in doing so prioritises vulnerable populations at greatest risk of disease and aims to reduce health inequalities. This approach aligns much more closely with those currently campaigning for collective action under a Global Framework Convention on Health.[52] Moreover, the challenge is not only that a collective approach is endorsed by a research ethics framework but further that practically it is also coordinated and financed.[3] New opportunities are emerging to define and fund health research priorities collectively with the establishment of the WHO Global Observatory on Research and Development and the proposed Global Research and Development Fund. [53] Recognising the social dimension of health commits collaborative research to, not only generate new data, but further establish relevant improvements for local conditions of health.

7.4.4 The Social Contract of Collaborative Research

To design collaborative research with a global population health approach requires structuring international partnerships across a collective theory of social contract. Defining and upholding a social contract is important because it establishes checks and balances between stakeholders that commits programmes of research to the objective of protecting and promoting local population health. The social contract of the global population approach states that collaborative partnerships form with permission to undertake research in vulnerable populations in exchange for the protection of their right to health. On this account then the social contract of a global population health approach is structured across four domains: i) Local leadership determines if the research goal is of value to the population, the methods of research are acceptable, and the standard of care is appropriate in accordance with their setting; ii) the sponsor-investigators and research teams assure a favourable risk-benefit ratio; iii) the participant is free to choose to participate (or not) because the risks are outweighed by benefits, and there is a prospect for society to gain; [38] iv) An independent ethics review committee oversees that stakeholders perform on their roles in the social contract, safety and interest of the participant and the conditions for the promotion of population health.

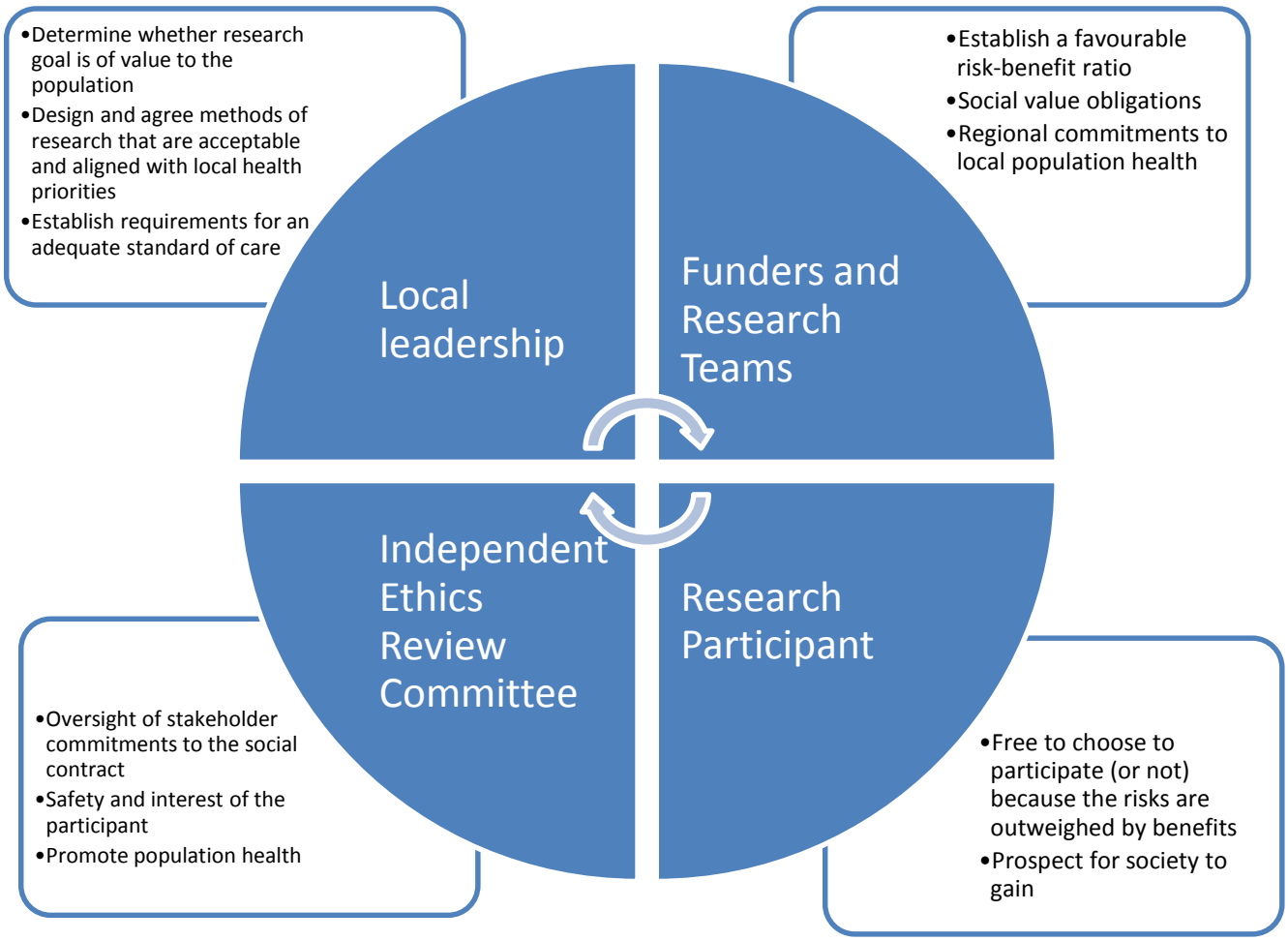

Figure 2 Schematic Diagram Representing the Four Domains of the Social Contract of the Global Population Approach to Collaborative Research

Attention to the social contract allows the ethics committee to fully evaluate the prospect of a project promoting local conditions of health, and creates accountability among stakeholders to honour their commitments. Worthy of note is that establishing a favourable risk-benefit ratio in collaborative research, and evaluation of this ratio in ethic review processes must include and, yet go beyond protecting the interests of research participants. This is not a further demand made by a public health approach, but rather inherent to research ethics that the social value of a project is accounted for in the risk-benefit calculations. The social contract scheme merely sets out a governance mechanism to bring greater transparency to partner roles and accountability for delivering on the social value of research. Social value being "the prospect of generating the knowledge and the means necessary to protect and promote people's health."[54] Importantly, the ethical enquiry of social value in a risk-benefit analysis, goes beyond only protecting participant interests and further safeguards the professional reputation of the research teams and the integrity of local health care systems involved in a collaborative

partnership.[55] The social contract provides a partnership structure that can generate new scientific data targeted at protecting and promoting the health of local populations.

7.4.5 Structural Foundations

To align research with population health requires the necessary structural foundations so that a society can profit from the generation of new health knowledge. As such obligations of research capacity strengthening and the wider development goals of healthcare access are required for performance of the social contract. No system of health is perfect, but when you participate in a health research study in a high-income country, there is a basic expectation that there are structures in place, so that health innovation can lead to improved systems of health.[31] Whereas, the same cannot be said of a low resource setting. The health system, research capacity and, wider translational factors are not necessarily assured or supported in low resource countries and; as a result, the social contract may (and does) fail vulnerable populations.[4, 56] As Buchanan and Miller explain, "From the duty to protect the population as a whole there needs to be a fiduciary obligation to realise the social value of research and the moral responsibility to distribute the benefits and burdens of research fairly across society."[38] The obligations of research capacity building are to be organised and provided in a manner that upholds the structures of the social contract because this commits stakeholders to anchor research within local health care settings and deliver on improving conditions of population health. This approach also addresses an astute observation raised by Rid that, "public interest goes beyond obtaining rigorous research results… the public interest is ensuring that the right kind of research is conducted and that the conduct of research does not unduly compromise and ideally enhances critical non research activities such as the provision of clinical care and public health measures."[57] Constructing health research with a global population approach requires establishing the structural foundations of a social contract that builds trust, transparency, accountability and sustainable systems of research with good collaborative practice.

7.4.6 Collective Endorsement

A public health approach has to be endorsed collectively in order to be successfully implemented.[50] This requires that all stakeholders of the research process are committed to upholding the social contract and foundational structures of research for development, with the intent of improving local conditions of health. Moreover committing to the structure of research across a social contract broadens the conversation from a narrow enquiry of what do researchers and sponsors owe participants, to; a broader enquiry of what are the responsibilities of all

stakeholders and whether the collaborative research is of value to public health.[5] For example, under the contract, the local community is required to lead - how is this achieved and upheld in a practical situation? A commitment to local leadership then engages wider stakeholders, such as what is the role of local government in achieving this objective and, and requires the participatory advancement of local systems as a crucial element of collaborative research. Collective endorsement of the global population approach with multidisciplinary stakeholders is important. This enables collaborative research to address the varied determinants of developing and integrating novel health interventions into low resource healthcare settings and improve local conditions of health.

7.5 Application of the Global Population Approach

A functioning health research ethical framework must offer practical stakeholder guidance to inform codes of practice, legislation, policy, ethics review processes and funding commitments. As Pratt and Loff eloquently state, there are "four justice aspects of health research conducted in low-resource settings – research targets, ancillary care, research capacity and, post-trial benefits - and a robust framework should offer instruction on these actions."[17] Informed by this project and based on the five guiding principles of The Global Population Approach (discussed above), each "justice aspect" is addressed in turn below.

7.5.1 Research Targets

Guided by a global population approach, the selection of valid research targets should aim to reduce the risks of ill health that people might impose upon each other or seek to address risky lifestyle behaviours that can cause harm to population health.[58] As an associated point, this requires protecting the weakest or most vulnerable in a population, children under 5 years of age being one example.[50] The selected targets must also give consideration to the interests of the individual. This results in a balancing act, between selecting a target (and proposed method of intervention) that protects individuals whilst also offering adequate value to populations. [59] This calculation is familiar to public health practitioners. Moreover it is an important tool of global health research to ensure resources, funding and, expertise are being prioritised and co-ordinated to meet urgent health needs with context-sensitive responses.

The research targets should originate from and be agreed by local populations. As defined by the social contract of research the final decision on the selection of health targets must be by local leadership. In a practical sense and as a preliminary step, this requires countries and local health authorities to devise clear policy on health priorities and research agendas. Notably in

the project, the interview respondents remarked that national governments, both in Ghana and Tanzania, had insufficient policy on health priorities and research agendas (Chapters 2 and 5). This lack of national support for research and research leadership was identified as a contributing factor to the power imbalances, which are often, experienced between partner organisations of high and low income settings. Setting health priorities and a research agenda is vital for all countries, and an important for informing the global distribution of resources for health research. The work of, World Health Organisation (WHO Framework for National Health Policies, Strategies and Plans)[60], INDEPTH Network,[61] and Council on Health Research for Development (COHRED),[62] act to support nations and local regions to develop health priorities and research agendas. Thus, both enabling local health empowerment and better informing the use of health resources and global co-ordination of collaborative partnerships. As the WHO states "policies, strategies and plans are not ends in themselves. They are part of the larger process that aims to align country priorities with the real health needs of the population, generate buy-in across government, health and development partners, civil society and the private sector, and make better use of all available resources for health"[60] On a related point, establishing reliable health surveillance and robust evaluations of local health needs in every country worldwide requires adequate infrastructure. Development of health systems and research capacity is in itself a massive advancement for better population health, and international partnership plays an important role in this objective (see Research Capacity, 7.5.3). A global population approach targets global health needs, through the development of research priorities with local leadership.

7.5.2 Ancillary Care

Endorsing a public health perspective in research requires that all activities - from the setup of research, through to conduct and end of trial - should aim to improve conditions of health. This aligns with a more general principle that the program of health research, as a tool of public health, should integrate to support health in the local setting. For example, the conduct of health research should operate to strengthen relations between the community and the local health facilities. As Richardson defines it, "ancillary care is a positive obligation that requires taking active steps to help another person, by contrast with the negative obligation simply to avoid harming someone." [63] Overall, the main conclusion from the project on this point emphasised that the care package provided in a program of research must take into account the wider public health implications and impact on routine healthcare services (Chapter 4). Moreover, unplanned health emergencies will arise and, the expertise and resources of a research project may be

required (and best placed to act). The implementation of ancillary care in a global population approach, most importantly, supports local public health through identifying where gaps or shortfalls may exist in routine health services. This component of research ensures that locally-relevant solutions are established to improve conditions in the local setting.

The level of ancillary care ultimately has to be agreed by the community, and early dialogue with appropriate representatives and health authorities is critical. The conclusions of any such discussions are then required to be detailed in the protocol, addressing fully the nature, coverage and time frame of any additional support.[64] Using the information provided the ethics committee must take a final decision on whether the care provisions adequately safeguard individuals in the study and support public health structures. Notably, The Global Population Approach to research does not prioritise the community over the rights and interests of the individual. Therefore regardless of the ancillary care benefits it remains critical that research participants are not exposed to excessive risks.[55] Under the social contract, it is the research team that has the final responsibility of maintaining a favourable risk/benefit ratio for participants throughout the study. The ethics committee are required to ensure that the research teams fulfil this duty. The risks of research and the impact of ancillary care provisions need to be carefully reviewed over the lifecycle of a research project (Chapter 4).

7.5.3 Research Capacity

A global population health approach to research obligates a capacity strengthening component alongside the process of research for the following reasons. First and foremost the structural foundations of research – infrastructure, scientific expertise and management skills – are required conditions of local leadership. Second, constructing health research in this way, for development, increases the number of scientists, improves standards of care and levels of research expertise in low and middle income countries.[3, 65] Third, capacity building supports the integration of research into health care systems and, more efficient translation of results. In turn, this leads to improved clinical practice and public health capacities which strengthens international collective health and, "human security."[15] The success of capacity strengthening activity requires establishing a process of meaningful engagement amongst the local research teams and systems of health. In Chapter 2, the procedural conditions of good collaborative practice governance are discussed in detail. The core objective of capacity strengthening being to create an environment of social inclusion, mutual learning and system development through i) shared research agenda setting with local leadership, ii) joint capacity

assessments with a co-ordinated development plan, and iii) construction of a memorandum of understanding (MoU) (Chapter 2).

The interview responses in this project showed that a co-ordinated capacity development plan should be a target of all collaborative research (Chapter 3). For example with the malaria vaccine trial, where research centres were established and improved across a number of sub-Saharan African countries. This led to better science, conditions of health and local research capacity. The establishment of health system infrastructure and advanced research skills has created an opportunity for local research centres to better manage population health, collaborate with new research projects, and develop further into training centres. For Example, Kintampo Health Research Centre, Ghana, has become a Malaria Diagnostic Centre of Excellence. Providing microscopy skills training to teams across Ghana Health Service and the African region.[66]

Moreover, research capacity building is an important step to empower and equate partners in dialogue, moving research partnerships away from constructs, where the funding partner determines all aspects of the project design (Chapters 2- 5).[56] In addition, capacity development requirements are not only required to ensure successful research planning between stakeholders but also to promote a decentralised system of healthcare, closing the translation gap between research results and local health system improvements (Chapter 3). The capacity strengthening activity of a global population approach incorporates development with the process of health research and, is a vital step in improving local conditions of health.

7.5.4 Post-Trial Benefits

Post-trial benefits and the translation of research into new health policy and procedure continue to be a major challenge for collaborative research programs, and yet there is no clear guidance on best practice.[11] This area needs further research, but the project findings indicate that current approaches to negotiations between ethics committees and research teams are not sufficient for securing post-trial availability for participants and their communities. The inability of the global health research community to agree upon an effective mechanism of governing post-trial availability is inconsistent with the widely accepted ethical requirement that participants and local communities should stand to benefit from research. Conscious of this point, the most recent update of the Declaration of Helsinki (DoH) (2013) and CIOMS(2016),[54] founding guidance documents of health research, have expanded the responsibility of post-trial availability from beyond the sole responsibility of the researcher to

include “sponsors, researchers and host country governments".[18] The wording of the latest CIOMS states “make every effort, in cooperation with government and other relevant stakeholders, to make available as soon as possible any intervention or product developed”[54] This aligns with the objective of a global population approach that research promotes and protects population health. Change in practice needs to follow these important recommendations. A broad stakeholder communication strategy approach was taken by the PMVT, as mentioned in the previous Chapter. It would be helpful to learn and share from this experience of broad stakeholder involvement and communication across the lifecycle of the project. A further novel idea proposed by the project in Chapter 5, is that the ethics committee could be mandated to chair a much wider board of stakeholders who are responsible for post-trial availability and country preparedness. An ethics review process may consider asking research teams to detail their post-trial availability strategy and set out the stakeholders that would be involved. This would need further critical research and debate, but as a means to promote population health, it is likely to be more effective than limited negotiations between the research team and ethics review committee. This is likely, given both ethic committee boards and research teams are independent of local health services and therefore have a limited role in national implementation structures. The current inability of research populations to be assured access to proven effective treatments undermines the social value and ethical acceptability of collaborative research. New procedural and political approaches are needed to reinvigorate this important ethical principle in practice. To make a commitment to post-trial availability is not a sole justification of research but remains an important feature for the distribution of fair benefits. New approaches are needed to ensure populations of low resource settings benefit from the local activities of global health research.[67] The global population approach endorses post-trial benefit to ensure that vulnerable populations have a real opportunity to share in the social value of health research and, thereby improve local conditions of health. Actionable commitments to post-trial benefits are not only ethical but also vital for research to combat global health disparities. So long as the objective of collaborative research is to successfully protect and promote population health, then renewed efforts are needed in the co-ordination (agreements and actions) of post-trial benefits.

7.6 References

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8 PROJECT LIMITATIONS

8.1 Study Limitations

This study had some limitations that stem from the selected empirical methodology. The basis of the empirical evidence in the study was informed by qualitative interviews with stakeholders of the GSK PATH/MVI Paediatric Malaria Vaccine Trial (PMVT) in Ghana, Tanzania and the related international partners. Relying on this single partnership example to explore the obligations of collaborative research presents some limitations. Eleven key limiting factors are set out below:

i. All the stakeholders were part of the same vaccine trial and, the interview questions explored specifically the challenges and problem-solving approaches in that specific context. As a result the perspectives and views provided by respondents have been shaped by similar research conditions, experiences, training and decision making processes. This may limit the generalisabilty of the results to all forms of collaborative research. In particular it must be taken into consideration that the PMVT and research-model of GSK PATH/MVI is a not-for-profit Product Development Partnership (PDP). There are other models of international health research, such as for-profit private enterprise. The definition and distinction of conducting health research through not-for-profit PDP organizations in contrast to private enterprise is detailed in the introduction section of Chapter 1. Different research partnership models will have different structures, objectives and interests. For example, in this instance the GSK and PATH MVI partnership was also working in collaboration with a research capacity developer, the Malaria Clinical Trial Alliance (MCTA) of the INDEPTH Network. This organisation was mandated to specifically co-ordinate and implement capacity strengthening activity at the research centres in Ghana and Tanzania (along with the other African countries involved with the vaccine trial.) This specific approach of working with a capacity developer and having a budget line for such activity is a particular feature of this collaborative research programme and represents a truly committed approach to ensure capacity development in the course of health research. However, it may not be a component of all health research. This finding is in itself a learning point to be considered by other programmes of research. In addition, there are a number of transferable learning opportunities for best practice which can be shared across different systems, and therefore the project findings retain relevancy, and add to the body of literature on collaborative research. Moreover, not for profit product development partnerships have become more common, and especially so for neglected disease research operating in low resource settings [1]

ii. The effectiveness of collaborative research in low resource settings is dependent on many variables: countries, healthcare settings, research programs, study objectives, disease targets, education levels, skills and expertise of partners, political and soci-economic settings, partnership formats, funding and, levels of association in partnerships etc. Each project will be presented with different conditions and ethical challenges which may limit the application of findings in this project. In support of the project, I would emphasise that although all the respondents were part of the same collaborative research program, the results were from stakeholders of four different research centres and, in two different countries - Ghana and Tanzania. This diversity between settings and amongst stakeholders adds tenacity to the findings and reinforces the robustness of final conclusions. In addition, the combination of ethical enquiry with practical import and field experience has helped bridge the gap between theory and practical guidance.

iii. The stakeholder recruitment for the project adopted the organisational structure of the PMVT. This resulted in a substantial total number of interviews (N=52) but the size of each stakeholder group varied, and in some instances there was only a single representative (n=1). The largest stakeholder group was made up of the trial managers (lab-, data-, pharmacy-, quality assurance-, field-) (n=15). The smallest stakeholder group was the Clinical Research Officer (n=1) and the representative of the Malaria Clinical Trial Alliance (MCTA) (n=1). Therefore the group size (the number of interview respondents in a stakeholder group) ranged from 1 – 15 representatives, with an average of 4 representatives per stakeholder group.

The strength of interviewing across the stakeholders of a single research collaborative provides an adversarial enquiry into the involvements and issues faced in the course of a research programme. The intention is to represent the various perspectives in a collaborative partnership and the group dynamic between partners, such as decision making processes around shared experiences. The ability to compare and contrast across stakeholders acts to triangulate findings and, provides robustness to the final conclusions. However in this project, the variation of numbers in stakeholder groups weakens the adversarial integrity of this process to some extent. On the whole other literature in this field has rather chosen to concentrate on individual stakeholder groups. There are strengths and weaknesses to both approaches. I recognise the strengthen of presenting in-depth data from the perspective of each stakeholder group in turn, but I

also think that to truly understand a collaborative it is important to consider the role of the stakeholder dynamic and its effect on decision making and ethics. More advanced and in-depth exploration in to collaborative dynamics would further add to this body of work.

iv. Professional relations between stakeholders may have biased interview responses. For example at the time of the interviews GSK was an ongoing client of the Clinical Research Officer (CRO). The Clinical Research Officer was engaged by GSK as an agent. Therefore the CRO was limited in their responses due to professional commitments to their client, and especially because the research questions were related to a specific project. The CRO provides clinical trial services on behalf of the study sponsor. It would be good to further explore the CRO-post in greater depth because they play a pivotal role in the formation of the collaborative partnership and the communication between the sponsor and the research centres.

v. This next point on the timing of the project links to the point above on professional relations. The trial was coming to an end at the research centres and there was concern across the stakeholders about future work opportunities. In particular some respondents were fearful about job security. This fear was notable amongst research mangers and fieldwork teams. A concern also reported in earlier literature.[2] These concerns may have constrained, or changed how respondents were answering questions. Respondents were fully informed and assured of their confidentiality before, and over the course, of the interview. To contrast the medical teams, clinicians and vaccination nurses, were on the whole returning to routine care and, gave the impression of being more confident to share on their experiences in the collaborative research partnership. Moreover, it is the role of senior researchers to attract and develop new programs of research at each research centre. It is possible that this also had some influence over the responses that senior researchers were providing given their professional responsibilities and intent to foster ongoing relations with study sponsors and generate new work. The sponsor-investigator group, GSK and PATH/MVI are also bound by codes of company conduct. However (as a strength) because all the data collection had closed at the time of the interviews, there was an openness and willingness to reflect and consider the successes and challenges of the multicentre collaborative partnership. In particular the PMVT was the largest Phase III paediatric trial to ever be conducted on the sub-Saharan African continent and there was a mutual feeling amongst stakeholders and in particular on the

part of GSK and PATH/MVI that it is important for the research community and wider fields to learn, share and improve on this experience for future work. Notably, it was for this reason that GSK and PATH/MVI granted permission for this empirical ethics study to go ahead.

vi. A further concern links with the timing of the interviews and limited strength of memory recall. On the one hand, as mentioned above, respondents had the luxury of being able to reflect back on the success of the collaborative partnership across the past 4 – 6 years. This provided great depth to answers and, an abundance of different illustrative examples across the lifespan of the partnership. In addition the timing of the project was very important for informing the final paper (Chapter 5) on ethics and end of trial obligations. A topic that has attracted limited previous attention. However as a limitation, the passage of time impacts on the memory recall of respondents. Future programmes of health research may consider involving a research ethicist throughout the conduct of the study to explore and report on different topics as they arise (separate to the oversight role of an ethics committee). This would provide an effective learning tool.

vii. The project did not interview the research participants (in this instance, mothers of infants). This decision was taken due to the research angle, which did not focus on clinical research issues and community engagement (both important topics in their own right). Rather the focus of this project was at the system level and the interested in the partnership dynamic. However not including the research participants had some disadvantages. Notably for the fact that the impact of collaborative research is defined by the experience of the local community. In part, the project captured this aspect through conducting interviews with fieldworkers (community liaison officers for the programme of research) were included in the interviews. This perspective from the community was very informative. The fieldworker responses presented many practical research examples of every day ethical decision-making in low resource settings.

viii. As the vaccine trial was ending a number of stakeholder representatives had already been disbanded. In particular it was only at the first research centre that vaccination nurses and fieldworkers were still present. I interviewed both these stakeholders in group interviews. There were 5 vaccination nurses and 5 fieldworkers in each respective interview group. These two groups worked very closely with the vaccine participants and communities, and as frontline staff mediated between the needs and interest of the

community and those of the research teams. The interview experience with these stakeholder groups was exceptionally informative, and I would invite future research to work closely with these teams when looking at the conduct of health research in low resource settings. At present there are only a few studies that have taken this approach.[3, 4]

ix. The study findings may have been influenced by researcher bias. My presence as an interviewer from abroad visiting the research centres may have caused respondents to tailor their answers in some respect. However the stakeholder groups were all professionals and used to working in international collaborative teams, so I think this impact is minimal. On the whole respondents were pleased to be able to discuss their work and debrief on the conduct of the PMVT and, the strengths and weaknesses of collaborative research. The other aspect of researcher bias, are the preconceptions that I may have imposed in process of analysing the research findings. I think it would be fictional to suggest all subjective bias can be totally removed, but I took steps to minimise this influence with the involvement of a secondary reviewer. David Shaw undertook a secondary review of raw data to consolidate findings.

x. All the interviews were conducted in English. Most stakeholders were speaking English as a second language. Notably the level of English amongst stakeholders was close to fluent because the respondents were professionals working on the vaccine trial, and English is a working language of the research centres. Language has three influences on the interview results. First it may influence how respondents articulated their views and opinions and second; it is likely to have also played a role in the analysis of results and evaluation of the comments and thirdly; it creates a bias in the selection of quotes that are presented. The quotes from respondents with stronger English tended to be selected, and this creates a language bias. Equally some sound recordings were better quality than others, and again this creates some bias in the evaluation of data. Conducting pilot studies greatly helped pick-up on technical recording issues early and informed the pace of interviews.

xi. This has been a highly interdisciplinary study, set up between the Institute of Biomedical Ethics and Swiss Tropical Public Health Institute at the University of Basel, along with INDEPTH Network, Ghana; and Ifakara Health Institute (IHI), Tanzania. In addition my own professional background is in pharmacology, medical law and ethics. In the main, “interdisciplinarity” has been a strength of the project, in terms of understanding

the structures and decision-making processes of collaborative research and, for engaging with a wide range of stakeholders. Each issue could be explored in much greater depth and through many different lenses. The angle of this project was one of ethical enquiry. To fully explore and develop guidance and policy on the variety of different topics raised would require further in-depth knowledge of the healthcare systems in Ghana and Tanzania along with; developed understanding of political science, comparative law, public health, community engagement, clinical trials and health research financing, economics and policy. The project touches upon all of these disciplines, but I recognise, that I am very much a student in most of these areas, and especially so in respect of context-specific knowledge of Ghana and Tanzania.

On average I spent about 2 weeks per research centre in the healthcare settings of Ghana and Tanzania, giving me a "snap-shot" view of the different systems and contexts. This reflection on the project has further strengthened my resolve on how important multi-stakeholder collaborations truly are for the conduct of locally responsive health research and system development. No individual alone will have specialisms in all the multi-dimensional factors that are needed to strengthen health systems, structure context-specific research and improve conditions of health for a population. A broad stakeholder representation is required to communicate, listen and work together to deliver on objectives of improved health and local development. Multiple disciplines were brought together in this project by including a broad range of expertise amongst the respondents and the collaborators of the project.

8.2 Limitation Summary

To conclude, there are some weaknesses to the study but overall the project has presented the views of stakeholders involved within a collaborative research programme of a paediatric malaria vaccine trial operating in Ghana and Tanzania. To the best of my knowledge it is the first time that an ethics project has presented the perspectives of stakeholders across a partnership. The study has brought together different stakeholders of research, their opinions and experiences and, presented these views with an ethics evaluation. The project reflected the dynamic of collaborative research and, in doing so explored what is good collaborative practice.

8.3 References

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3. Molyneux, S., et al., *Field workers at the interface.* Developing world bioethics, 2013. **13**(1): p. ii-iv.
4. Kamuya, D.M., et al., *Evolving friendships and shifting ethical dilemmas: fieldworkers' experiences in a short term community based study in Kenya.* Developing world bioethics, 2013. **13**(1): p. 1-9.

9 IMPLICATIONS FOR FUTURE RESEARCH

9.1 Next Steps

This project on good collaborative research has led to a number of possible future areas of investigation across different disciplines. The suggestions are presented below.

9.1.1 Ethics

The thesis has developed good collaborative practice recommendations based on the experiences and perspectives of stakeholders in Ghana and Tanzania involved in a research partnership of a paediatric malaria vaccine trial. Greater opportunities to share between different programmes of research would help to continue to inform best practice in global health research. A recommendation for a future study would be to create a system of ethics reporting across different health research programmes from inception through to the end of the trial looking at stakeholder engagement and deliberation across partnerships based on a variety of issues faced in the field. This could be achieved through embedding ethicists across different research programmes as a component of a research team. For example this project has found in line with other commentators that locally-led leadership is a requirement of good collaborative practice, a vital component of research and health system strengthening and, a necessary step to sustain good conditions of health in a community. A future study would assist in defining the components of leadership, how are they achieved, and what the enablers and barriers of locally-led research are in low resource settings. On related point future research should investigate the role and responsibilities of Clinical Research Officers (CROs) in respect of good collaborative practice and equitable partnership. Wider ethical reporting in this respect would assist in further capturing the collaborative dynamic in different programmes of research, sensitive on-the-ground dilemmas and clearer insight into the achievements and set-backs of collaborative research programmes.

On a related point, it would be extremely beneficial to construct a mixed method approach, by including quantitative data in combination with qualitative data. Establishing quantitative indicator measures of partnership equality, system integration, capacity strengthening and sustainability along with the translation of results would have two advantages: the quantitative findings could both help triangulate the qualitative findings and assist in quantifying the extent to which these goals are achieved, and change over time. Quantitative measures can also operate as a means for partnerships to optimise shared system learning, and compare across different research activities of collaborative research programmes.

9.1.2 End of Trial of Obligations

The project has demonstrated that the end of trial obligations remain a challenging topic at the level of implementation, even though there is strong agreement amongst stakeholders that research participants and communities should stand to benefit from the conduct of research. Practically, performance on end of trial commitments has been limited due inadequate implementation guidance. The globalisation of health research and the vast variety of settings in which health research now takes place, along with various interdisciplinary stakeholders, needs informed and coordinated decision making to deliver on post-trial commitments. A future study would be helpful to identifying the best approach to agreeing on the end of trial obligations and; establishes a functional treatment access pathway that links collaborative health research to improved conditions of good health. At present, the ambiguity and limited direction on how participants, local communities and health care settings can stand to benefit from research has led to uncertainty resulting in post-trial responsibilities being poorly addressed, if at all. Therefore finding an implementation approach is vital. A future study needs to look closely at what implementation pathways could deliver on this widely accepted ethical principle, and better connect research to improved population health.

9.1.3 Governance

The project has identified a number of governance provisions that would better support good collaborative practice and the design of health research for development in low resource settings. A future study would now assist to establish an adequate governance framework of good collaborative practice that is internationally recognised, nationally implemented and enforceable, to direct, regulate and monitor the constructs of international partnerships amongst stakeholders and, in local healthcare settings worldwide. Further research would help to define stakeholders' responsibilities, mechanisms of accountability and the educational implications (for example for researchers, healthcare systems, ethic committees and funders). Beyond principles of bioethics, partnership governance needs to be able to embed research with global population health and the development of sustainable health research systems worldwide. There is a growing awareness of collaborative partnership responsibilities amongst research teams, policy documents and in some ethics guidance. However, at present without a clear governance structure, there is little detail on equitable partnerships processes and, how responsibilities and rewards are shared amongst stakeholders. Also, greater clarity is needed on how collaborative

research activity can be regulated with necessary oversight. Regulatory incentives, measurable indicators, and oversight of these functions would better support the connection between health research and improving local conditions of health. A future study would be beneficial to develop a clear governance framework in this respect.

9.1.4 Economics

Good collaborative practice generates obligations that are wider than merely researcher-participant responsibilities. As a result, constructing health research to serve population health and development may need different research structures and funding. The format and financing of global research have changed over the past 20 years with innovation such as product-development-partnerships, and further change may be needed to support system development in partnerships alongside product development. Often the greatest causes of contention amongst stakeholders against system strengthening are money and time - functions of economics. A future economics study to evaluate novel funding mechanisms of capacity building in research partnerships would complement good collaborative practice governance and conduct. For example, at present, a proposal is being made for an international Health Product Research and Development Fund.(Organization & UNICEF, 2016) An important line of inquiry would be to see how such a fund will be structured to promote health, prioritise population needs and reduce health inequity.

9.2 References

Organization, W. H., & UNICEF. (2016). Health product research and development fund: a proposal for financing and operation *Health product research and development fund: a proposal for financing and operation*.

10 Conclusion

In conclusion the past 30 years have seen rapid changes in the format and organisation of international health research partnerships. There has been an increase in funding and variety of new collaborative research structures; involving more countries and more institutions than ever before. This has importantly taken health research to local communities which had previously been neglected by science and health innovation. Collaborative research in low resource settings has generated new knowledge and advanced scientific understanding of diseases that disproportionately affect populations living in poverty. Global health research has undoubtedly led to improvements in population health and gains in life expectancy. However the gains have been uneven and major health inequalities persist within and among countries; disproportionately affecting populations of low and middle income countries. Growing concerns question whether the conduct of research and knowledge produced by international partnerships improves local conditions of health. This raises the question of whether the research is of value to the populations living in low resource settings, or whether local resources and populations living in poverty are being exploited for the benefit and accolades of institutions of high income countries. In recent years more critical thinking in academic literature has been given to this point. In addition, some policy and research governance documents have also started to reflect the need for equitable partnerships and development obligations in collaborative research to improve local conditions of health. Equally, some collaborative research programmes have added explicit development objectives, the paediatric malaria vaccine trial (considered in the empirical part of this project, Chapters 3 - 5), being one example. Yet it remains that there is limited implementation guidance on good collaborative practice.

The conduct of health research in low resource settings has led to extensive changes in legislation and ethics guidance on issues of human participant protections and community engagement in the past 30 years. Yet, less attention has been given to how partners of international collaborative research function and whether these constructs serve local population health. The empirical study for this project has been based on the perspectives of stakeholders involved with a collaborative research project conducting a Phase II/III paediatric malaria vaccine trial operating in Ghana and Tanzania. The project demonstrated that for international research partnership to serve improved population health then this requires developing local-leadership, building research capacity and effective integration with local health care settings. Crucially there is a need to recognise research as a tool of public health. The project concludes with a proposition for a new research ethics framework based on principles of public health ethics entitled, The Global Population Approach. The ethical

foundation of the framework guides partnerships to form a social contract that equally distributes risks and promotes common interests. In addition there needs to be a commitment to build capacity in accordance with shared goals to improve conditions of local population health. Important to this goal is transparent, equitable and accountable partnership governance. In this respect, research governance and regulatory frameworks need to endorse good collaborative practice that supports and co-ordinates a network of robust research systems worldwide. International collaborative partnerships can support this goal by developing local research capacity (leadership, skills and infrastructure) that delivers on context-sensitive health solutions and protects and promotes population health, both locally and globally.

11 APPENDICES

Index

1. Project Summary Information Brochure (graphic design by Rafaël Schütz). Content and Presentation delivered by Claire Leonie Ward at the Health for All in an Unequal World, 14th World Congress of Bioethics, Bengaluru, India, December 2018
2. Bestätigung Doktoratsexamen in Bio- und Medizinethik, Die Medizinische Fakultat der Universität Basel July 2017
3. Semi-structured Qualitative Interview Guide, Claire Leonie Ward, September 2014

Contributing Research Centres

Ghana

Malaria Research Centre, Agogo Presbyterian Hospital, Agogo, Ashanti (administered by the School of Medical Sciences, Kwame Nkrumah University of Science and Technology, Kumasi)

Kintampo Health Research Centre, Ghana Health Service, Kintampo

Tanzania

Ifakara Health Institute (IHI), Bagamoyo

Tanga Research Centre, Korogwe, National Institute for Medical Research (NIMR)

References

Ward, C.L., Shaw, D., Anane-Sarpong, E., Sankoh, O., Tanner, M. and Elger, B., 2018. The ethics of health care delivery in a pediatric malaria vaccine trial: The perspectives of stakeholders from Ghana and Tanzania. Journal of Empirical Research on Human Research Ethics, 13(1), pp.26-41.

Ward, C.L., Shaw, D., Sprumont, D., Sankoh, O., Tanner, M. and Elger, B., 2018. Good collaborative practice: reforming capacity building governance of international health research partnerships. Globalization and health, 14(1), p.1

Ward, C.L., Shaw, D., Anane-Sarpong, E., Sankoh, O., Tanner, M. and Elger, B., 2017. The Ethics of Health Care Delivery in a Pediatric Malaria Vaccine Trial: The Perspectives of Stakeholders From Ghana and Tanzania. Journal of Empirical Research on Human Research Ethics, 13(1), pp. 26 - 41

Ward, C.L., Shaw, D., Anane-Sarpong, E., Sankoh, O., Tanner, M. and Elger, B., 2017. Defining Health Research for Development: The Perspective of Stakeholders from an International Health Research Partnership in Ghana and Tanzania. Developing world bioethics, pp. 1–10

Event

Health for All in an Unequal World, 14th World Congress of Bioethics, Bengaluru, India, 5 - 7 December 2018

Contact for further information

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« Thank you to everyone who has been involved with the development of this project and participated in the stakeholder interviews»

GOOD COLLABORATIVE PRACTICE: PERSPECTIVES FROM A PAEDIATRIC MALARIA VACCINE TRIAL IN GHANA AND TANZANIA

University of Basel / 2014 – 2018

University of Basel, Institute for Biomedical Ethics; Swiss TPH, Swiss Tropical and Public Health Institute, Schweizerisches Tropen- und Public Health-Institut, Institut Tropical et de Santé Publique Suisse, Associated Institute of the University of Basel; IFAKARA HEALTH INSTITUTE, research | training | services; INDEPTH Network, Better Health Information for Better Health Policy

Contributing Authors

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Objectives

- **EXPLORE** what are the roles and responsibilities of collaborative health research programmes operating in resource constrained settings.
- **DETERMINE** what are the components of good collaborative practice in international research partnerships.

Background

The United Nation Sustainable Development Goals (2015) provide renewed policy commitments to international collaboration and the need for local system strengthening. In particular goals (SDGs) 3 and 17 recognise that partnership must facilitate skills development and structural advancement along with the generation of new science and technology to improve health outcomes and reduce global health inequalities. This project adds to current debate on how these policies can be implemented in practice.

Methods

- Review of current academic literature
- Analysis of relevant research governance documents
- Key informant interviews (N=52)*

*Individual semi-structured 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 (involving four individuals per group). The interview data collected recorded the experiences of stakeholders involved with a Phase II/III paediatric malaria vaccine trial: (vaccine candidate RTS, S) (NCT00866619). The respondents included in-country stakeholders from Ghana and Tanzania and representatives of the international partners involved with the conduct of the RTS, S malaria vaccine trial.

Number of respondants by location

Respondants by stakholders roles (N=52)	
Research Managers	23%
Senior researchers	19%
Clinicians	11%
Sponsor-investigators/Funders	11%
Health System Representatives	10%
Fieldworkers and Field-coordinators	8%
Ethics Review Committee Members	8%
National Government Bodies	8%
Vaccination Teams	2%

Results

This empirical ethics study has provided vital insight into the complex decision making associated with an international research partnership operating in resource constrained settings.

Key Learning Points:

These points define an approach for the successful implementation of good collaborative practice in international health research partnerships.

Ethical governance inclusive of local stakeholders with equitable, transparent, and accountable decision-making

Build a culture of research and shared system learning with local health-care services

Promote trust through capacity building and collaboration with local leadership and institutions

Establish multidisciplinary stakeholder commitments to sustain local conditions of good health and access to innovation

Study Findings

These findings and thematic concepts have formed the basis of a number of peer reviewed journal articles
(see *References)*

Overall, an unequivocal commitment to equity and unity is needed between partners to deliver on the public health goals of research, support system development and improve local conditions of health.

Equitable Partnership

- Establish equitable partnerships: i) shared research agenda-setting with local leadership; ii) system capacity assessments; and iii) construction of a memorandum of understanding (MoU).
- Acknowledge and comply with, international and local, laws and regulation requiring ethical research partnerships and sustainable capacity strengthening in resource-limited regions.

Sustainable Structures

- Align research agendas and activities with local health priorities
- Know the country specific context - map the social, health, legislative, and political setting.
- Define an explicit development component with the research and a plan of action.
- Address the barriers and opportunities to sustain system developments.
- Establish public health indicators to monitor change to local systems of health.

Health System Integration

- In partnership with the local health system, agree on care provisions supported by the collaborative research programme.
- Design and establish a context-relevant education strategy that explains the objective of the health research to respective communities.
- All healthcare provision associated with research should be accompanied with joint clinical service reviews to promote local health system strengthening.

Regional Commitment

- Design and implement a gradual exit strategy from the healthcare setting.
- Uphold continuity of care when planning end of trial service handover.
- Establish a post-trial access board composed of diverse stakeholders to devisie an actionable treatment access pathway.

University of Basel

Faculty of Medicine

BESTÄTIGUNG

Die Medizinische Fakultät
der Universität Basel bestätigt, dass

CLAIRE WARD

von England,
geboren am 29. Januar 1985,

am 13. Juli 2017 das

DOKTORATSEXAMEN

in

BIO- UND MEDIZINETHIK

bestanden hat.

Das Diplom "Master of Laws in Medical Law and Ethics" der De Montfort University von Leicester ist datiert vom 01.11.2013.

Im Laufe des Doktoratsstudiums wurden 33 KP erworben.

Die Promotionsurkunde wird ausgestellt, sobald die Dissertation

"Good Collaborative Practice – Perspectives from a Paediatric Malaria Vaccine Trial in Ghana and Tanzania"

in der vorgeschriebenen Anzahl von Exemplaren der Universitätsbibliothek Basel abgeliefert worden ist.

Basel, den 13. Juli 2017

Prof. Dr. Bert Müller
Vorsitzender am Doktoratsexamen

UNIVERSITÄT BASEL

INSTITUT FÜR BIO- UND MEDIZINETHIK

N.B. This Interview Guide sets out the broad areas of interest in accordance with the topic of the project. The questions may change, or require additional prompts, to suit the cultural context.

PRESS RECORD BUTTON TWICE. CHECK BOH DEVICES ARE ON RECORD.

* * *

Interview Guide for key informants of Pediatric Malaria Vaccine Trial

The Role of International Vaccine Studies in the Healthcare Development of Resource Limited Regions

Unique Participant Number:

Three Letter Participant Code:

Expected duration of the interview: 1 hour.

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 healthcare 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 positive 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 Process with Signing of Informed Consent Form]

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 healthcare?
- 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 *multi-centre 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. 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:

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Nudges:

(a) capacity building

(b) provision of health services

(c) Standard of care.

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

A warm thank you for your time and support with the project. Your contributions have been extremely informative and helpful. My email details again, should you wish to contact me, claireleonie.ward@unibas.ch.

Please feel free to contact me if you have any new questions or need further clarification. Equally feel free to contact me again, in case you have some other thoughts/insights on this topic. I will be more than happy to incorporate these responses with your interview. After data analysis, I will ensure that a report is provided from the outcome of this meeting. The health research center will have access to any publications written, with the view that this project advances the best conditions for health research.

It was a real pleasure speaking with you, thank you.

September, 2014